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## Clinical Trials with medicinal products on humans

Ad hoc Statement

regarding the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

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## I. Summary

### **Current situation**

Under European Union law, clinical trials carried out on human subjects for medicinal products are regulated by Directive 2001/20/EC. This stipulates that the foreseeable risks and burdens must be weighed against the anticipated benefit associated with a clinical trial for both the trial subjects and for other current and future patients. A potential group benefit alone can be justified only if there is only a minimal risk or minimal burden. Minors and incapacitated persons are given special protection. Further important elements in this are the assessment and vote by an independent ethics committee. In addition to the Directive, national law is to be applied if it is stricter.

### **The Consequences of Directive 2001/20/EC**

In the past this Directive has been criticised for the following aspects, among others: it does not adequately stimulate clinical research within the EU and the lack of harmonisation puts the safety of participants in clinical studies at risk. A further point of criticism relates to the level of bureaucracy, which makes applying for and carrying out non-commercial (long-term) studies for the continual improvement of intervention with medical products and the safety of therapy for serious illnesses such as cancer – especially for children – more difficult.

### **Amendments to be introduced by a new EU Regulation**

It is emphatically to be welcomed that the proposal for a new regulation concerning clinical trials of medicinal products for human use is intended to harmonise,

shorten, simplify and make more cost-efficient the procedure involved. Furthermore, clinical trials for the treatment of particularly vulnerable patients are to be facilitated or made possible. In order to ensure harmonisation across the EU the new regulation should take precedence over national law. This too we explicitly endorse.

### **Problematic consequences of the draft of the new Regulation**

Nonetheless, however welcome the intention, the proposal, if implemented without amendment, would have the following ethically questionable consequences: (1) The protection of minors and incapacitated persons could be reduced compared to existing legislation, since more extensive national protective regulations, such as the German Medicinal Products Act (Arzneimittelgesetz, AMG), could become ineffective. (2) The inclusion of an independent and comprehensive ethical assessment could be dropped. (3) For cross-border studies, a reporting Member State with lower standards could be selected in order to avoid having to meet more stringent standards. (4) In any assessment of tenability, the non-reporting Member States would be almost completely excluded from the ethical review of the clinical trial.

The Bundestag, the Bundesrat and the relevant committee of the European Parliament have all taken a critical stance in response to this Regulation. Against this background, the following ad hoc report records points of criticism expressed by the aforementioned, addresses other critical points and formulates recommen-

dations, particularly with regard to the areas (A) protection of clinical trial subjects, (B) Europe-wide harmonisation, (C) the role of the Ethics Committee and (D) the procedure for arriving at consensus across the EU states involved.

### Summary recommendations

- Clinical trials for particularly vulnerable patients are to be welcomed, since these patients also have a right to evidence-based treatment. However, these vulnerable patients require strict protection in terms of their autonomy and well-being, as well as for any therapeutic benefits.
- If a minor or an incapacitated person is in a position to evaluate the information provided and does not consent to participating in a clinical trial, they must be excluded from the clinical trial.
- No permanently incapacitated adults must under any circumstances be included in a study without prior informed consent being given by their legal representative after receiving proper information.
- Clinical studies for emergency situations are necessary. However, in an emergency situation consent to participation in the study must be given or there must be grounds to presume that it would be given by the participant or their legal representative.
- Clinical trials with low rates of incidence for patients with rare diseases or for multi-morbid patients should be facilitated.
- It is recommended that strict requirements for research on human subjects be formulated within the regulation itself in order to ensure a consistently high level of protection throughout the EU.
- In every affected Member State an autonomous, independent, certified, legally regulated Ethics Committee should be fully involved.
- Approving authorities and Ethics Committees should be given sufficient time to carry out a careful evaluation and assessment of the trial.
- Written information and the consent of the proposed trial subjects should, without exception, be provided for the relevant Ethics Committee in its own national or regional language.
- A right of consultation in the final ethical and scientific assessment of the study is necessary in all Member States involved.

## II. Definitions <sup>1</sup>

### **Individual benefits**

Any potential positive effects for the patients or subjects participating in the clinical trial, there are, such as an alleviation of their suffering or the restoration of their health.

### **Group benefits**

In this there are potential benefits to the group of persons suffering from the same ailment/ the same disease/ of the same age as the persons participating in the trial.

### **Benefits to others**

The clinical trial points to the possibility of use in a third-party group, particularly for persons not suffering from the same ailment/ the same disease / not of the same age as the persons participating in the trial. This may, for example, include potential benefits for science.

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<sup>1</sup> In view of the lack of uniform, binding definitions, the following contains a description of how these terms are applied in the course of this report. These are based on a simplified version of the guidelines for reviewing clinical trials from the DFG.

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### III. Background

At EU level clinical trials of medicinal products on human subjects are currently regulated by Directive 2001/20/EC<sup>2</sup>. This Directive has the following consequences:

It allows different forms of implementation in the individual EU Member States. Its coming into force changed the requirements for conducting clinical studies, which also, in part, entailed considerably increased outlay in terms of staff, finances and time. As a result of the different regulatory requirements in the various Member States, the expense involved in multinational studies within the EU has increased still further.<sup>3</sup>

Research into medicinal products using previously tested products with market authorisation has been placed on the same footing as studies with new, as yet unauthorised medicinal products<sup>4</sup> insofar as they have been made subject to the same regulatory conditions and thereby made more difficult to carry out. This applies in particular to academic clinical trials without the involvement of the pharmaceutical industry.

The requirement to report consensus after assessment by several Ethics Committees for multi-centre medicinal product studies has also resulted in an increased workload after opinions had been collected from clinicians. Even after a comprehensive assessment had been undertaken by a first Ethics Committee, subsequent Ethics Committees have in fact, despite there being no legal basis for this,<sup>5</sup> sometimes undertaken a further comprehensive assessment. In addition to the extra workload, this procedure can sometimes result in different and sometimes even contradictory ethical assessments.

It is therefore to be explicitly supported that the Draft Regulation in its current form has the aim of improving conditions for clinical research in Europe over the long term. In particular, science-based trials without involvement from the pharmaceutical industry should be encouraged.<sup>6</sup>

Particularly to be welcomed is the planned regulation by means of a binding, EU-wide Regulation in place of the previous Directive. This – unlike a Directive –

<sup>2</sup> Directive 2001/20/EC (OJ 2001, No. L 121/34) dated 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in conducting clinical trials on medicinal products for human use.

<sup>3</sup> In spite of this the number of medicinal product trials in Germany within this period has not decreased (Source: BfArM). The fact that there has been a qualitative change in medical product trials can be overlooked. Thus cross-phase studies (Phase 1/2) are conducted as a single trial, and, likewise, short-term and long-term studies are planned as a single study. Moreover, merely demonstrating an increase in cost is not meaningful; rather, we should consider the relationship between cost and benefits.

<sup>4</sup> Applies as a matter of principle: however, the Directive does not apply to non-interventional trials (Art. 1 para... 1 sentence 2 of the Directive), so that monitoring the use of authorised medicinal products remains exempt from the regulatory requirements of the Directive.

<sup>5</sup> In Germany, since the introduction of the 12<sup>th</sup> Amendment to the German Medicinal Products Act 2004, there has been a Senior Ethics Committee (Sen EtC, or the EtC which is legally responsible for the leaders of the clinical trials). Only this Sen EtC evaluates the trial plan and the supporting documents. Since 2004 there has been no legal basis for the responsible Ethics Committee to ask a sponsor questions or provide them with comments or an assessment of the trial plan and the documents for providing information or obtaining consent. Furthermore, the Sen EtC may ask questions or request additional information only once, and deadlines have been imposed for delivering the assessment (30 calendar days for single-centre and 60 calendar days for multi-centre trials). Nonetheless, in Germany it is clearly not certain that the applicant will be granted only one vote.

<sup>6</sup> Compare Draft Regulation Explanatory Memorandum 3.3 Interface with “scientific advice”.

can create uniform legislation across Europe. As a result of this EU-wide harmonisation, the potential endangerment of subject safety arising from different national regulations can be eliminated and consistent ethical standards introduced.

The Draft Regulation represents an ethical basic concept for the protection of adults. In the case of incapacitated adults, the applicable standard should be that the anticipated benefits (derived from the benefits to the individual trial subject and the public health/therapeutic benefits) outweigh the anticipated risks.<sup>7</sup>

By contrast, some of the amendments to the Regulation proposed by the European Parliamentary Committees (EP Committees) bring the well-being of the patient alone to the fore.<sup>8,9</sup> In contrast to the formulation in the Draft Regulation, it is the opinion of the EP Committees on the Environment, Public Health and Food Safety and on Civil Liberties, Justice and Home Affairs that the interests of the patient should outweigh the benefits to science and society.<sup>10</sup>

Furthermore, the Draft Regulation aims to stimulate clinical studies and thereby both the development of new medicinal products and the improvement of existing treatments using medicinal products for all groups of patients in the long

term. Particularly welcome in this is the possibility of improving the treatment of children, of permanently incapacitated adults and of patients in emergency situations, since a lack of studies to date has resulted in insufficient concrete knowledge on many of the ailments suffered by these groups of patients. However, the Regulation should also establish a higher level of protection for these particularly vulnerable groups of patients.

Combined with some of the proposed amendments from the EP Committees and other institutions<sup>11</sup> the new regulation seems, on the whole, well-suited to shortening, simplifying and rendering more cost-effective the whole process for approving clinical trials. A new approval procedure should also contribute to this. This includes the introduction of a common application dossier for the entire EU and the electronic submission of this dossier once only via the so-called EU Portal<sup>12</sup>, as well as the stipulation of deadlines within which the authorising authorities must arrive at a decision with respect to the application. For academic networks the concept of “co-sponsoring”<sup>13</sup> is to be introduced. Proposed amendments by the EP Committees further recommend that academic sponsors should be exempted from fees.<sup>14</sup>

The clear differentiation reflecting the different levels of risk between

7 This would, however, contradict points 6 and 21 (among others) of the Declaration of Helsinki.

8 “In accordance with the Declaration of Helsinki, ‘well-being’ applies throughout the text whenever the safety and rights of the subjects are mentioned” Recital 1, Recital 66, Art 49(2) (Committee on the Environment, Public Health and Food Safety, Amendment 1, Recital 1).

9 “Ensuring first and foremost the safety and well-being of all subjects” (Committee on the Environment, Public Health and Food Safety, Amendment 7, Recital 8).

10 “The interest of the patient shall always prevail over those of science and society” (Committee on the Environment, Public Health and Food Safety, Amendment 181, Article 31 – paragraph 1 – point h a (new)). “The interest of the patient shall always prevail over those of science and society” (Opinion of the Committee on Civil Liberties, Justice and Home Affairs, Amendment 5, Article 31 – paragraph 1 – point h a (new)).

11 Compare the critical statements made by the working group of the German Medical Ethics Committee, the German Medical Association and in the cross-party resolution of the German Bundestag and the comparable resolution of the German Bundesrat, as well as the report by the European Parliamentary Committee on the Environment, Public Health and Food safety (see also the full version of this statement).

12 “It should be ensured that this portal is user-friendly and meets the requirements of the user.”

13 Compare Explanatory Memorandum under 3.8 of the Draft Regulation.

14 “Measures should be put in place by Member States to make appropriate exemptions from fees (application fees, inspection fees etc.) for trials conducted by academic sponsors” (Committee on the Environment, Public Health and Food Safety, Amendment 19, Recital 10 b (new)). “Inspection fees, if any, shall be waived for non-commercial sponsors” (Committee on the Environment, Public Health and Food Safety, Amendment 237, Article 75 – paragraph 3 a (new)).

the different types of trial, “clinical trials”, “low-intervention clinical trials” and “non-interventional trials” should also be helpful, even if proposed amendments from the ranks of the European Parliaments recommend a non-specific and therefore less clear division based on the level of risk of the intervention rather than by the type of study.<sup>15</sup>

According to the Draft Regulation, “clinical trials” will be conducted using as yet unauthorised medicinal products, whilst “low-intervention clinical trials” and “non-interventional clinical trials” are conducted using medicines which already have a market authorisation. For low-intervention clinical trials, the Regulation fortunately provides for the further streamlining of the administrative procedures and a further reduction in the time allotted for the assessment and approval of the studies. The documents that must be submitted for studies with an authorised investigational product should also

be simplified.<sup>16</sup> Non-interventional studies are defined by the Regulation, but explicitly not further regulated by it.

In order to further reduce the organisational burden, the Draft Regulation allows appropriately qualified experts to undertake the task of providing the patient with the necessary information. Another important point is that investigational medicinal products should be provided without charge for patients throughout the EU.<sup>17</sup> Finally, according to the Draft Regulation, those assessing such applications should be free of any conflict of interest.<sup>18</sup>

In summary, this report explicitly welcomes and supports the intention of the legislators. However, before being enacted, important points of the Regulation should be adapted and improved by the legislators. This ad hoc response contains recommendations<sup>19</sup> for such improvements. In summary, the recommended improvements primarily affect (A) the protection of clinical trial subjects, (B) EU-wide harmonisation of the protective provisions, (C) the role of the Ethics Committee and (D) the process for reaching consensus among EU states.

15 “Given that low-intervention-risk clinical trials have only a very limited and temporary adverse effect – if any – on the subject’s health, (Committee on the Environment, Public Health and Food Safety, Amendment 9, Recital 9)”... “It is preferable to define the second category of research in terms of the level of risk to the subject rather than the type of intervention. This is in line with the main aim of the proposal for a regulation, namely to develop a risk-based approach. The provisions of the regulation should also be brought into line with those of the Oviedo Convention, ratified by a number of EU Member States, Article 17 of which establishes the concept of ‘minimal risk’”(Committee on the Environment, Public Health and Food Safety, Amendment 58, Article 2 – paragraph 2 – point 3 – introductory part). ‘minimal-risk clinical trials’ (Opinion of the Committee on the Internal Market and Consumer Protection, Amendment 3, Recital 9) poses only a low risk (Opinion of the Committee on the Internal Market and Consumer Protection, Amendment 6, Recital 11) (The amendment seeking to replace the term ‘low-intervention clinical trial’ by the term ‘minimal-risk clinical trial’ applies to the whole text. If it is adopted, changes will have to be made throughout.) It would be better to define the second category of research by the level of risk incurred by the subject rather than the type of intervention. This reflects the main objective of the Draft Regulation, which is to establish a risk-based approach. Furthermore, the regulation should be brought into line with the provisions of the Oviedo Convention. Article 17 of that convention, which has been ratified by several Member States, contains a definition of the term ‘minimal risk’ (Opinion of the Committee on the Internal Market and Consumer Protection, Amendment 29, Article 2 – paragraph 2 – point 3 – introductory part).

16 Compare Explanatory Memorandum 3.12 of the Draft Regulation Simplification of important provisions for clinical trials with previously authorised medicinal products and low-intervention trials; Draft Regulation Appendix I, 7.1.2. Simplified documentation for investigational medicinal products through cross-referencing with other documents.

17 This is already applicable law in Germany.

18 Article 9 (1) Draft Regulation: “[...] that the persons validating and assessing the application do not have conflicts of interests, are independent of the sponsor, the institution of the trial site and the investigators involved as well as from any other undue influence.” However, there is no discussion on how a pharmaceutical authority which is responsible for authorisation and which may later require a safety or efficacy study (see. Article 28 paragraph. 3a No. 6 AMG) can independently assess and validate the same study.

19 The essential points of the recommendations are included in the summary, the full explanations in the full version of this statement.

## IV. Statement (Abridged version)

*Preliminary Remarks: The abridged version of this statement deliberately focusses on the core aspects and essential points of the issues discussed. The full disquisition – with sources and comprehensive justifications – is to be found in the full version of the statement (Chapter V).*

### 1 Current situation – core aspects

In contrast to the planned EU Regulation, current EU regulations concerning clinical trials are based only on an EU Directive. The principle established in Directive 2001/20/EC stipulates that in a clinical trial, “the foreseeable risks and burdens” are to be weighed “against the anticipated benefit for the individual trial subject and for other present and future patients”. Minors and incapacitated persons are to be given special protection. Furthermore, the assessment and vote by an independent Ethics Committee, as important elements in the process, are indispensable prerequisites for conducting a clinical trial of medicinal products.

In order to protect the rights, well-being and safety of clinical trial subjects, the Directive introduced changes to the requirements for approval for conducting a clinical study, among other things. However, since this Directive was not applied uniformly across the individual EU Member States, risks to participants in clinical trials of medicinal products arose as a result of nationally varying provisions for trials.

Further criticism was aimed at the fact that both the altered requirements for approval and the differing regulations across the Member States have resulted in an intensification of the expense involved in certain aspects of a clinical trial.

Another point of criticism is that Directive 2001/20/EC made clinical trials with already approved medicinal products subject to the same elaborate regulato-

ry provisions as clinical studies intended to gain authorisation for unauthorised products. By thus treating the two types of products as equal from the administrative point of view, Directive 2001/20/EC made it more difficult to carry out clinical trials with approved medicinal products.

The procedure for arriving at consensus among the various Ethics Committees in multi-centre clinical trials has also been criticised.

Finally, the stimulation of the development of new medicinal products and the improvement of existing therapies should also apply for rare diseases<sup>20</sup>, persons suffering from multiple illnesses and those suffering from dementia. It is, therefore, justifiable that the proposed amendments to the Draft Regulation put forward by the EP Committees take account of the peculiarities of rare diseases and those suffering from multiple illnesses, each with low levels of incidence in their respective groups of patients<sup>21</sup> or, for

<sup>20</sup> “Clinical trial applications shall be prioritised by Member States to improve, where possible, the defined timelines when the clinical trial is related to a condition that is a rare or ultra-rare disease, as defined in the third indent of point (a)(i) of Article 6(1), and, as such, is subject to significant administrative burden due to the extremely small patient populations” (Committee on the Environment, Public Health and Food Safety, Amendment 127, Article 11a (new)).

<sup>21</sup> Low incidence levels can seriously reduce the level of evidence, which would mean that unless special provisions were made, the trial would not be approved.

example, of dementia patients<sup>22</sup> where the measurable parameters of efficacy are less easily defined, in order to enable clinical trials for those affected.

## 2 EU Commission proposal – key points

As welcome as the proposal and its intention are, implementation in its unamended form would lead to undesired consequences, particularly in the form of a serious reduction in protection for patients. This is reflected in the amendments proposed by, for example, the EP Committees<sup>23</sup>.

The following ad hoc report critically examines the European Commission proposal, particularly with regard to areas (A) protection of clinical trial subjects, (B) Europe-wide harmonisation, (C) the role of the Ethics Committee and (D) the procedure for arriving at consensus across the EU states involved, and formulates recommendations in response to these.<sup>24</sup> In this we refer to the explanations of points of criticism raised by German institutions included in Chapter III and to the proposed amendments recommended by the EP Committees.<sup>25</sup>

<sup>22</sup> “In order to improve treatments available for vulnerable groups such as frail or older people, people suffering from multiple chronic conditions, and people affected by mental health disorders, medicinal products which are likely to be of significant clinical value should be fully and appropriately studied for their effects in these specific groups, including requirements related to the groups’ specific characteristics and the protection of their health and well-being” (Committee on the Environment, Public Health and Food Safety, Amendment 18, Recital 10a (new)).

<sup>23</sup> Compare the Response from the European Ethics Board Committee of the Expert Group on Ethics in Science and new Technologies (EGE) ([http://ec.europa.eu/bepa/european-groupethics/docs/pdf/proposal\\_for\\_a\\_regulation\\_of\\_the\\_european\\_parliament\\_and\\_the\\_council\\_on\\_clinical\\_trials\\_on\\_medicinal\\_products\\_for\\_human\\_use.pdf](http://ec.europa.eu/bepa/european-groupethics/docs/pdf/proposal_for_a_regulation_of_the_european_parliament_and_the_council_on_clinical_trials_on_medicinal_products_for_human_use.pdf)).

<sup>24</sup> The essential points of the recommendations are included in the abridged version of the statement. The full recommendations are included in the full version of the statement.

<sup>25</sup> Working Group or the Medical Ethics Committee of Germany, German Medical Association, cross-party resolution of the German Bundestag, Resolution of the German Bundesrat. Report by the European Parliamentary Committee for the Environment, Public Health and Food Safety and other European Parliamentary Committees.

### 2.1 Protection of clinical trial subjects (A)

#### 2.1.1 The reduced protection of particularly vulnerable clinical trial subjects

In contrast to Directive 2001/20/EC, the future Regulation will not merely define a minimum standard, but provide an absolute regulation (known as full harmonisation). This means that as a consequence, more extensive national protective regulations with higher standards, particularly with respect to more vulnerable groups, would no longer apply. This has the following consequences:

##### 2.1.1.1 A restriction of protection for minors and incapacitated persons

Protection for minors and incapacitated persons would be reduced in Germany. For example, for all study subjects, and, therefore, also for these particularly vulnerable minors and incapacitated persons, the minimum level of acceptable risk – except in emergency situations – is “as low as possible”. This, in principle, includes the possibility of higher risks, since this could constitute the lowest level of risk possible.

##### 2.1.1.2 Lack of a subsidiarity provision

In the interest of providing particular protection for vulnerable patients, a subsidiarity provision is needed. This should preclude any research involving particularly vulnerable patients where this could be carried out using less vulnerable patients or where the results of the research are already known.

##### 2.1.1.3 The issue of the approval of clinical studies for rare diseases

Desirable clinical studies for patients with rare diseases, with multiple illnesses or even with dementia, may possibly not be approved. As stated by the EP Commit-

tees<sup>26</sup> on Industry, Research and Energy; on Civil Liberties, Justice and Home Affairs and on the Environment, Public Health and Food Safety, there is no specific provision for the particularities of clinical studies for these patients. This could result in studies for these patients not being approved.

#### 2.1.2 Group benefits and the benefits to others of research on vulnerable patients

##### 2.1.2.1 *Deterioration of the level of protection for vulnerable patients*

The level of protection for vulnerable patients (in particular minors and incapacitated persons) would be diminished:

- The Draft Regulation approves group benefits without limitation, also for healthy children and incapacitated persons.
- At the same time, the beneficiaries of research conducted in order to benefit a group can be understood to be both the group of patients suffering from a particular illness and the same childhood age group, which is to be welcomed in principle, but which, in the Draft Regulation, as already mentioned, allows for undesirable research on healthy children.
- Article 32 of the Draft Regulation reasonably allows the carrying out of clinical studies in emergency situations. However, it unfortunately allows it even if this does not benefit the individual patient.
- In Article 30, the Draft Regulation permits, provided that certain provisions

have been met, the inclusion of incapacitated adults in studies where the only benefit is to the group. This regulation is to be welcomed in the case of dementia patients, for example. However, it should be implemented only if the criteria for minimal risk and minimal burden are met, and not if the level of risk is defined to be as low as possible, as in the text of the Draft Regulation.

#### 2.1.3 Lack of legislative stipulations on providing information

The Draft permits study subjects to be given information about the study by a person who is not a doctor. In exceptional cases, and subject to strict conditions, this seems to be both helpful and possible from an organisational point of view. However, there is a lack of legal stipulation as to the conditions, the standards of which should not be lower than those required for a doctor.

#### 2.1.4 Statements regarding consent

##### 2.1.4.1 *Exceptional provisions for studies in emergency situations*

Article 32 of the Draft Regulation reasonably provides for studies conducted in emergency situations to be exempted from the requirement for prior consent:

- In the interests of providing particular protection for patients in emergency situations, however, as previously mentioned, a subsidiarity provision is needed.
- The required levels of benefits for incapacitated adults and for minors in studies in emergency situations are different. No justification is given for this difference.
- Article 32 of the Draft Regulation dispenses with the need to provide information and obtain de facto consent in emergency situations. Reasonably, this

<sup>26</sup> Committee on Industry, Research and Energy, Amendment 8, Recital 22 a (new); Committee on Civil Liberties, Justice and Home Affairs, Amendment 63, Annex 1 – part 2 – point 6 – point 6 a (new); Committee on the Environment, Public Health and Food Safety, Amendment 92, Article 6 – paragraph 1 – point a – point i – indent 3; Amendment 114, Article 7 a (new).; Amendment 188, Article 31 b (new).; Amendment 189, Article 31 c (new).

also applies for incapacitated persons as well as minors. Unfortunately, this also applies to minors even if there are no benefits to them as individuals.

#### *2.1.4.2 Disregarding the autonomy of minors and incapacitated adults*

The autonomy of minors, incapacitated persons and patients in an emergency situation are accorded too little importance in the current formulation of the Draft Regulation.

#### 2.1.5 Unauthorised investigational medicinal products

The Draft allows the possibility of an investigational medicinal product which has not been authorised in a particular Member State, but which is authorised in another Member State, being used as the control medicinal product in the course of a clinical trial in the first-mentioned Member State. The use of an unauthorised control medicinal product can result in a significantly increased risk to the study subjects.

## **2.2 EU-wide harmonisation of the protection of clinical trial subjects (B)**

As already mentioned, the Regulation will become legally binding throughout the EU without the involvement of national parliaments. In contrast to Directive 2001/20/EC, it does not simply set out a minimum standard, but will bring about a desirable harmonisation. However, as a consequence, this means that currently applicable national standards providing a higher level of protection will be undermined.

## **2.3 The role of the Ethics Committee (C)**

### 2.3.1 Renunciation of the principle of separation between the pharmaceutical authorities and the Ethics Committee

An important innovation in the Draft Regulation is a renunciation of the compulsory separation between the pharmaceutical authorities and the Ethics Committee.

According to the Draft Regulation, it is up to the Member State whether an autonomous, independent Ethics Committee is required. However, the autonomy and independence of the Ethics Committees is a significant basic requirement for public trust in conducting clinical trials. Any actual or perceived connection between the Ethics Committee and the pharmaceutical authorities or industry can lead to a loss of trust among the public. The loss of an independent Ethics Committee can in fact lead to a reduction in the safety of clinical trial subjects. The assessment of the ethical aspects is no longer comprehensive, but is limited to “consent after proper information”. The EP Committee<sup>27</sup> on the Environment, Public Health and Food Safety has also commented that this is inadequate. Issues relating to the promotion of patient well-being, potential benefits and the autonomy of trial subjects as well as the avoidance or minimisation of potential harm are no longer evaluated.

### 2.3.2 The setting of deadlines and tacit approval

The different deadlines for clinical trials, low-intervention clinical trials and new therapies provided for in the Draft Regulation are, in principle, appropriate. However: even if an assessment by an Ethics Committee should be received within a limited time frame, some of the deadlines set by the Draft Regulation are too tight. It is impossible for an Ethics Committee to carry out its task responsibly and properly in every case within too short a time frame. The opinion pronounced by the EP Committee<sup>28</sup> on Industry, Research and Energy, that the time frame must be competitive, cannot be reconciled with the time required for the necessary level of diligence in ethical assessment.

<sup>27</sup> Committee on the Environment, Public Health and Food Safety, Amendment 107, Article 7 – paragraph 1 – subparagraph 1 – point a.

<sup>28</sup> “The timing between submission and decision must be competitive” (Opinion of the Committee on Industry, Research and Energy, Amendment 37, Article 14 – paragraph 3 – point a).



Although welcomed by the EP Committee on the Environment, Public Health and Food Safety, the aforementioned regulation on deadlines also has particular significance because tacit approval<sup>29</sup> is widely assumed once the deadline for approval has expired. This entails significant endangerment of trial subjects. It must also be mentioned that competitiveness<sup>30</sup> and incentive mechanisms<sup>31</sup> have no role to play in connection with ethical assessments.

### 2.3.3 National language

Informative documents and the documents for acquiring consent from study subjects can be provided in a language other than the national language. However, the information provided and the consent forms must be thoroughly checked from a language point of view by the responsible Ethics Committee in order to ensure that all study subjects or those responsible for them are able to understand them. This cannot be achieved if the documents mentioned are not provided in the national language.

### 2.3.4 Division of the assessment report

The proposal includes a division of the assessment report. This division makes the comprehensive ethical assessment of the whole application more difficult, since there is no compulsory requirement that the assessment of part I be provided for the ethical assessment of part II.

## 2.4 The procedure for arriving at consensus across the EU states (D)

Additional points of criticism relate to the division of labour and the procedure for arriving at consensus between the reporting country and other Member States affected.

### 2.4.1 Points of criticism relating to the division of labour

The assessment of tenability for all participating countries is carried out by the responsible authority in the reporting Member State alone, whereas the influence exerted by the other states is largely limited to the assessment of the information provided and the local trial venues. The other Member States are almost completely excluded from the ethical assessment of the clinical trial of medicinal products. The non-reporting Member States are further bound by the assessment of the reporting Member State. The fact that this leads to mutual recognition of medical ethical standards throughout the EU is to be welcomed. However, the Draft Regulation does not contain common high standards, comprehensive procedures for arriving at consensus or national rights of withdrawal.

### 2.4.2 Points of criticism relating to the procedure for arriving at consensus

The procedure for arriving at consensus between EU Member States proposed in the Draft Regulation to date does not take adequate account of the possibilities presented by modern communication technologies.

## 2.5 Miscellaneous (E)

### 2.5.1 Ensuring funding

The necessity for the sponsor to provide funding has been dropped. This meets the demands of clinical testers from the field of academia. However, the safety of the trial subjects and the success of the study may be endangered without adequate financing throughout the trial.

<sup>29</sup> “The concept of tacit authorisation should apply automatically” (Committee on the Environment, Public Health and Food Safety, Amendment 7, Recital 8).

<sup>30</sup> “The timing between submission and decision must be competitive” (Opinion of the Committee on Industry, Research and Energy, Amendment 37, Article 14 – paragraph 3 – point a).

<sup>31</sup> “The concept of tacit approval will provide a real incentive for those authorising trials to do so on time” (Committee on the Environment, Public Health and Food Safety, Explanatory statement, Approval times).

### 2.5.2 The problems of cross-border studies

For cross-border studies, a reporting Member State with lower standards could be selected in order to avoid having to meet more stringent standards.

### 2.5.3 Factually flawed formulations

In describing the anticipated gain from the study, the regulation proposal used some incorrect terms, as demonstrated, above all, by the inappropriate term benefits. Scientifically correct terms such as potential or possible benefits are frequently not used, which renders the content of the Regulation incorrect.

### 2.5.4 Lack of differentiation between healthy study subjects and patients

The Draft Regulation does not differentiate between a healthy volunteer<sup>32</sup> and a patient, although this distinction is of fundamental importance to ethical assessment.

### 2.5.5 Provision for representation in lieu of the sponsor being established in the EU

Article 70 of the Draft Regulation only requires the sponsor to have a “contact person” in the EU; it is no longer a requirement that the sponsor be established in the EU.<sup>33</sup> This is untenable, since a contact person cannot reliably ensure in every case that urgent safety measures required by the authorities will be implemented immediately.

### 2.5.6 Limitation of the guarantee of the right of access to legal redress

As a result of the approval procedure, for which the (at times foreign) reporting state is responsible, legal action in the case of

misconduct or negligence must be taken against the Member State or its authorities (insofar as this is permissible under the law of the Member State) This significantly restricts the guarantee of the right of access to legal redress and its application for German citizens.<sup>34</sup>

### 2.5.7 A problematic recommendation in the EU report

#### *Abandonment of the requirement to obtain consent*

In the European Parliamentary Report dated 7.6.2013, some new recommendations were adopted which are in part problematic. Particularly worthy of mention is Amendment 167 for a new Article 29 para. 3a, which, for particular constellations, seeks to abandon the requirement to obtain consent and to replace it with a mere right to object to participating. This provision is in clear contravention of customary principles.

<sup>32</sup> Preferred for Phase I studies.

<sup>33</sup> “Where the sponsor of a clinical trial is not established in the Union, that sponsor shall ensure that a contact person is established in the Union“ In principle, this means that a “post office box” within the EU is sufficient.

<sup>34</sup> The chances of success for a citizen of a particular state instigating legal action abroad are significantly reduced by, among other things, being confronted with a foreign language, a foreign legal system and a foreign venue.

### 3 Recommendations – core pronouncements

#### 3.1 Protection of clinical trial subjects (A)

##### 3.1.1 The protection of particularly vulnerable clinical trial subjects

The autonomy and well-being of particularly vulnerable subjects, as well as any therapeutic benefits for them, require strict protection. Where there are no potential benefits to the individual, particularly vulnerable patients should be included in clinical trials with potential group benefits only where this does not entail more than minimal risk or minimal burden for them. Clinical trials in emergency situations should be allowed only where there are direct benefits to the individual patient.

##### 3.1.1.1 Protection for minors and incapacitated adults

Incapacitated patients should be included in clinical trials offering only potential group benefits provided that the risks and burdens to them are minimal. This would place children and incapacitated adults on an equal footing in Germany, in contrast to the former legal situation. Research which offers potential group benefits alone should not be permitted for healthy minors.

##### 3.1.1.2 Need for a subsidiarity provision

The provisions for particularly vulnerable study subjects should be based entirely on a subsidiarity principle.

##### 3.1.1.3 Easier approval for clinical studies on rare diseases

Clinical trials for patients with rare diseases or with multiple illnesses where there are very small groups of patients, or those suffering from dementia where the effectiveness can only be measured against difficult-to-define parameters of efficacy, should be facilitated.

##### 3.1.2 Group benefits and the benefits to others of research on vulnerable patients

##### 3.1.2.1 Appropriate level of protection for vulnerable patients

Without research being undertaken on healthy and sick trial subjects where there is only a potential benefit for the group or for others, important medical insights could not be gained. From the ethical point of view, such trials of medicinal products are not unproblematic, since they cannot be compensated for by a medical personal interest on the part of the trial subject. In contrast to the statement issued by the EU Parliamentary Committee on the Environment, Public Health and Food Safety, they can, however, be legitimated on the basis of a minimal, solidarity-based obligation to tolerate, enhanced by prior consent, given for minors and incapacitated adults by their legal representative, which is linked to the well-being of the affected party.<sup>35</sup> The strict criteria of the EU Regulation must be the legal basis.

If, however, there is no potential benefit to the individual for particularly vulnerable groups of trial subjects (minors, incapacitated adults, patients in emergency situations), inclusion in research which offers potential group benefits alone can be justified only if there is only minimal risk or minimal burden.<sup>36</sup> Consequently, where there are no potential benefits to the individual, for particularly vulnerable patients, minimal risk or a minimal burden should be stipulated as the threshold (absolute requirement of the minimum). This, of course, results in

<sup>35</sup> In the case of minors and incapacitated adults, this applies only for research which offers potential group benefits only.

<sup>36</sup> This differs somewhat from the statement by the Committee on the Internal Market and Consumer Protection: "For example, in cases where the research needs to start without delay and there is reason to expect that the potential benefit to the subject of taking part in the clinical trial outweighs the risks or the subject's participation entails only a minimal risk, it should be possible for the clinical trial to begin without his or her prior consent" (Opinion of the Committee on the Internal Market and Consumer Protection, Amendment 17, Recital 23).

a reduction in the autonomy of the legal representatives of incapacitated adults and of children (namely their right to give consent even when there is a high level of risk or burden). However, in the case of a conflict between autonomy and well-being, where there is only a potential group benefit, the well-being of the charge must take precedence over the autonomy of the legal representative.

This further means that admission to clinical trials of medicinal products for which there are only potential group benefits is also to be recommended for permanently incapacitated adults. As far as minors are concerned, their participation should be limited to studies where the risks and burdens are minimal, i.e. very minor and temporary impairment of the health and well-being (absolute requirement of the minimum).<sup>37</sup> This would place children and incapacitated adults on an equal footing in Germany, in contrast to the former legal situation. This equality is to be welcomed, since there is no ethical justification for treating incapacitated adults differently from children to be found anywhere in the EU.

Research which offers no more than potential group benefits should not be permitted for healthy minors.

What should, however, be preserved is the principle underlying the Draft Regulation that a clinical study with subjects capable of giving consent should be possible even where there are no potential benefits to the individuals, only the group or other people, and that this should not be limited by the requirement of minimal risk, but rather by proportion-

al risk<sup>38</sup> (relative requirement of minimisation).

### 3.1.3 Legislative stipulations on providing information

The provision of proper information may be undertaken not only by a doctor or dentist, but also by a comparably qualified and certified (from a legal standpoint) medical expert. The level of protection for trial subjects should not be reduced thereby.

### 3.1.4 Regulations regarding consent

#### 3.1.4.1 *Exceptional provisions for studies in emergency situations*

In the case of clinical trials in which the majority of subjects are incapacitated adults, or for cases involving minors in emergency situations, it can be assumed that consent would be forthcoming from the affected party or their legal representative provided there is no indication of them having previously expressed objections. Moreover, there must be a potential individual benefit to the patient. Furthermore, there should be no more than a minimal perceptible additional risk and a minimal additional burden to the patient.

#### 3.1.4.2 *Taking account of the autonomy of minors and incapacitated adults*

If a minor or an incapacitated person is in a position to evaluate the information provided and does not consent to participating in a clinical trial, they must be excluded from the clinical trial.

Permanently incapacitated adults must under no circumstances be included in any study without prior informed con-

<sup>37</sup> In Art. 30 h the Draft Regulation stipulates a requirement of no risk for participation in studies where the potential benefits are limited to the group. This should be replaced with the protective stipulation "minimal risk / minimal burden".

<sup>38</sup> Directive 2001/20/EC and the AMG do not provide for a general limitation of studies / investigations where the potential benefits are limited to the group or other people only based on minimal risk or burden, nor do they do so for patients (compare Section 41 para. 1 No. 2 of the AMG for studies involving adults where the potential benefits are for the group). Compare also Section 6 para. 2 of the Protocol to the Convention on Bioethics: Here the issue of a lack of direct benefit is explicitly addressed, but the threshold is set not as minimal, but rather acceptable risk.

sent being given by their legal representative after receiving proper information.

### 3.1.5 Unauthorised investigational medicinal products

The use of a medicinal product which is not authorised in a particular Member State as a control product should be explicitly forbidden.<sup>39</sup>

### 3.2 EU-wide harmonisation of the protection of clinical trial subjects (B)

It is recommended that strict requirements for research on human subjects be formulated within the regulation itself in order to ensure a consistently high level of protection throughout the EU.

### 3.3 The role of the Ethics Committee (C)

The existing regulations regarding assessment by an independent Ethics Committee must be retained in principle and drawn together in a dedicated article. In every affected Member State, an autonomous, independent and certified Ethics Committee with a legal basis should be fully involved.

Approving authorities and Ethics Committees should be given sufficient time to carry out careful evaluation and assessment.

Written information and the consent obtained should, without exception, be provided for the relevant Ethics Committee in its own national or regional language.

The results of Part I of the report should be assessed along with Part II of the application by the relevant independ-

ent Ethics Committee.<sup>40</sup> In every affected Member State, the comprehensive ethical review should be limited to just one senior Ethics Committee. It should be expressly permitted for an ethical discussion to be held between the Ethics Committees from the non-reporting Member States and that of the reporting Member State.

### 3.4 The procedure for arriving at consensus across the EU states (D)

The right of consultation in the final ethical and scientific assessment is necessary in all Member States involved.

The procedure for arriving at consensus should explicitly allow the use of electronic media and permit queries made by means of these media.

Any comments received by the reporting Member State should be included in the report. Variations in the decision must be justified by the reporting Member State. In the event that the independent Ethics Committee of a Member State determines that the balance of benefits to risks is untenable, the Member State in question should have the opportunity to refuse to authorise the part of the clinical trial that was to take place on its territory.

### 3.5 Miscellaneous (E)

#### 3.5.1 Ensuring funding

The abandonment of the requirement that sponsors provide funding is to be welcomed as this promotes opportunities for long-term non-commercial studies. However, the sponsor must be obliged to provide full details of how the study is to be financed, including the after-care of the subjects.

<sup>39</sup> In the case of a medicinal product which is not authorised for this particular indication only, the ban shall not apply.

<sup>40</sup> Part II of the approval dossier (patient information, suitability of the trial site, etc.) can be drawn up only if the assessment of Part I has been provided. Without the approved testing plan, the content of the patient information cannot be formulated in a binding manner or evaluated. The same applies for the assessment of the suitability of the testers and the trial site.

### 3.5.2 Clarification of the problem of cross-border studies

In order to reduce the possibility of avoiding higher standards by selecting a reporting Member State with lower standards, the Member State with the highest number of participants should be the reporting Member State.

### 3.5.3 The use of factually correct formulations

Where factually appropriate, the term benefits should be replaced with the term potential benefits.

## V. Statement (Full version)

*Preliminary Remarks: In the following full version of this response, the reader will find a description, complete with comments, of the current situation, the proposal by the European Parliament and Council and the recommendations including justifications and sources.*

### 1 Current situation

In addition to the EU Directive 2001/20/EC, clinical trials of medicinal products on human subjects in Germany are regulated by the German Medicinal Products Act (AMG) and the physicians' professional code.<sup>41</sup> The bases for these regulations are the Declaration of Helsinki<sup>42</sup> of the World Medical Association and the guidelines for "Good Clinical Practice" (GCP).<sup>43</sup> Similar guidelines can be found in the "International Ethical Guidelines" of the CIOMS<sup>44</sup> in collaboration with the World Health Organisation (WHO).

At the international level, regulations on clinical trials of medical products for human use can also be found in the Oviedo Convention (Bio-ethics Convention)<sup>45</sup> as well as in the Additional Protocol to the Convention on Human Rights and Biomedicine concerning medical re-

search.<sup>46</sup> However, the Federal Republic of Germany has neither signed nor ratified the Oviedo Convention or the Additional Protocol. Nonetheless, the Convention has been ratified by 29 Member States of the European Council, including some EU Member States.<sup>47</sup> The Additional Protocol has also been ratified by a few EU states.

The principle established in Directive 2001/20/EC stipulates that in a clinical trial, "the foreseeable risks and burdens" are to be weighed "against the anticipated benefit for the individual trial subject and for other present and future patients." Minors and incapacitated persons are to be given special protection. Furthermore, the assessment and vote by an independent Ethics Committee, as important elements in this, are indispensable prerequisites for conducting a clinical trial of medicinal products.

In order to protect the rights, well-being and safety of clinical trial subjects, the Directive introduced changes to the requirements for approval for conducting a clinical study, among other things.<sup>48</sup> However, since the Directive was not applied uniformly across the individual EU Member States, risks to participants

41 State Chambers of Physicians in Germany: Professional Code of Conduct for doctors practising in Germany.

42 World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (available online at: <http://wma.net/en/30publications/10policies/b3/17c.pdf>).

43 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (available online at: <http://ichgcp.net/pdf/ich-gcp-en.pdf>).

44 Council for International Organizations of Medical Sciences (CIOMS): International Ethical Guidelines for Biomedical Research Involving Human Subjects (available online at: [http://www.cioms.ch/images/stories/CIOMS/guidelines/guidelines\\_nov\\_2002\\_blurb.htm](http://www.cioms.ch/images/stories/CIOMS/guidelines/guidelines_nov_2002_blurb.htm)).

45 Convention of the European Council of 4<sup>th</sup> April 1997 for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (Oviedo Convention), also: Bioethics Convention or Biomedicine convention (available online at: <http://conventions.coe.int/Treaty/EN/Treaties/Html/164.htm>).

46 Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (dated 25.05.2005; ratified by eight states including four EU states) (available online at: <http://conventions.coe.int/Treaty/EN/Treaties/Html/195.htm>).

47 The failure to sign the convention by the Federal Republic of Germany is principally due to the fact, not least for historical reasons, that the Federal Republic of Germany wishes to see incapacitated persons included in clinical studies only within very strict limits.

48 This, in combination with the previously mentioned increased expense, has contributed to an improvement in the safety and quality of clinical trials. In Germany, there have been no further serious incidents within the framework of AMG studies.

in clinical trials of medicinal products could have arisen as a result of nationally varying provisions for trials.<sup>49</sup>

It was further criticised that both the altered requirements for approval<sup>50</sup> and the differing regulations across the Member States have resulted in clinical trials involving greater expense.<sup>51</sup>

Another point of criticism is that Directive 2001/20/EC made clinical trials with already approved medicinal products<sup>52</sup> subject to the same elaborate regulatory provisions as clinical studies intended to gain authorisation for unauthorised products.<sup>53</sup> Clinical trials with previously authorised medicinal products can also be what are known as “low-intervention clinical trials”. They serve to improve existing therapies with medicinal products. By definition, they entail no or only a very small additional risk or no or only a very small additional burden for the safety of the patients who are to be treat-

ed. By thus treating them equally from the administrative point of view, Directive 2001/20/EC made it more difficult to carry out clinical trials with approved medicinal products.<sup>54</sup>

The procedure for arriving at consensus from the various Ethics Committees in multi-centre clinical trials has also been criticised, although only in Germany.<sup>55</sup>

Finally, the stimulation of the development of new medicinal products and the improvement of existing therapies should also apply for rare diseases, persons suffering from multiple illnesses and those suffering from dementia. It is thus justifiable that the proposed amendments to the Draft Regulation put forward by the EP Committees take account of the peculiarities of rare diseases<sup>56</sup> and those suffering from multiple illnesses, each with low levels of incidence or, for example, of de-

49 Klinkhammer, G.: Working Group of the Medical Ethics Committee Flickwerk in Europa. Deutsches Ärzteblatt 2010; 107(27): A-1340 / B-1184 / C-1164.

50 Compare Explanatory Memorandum 1 of the Draft Regulation Background to the proposal.

51 In Germany, the number of clinical AMG trials in previous years has hardly fallen (compare BfArM data at: [http://www.bfarm.de/DE/Arzneimittel/1\\_vorDerZul/klinPr/klin\\_prf\\_genehm/Statistik.html?nn=1015162](http://www.bfarm.de/DE/Arzneimittel/1_vorDerZul/klinPr/klin_prf_genehm/Statistik.html?nn=1015162)). Further, the fact that there has been a qualitative change in medical product trials can easily be overlooked. Thus cross-phase studies (Phase 1/2) are conducted as a single trial, and, likewise, short-term and long-term studies planned as a single study. This indicates that the EU Directive has not hindered clinical trials in every case, but rather that regional implementation has largely contributed to the problem.

52 According to Art.1 para. 1 sentence 1 of the Directive, however, non-interventional trials are excluded from the scope of the Directive. The Draft Regulation likewise explicitly excludes non-interventional studies from its scope of application. Compare Explanatory Memorandum Chapter 3 Legal Aspects of the Proposal, 3.1 scope: “For ‘non-interventional studies’ which are postauthorisation safety studies initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to obligations imposed by the competent authority for marketing authorisations, the rules are set out in Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.”

53 Compare also the response by the German Society for Haematology and Oncology to the Draft Regulation dated 27.09.2012 (available online at: <http://www.dgho.de/informationen/presse/pressemitteilungen/onkologen-begrueßen-die-geplante-eu-verordnung-zu-klinischen-studien>).

54 Overall, the increase in difficulty for large, medium-sized and small manufacturers, as for hospitals and universities, along with other factors, has contributed to the fact that the costs have risen. The increased costs cannot always be met by small and medium-sized enterprises (SMEs), nor by universities and hospitals. For the other factors compare the working group of the medical Ethics Committees: “False premises by the European Union”. In: Statement to the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC. 21.8.2012 (available online at <http://www.ak-med-ethik-komm.de/documents/StellungnahmeEU-VerordnungklinischePruefungen.pdf>).

55 German society for Haematology and Oncology: Oncologists welcome the planned EU Regulation on clinical studies, Press release, Berlin 27.09.2012 (available online at: <http://www.dgho.de/informationen/presse/pressemitteilungen/onkologen-begrueßen-die-geplante-eu-verordnung-zu-klinischen-studien>). This shows that in practice it can become very costly if, in addition to the comprehensive assessment by a first Ethics Committee, further comprehensive assessments are undertaken by consecutive Ethics Committees and these latter do not confine themselves only to the suitability of the testers and the trial sites within their area. Even if in Germany the senior Ethics Committee for the particular case apparently without exception consults with the other Ethics Committees, the time and bureaucracy involved can exceed what is possible for a university or hospital.

56 “Clinical trial applications shall be prioritised by Member States to improve, where possible, the defined timelines when the clinical trial is related to a condition that is a rare or ultra-rare disease, as defined in the third indent of point (a) (i) of Article 6(1), and, as such, is subject to significant administrative burden due to the extremely small patient populations” (Committee on the Environment, Public Health and Food Safety, Amendment 127, Article 11a (new)).



mentia<sup>57</sup> where the parameters of efficacy are difficult to measure, in order to facilitate clinical trials for those affected.

## 2 European Commission proposal

As welcome as the proposal and its intention are, implementation in its unamended form would lead to undesired consequences, particularly in the form of a serious reduction in protection for patients. This is reflected in the critical statements made by the working group of the German Medical Ethics Committee,<sup>58</sup> the German Medical Association<sup>59</sup> and in the cross-party resolution of the German Bundestag<sup>60</sup> and the comparable resolution of the German Bundesrat,<sup>61</sup> as well as the report by the EP Committee on the Environment, Public Health and Food Safety.<sup>62</sup> To this are added recommended amendments from other EP Committees.

The following joint ad hoc report critically examines the European Commission's proposal and the amendments recommended by the EP Committees,

particularly with regard to the areas (A) Protection of clinical trial subjects, (B) Europe-wide harmonisation, (C) the role of the Ethics Committee and (D) the procedure for arriving at consensus across the EU states, and formulates recommendations in response to these. In this it also deals with points of criticism raised by the institutions mentioned above.

### 2.1 Protection of clinical trial subjects (A)

#### 2.1.1 The reduced protection of particularly vulnerable clinical trial subjects

In contrast to Directive 2001/20/EC, the Draft Regulation will not merely define a minimum standard, but provide an absolute regulation (full harmonisation). As a consequence, this means that more extensive national protective regulations of a higher standard, particularly with respect to more vulnerable groups – such as the Medicinal Products Act in Germany – would no longer apply.

##### 2.1.1.1 A restriction of protection for minors and incapacitated persons

Protection for minors and incapacitated persons would be reduced compared to current applicable law. For all study subjects, and, therefore, also for these particularly vulnerable participating groups of minors and incapacitated persons, the minimum level of acceptable risk – except in emergency situations<sup>63</sup> – is “as low as possible”.<sup>64</sup> This, in principle, includes the possibility of higher risks, since this (except in the aforementioned emergencies)

57 “In order to improve treatments available for vulnerable groups such as frail or older people, people suffering from multiple chronic conditions, and people affected by mental health disorders, medicinal products which are likely to be of significant clinical value should be fully and appropriately studied for their effects in these specific groups, including requirements related to the groups' specific characteristics and the protection of their health and well-being” (Committee on the Environment, Public Health and Food Safety, Amendment 18, Recital 10a (new)).

58 Statement to the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC. 21 August 2012 Working party of the German Medical Ethics Committees. 21 August 2012 (available online at: [http://www.ak-med-ethik-komm.de/documents/StellungnahmeEU\\_VerordnungsklinischePruefungen.pdf](http://www.ak-med-ethik-komm.de/documents/StellungnahmeEU_VerordnungsklinischePruefungen.pdf)).

59 Statement of the German Medical Association to the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC. (KOM (2012) 369), Berlin 27.8.2012 (available online at: [http://www.bundesaeztekammer.de/downloads/STN\\_BAeK\\_EU-VO-Vorschlag\\_KOM\\_2012\\_369\\_27082012.pdf](http://www.bundesaeztekammer.de/downloads/STN_BAeK_EU-VO-Vorschlag_KOM_2012_369_27082012.pdf)).

60 Bundestags-Drucksache (Parliamentary publication) 17/12183.

61 Bundestags-Drucksache (Parliamentary publication) 413/12.

62 Available online at <http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//NONSGML+REPORT+A7-2013-0208+0+DOC+PDF>.

63 Art. 32 para. 1 point e of the Draft Regulation: “minimal risk and minimal burden”.

64 Art. 30 para. 1 point g of the Draft Regulation (Incapacitated subjects) is identical to Art. 31 Para. 1 point g of the Draft Regulation (Minors): “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.” In the English version, however, the Draft Regulation also stipulates compliance with the minimal requirement (Article 32 para. 1 point e of the Draft Regulation: “poses a minimal risk, and imposes a minimal burden on”). Taking into account the fact that all official languages of the EU are legally binding, such fundamental deviations can lead to varying standards in the interpretation within Member States.

could constitute the lowest possible level of risk stipulated in the Draft Regulation. The Helsinki Declaration and the Oviedo Convention, by contrast, stipulate “minimal risk” and “minimal burden”<sup>65</sup> as the strict requirement<sup>66</sup> for risk to minors. For the group of minors, the German Medicinal Products Act further differentiates between healthy and sick minors and applies different levels of protection.<sup>67</sup> In this, the aforementioned strict requirements with respect to risk apply only for patients below the age of consent within the framework of research offering only potential group benefits, whereby the potential group benefits must apply to the group of patients suffering from the same disease as the subject.<sup>68</sup> Another problematic issue is the fact that the definition of incapacitated persons is not consistent across the EU states.<sup>69</sup>

#### 2.1.1.2 Lack of a subsidiarity provision

In the interest of providing particular protection for patients in emergency situations, a subsidiarity provision is needed. Only a subsidiarity provision would ex-

clude the possibility of studies on emergency patients still being undertaken when studies in a non-emergency situation would suffice to achieve the objectives of the study. Studies to validate the data could also be undertaken, even if they were not strictly necessary.

#### 2.1.1.3 The issue of the approval of clinical studies for rare diseases

As already mentioned by the EP Committees on Industry, Research and Energy, on Civil Liberties, Justice and Home Affairs and on the Environment, Public Health and Food Safety, there is no specific provision for the peculiarities of clinical studies with low prevalence for patients with rare diseases<sup>70</sup> or with multiple illnesses where there are very small groups of patients, or those suffering from dementia<sup>71</sup> where

65 To be achieved in a phase I study, for example, through a careful increase to find the correct dosage. The Oviedo Convention demands, in Article 6 paragraph 1, that there be a direct benefit to persons not capable of giving informed consent, or in Article 17 paragraph 2 No. 1, that there be group benefits (grouped by age or disease) combined with minimal risk or burden according to Art. 12 para. 2 No. ii.

66 The material level of protection afforded to minors by Art. 32 is reduced as a result of the requirement for minimal burden being reduced from an absolute to a relative requirement (minimisation rather than minimal).

67 Compare Section 40 para. 4 AMG (health minors); Section 41 para. 2 AMG (patients below the age of consent); compare also Kügel/Müller/Hofmann, AMG | AMG Section 40 Recital. 98 with citations.

68 At present, medical product research offering only potential group benefits may be undertaken on minors in Germany, but only if the threshold of “minimal risks and burdens” is not surpassed. As the Regulation would lead to harmonisation, nationally applicable, more extensive, protective measures, such as the Bioethics Convention in some EU states or the Medicinal Products Act in Germany, would no longer apply.

69 As this definition relates solely to legal incapacity, it excludes other forms of incapacity covered by national legislation to which specific consent rules apply. French law, for example, draws a distinction between persons lacking legal capacity (e.g. persons placed under statutory guardianship or supervision, and minors) and persons who are de facto incapable of giving informed consent (as a result of cognitive impairment). Different provisions apply to these two types of incapacity (Opinion of the Committee on the Internal Market and Consumer Protection, Amendment 36, Article 2 – paragraph 2 – point 17).

70 “Whereas most clinical trials are implemented for the assessment of therapies consisting of large samples of patient populations, this Regulation should not discriminate against patients suffering from rare and ultra-rare diseases and should integrate the specificities of low-prevalence conditions when assessing a trial” (Opinion of the Committee on Industry, Research and Energy, Amendment 8, Recital 22 a (new)).

“Many rare and ultra-rare diseases are not yet correctly identified or remain partially understood. In clinical trials associating patients affected by such conditions, the knowledge of these illnesses may be significantly improved by the resulting assessment of data. The reporting Member State must have knowledge of this added value” (Opinion of the Committee on Civil Liberties, Justice and Home Affairs, Amendment 63, Annex 1 – part 2 – point 6 – point 6 a (new)). And the prevalence of the condition, especially for rare diseases (defined as severe, debilitating and often life-threatening diseases which affect no more than five persons per 10 000), and ultra-rare diseases (defined as severe, debilitating and often life-threatening diseases which meet a prevalence threshold of no more than one affected person per 50 000) (Committee on the Environment, Public Health and Food Safety, Amendment 92, Article 6 – paragraph 1 – point a – point i – indent 3). “Clinical trial applications shall be prioritised by Member States to improve, where possible, the defined timelines when the clinical trial is related to a condition that is a rare or ultra-rare disease, as defined in the third indent of point (a) (i) of Article 6(1), and, as such, is subject to significant administrative burden due to the extremely small patient populations” (Committee on the Environment, Public Health and Food Safety, Amendment 127, Article 11a (new)).

71 “In order to improve treatments available for vulnerable groups such as frail or older people, people suffering from multiple chronic conditions, and people affected by mental health disorders, medicinal products which are likely to be of significant clinical value should be fully and appropriately studied for their effects in these specific groups, including requirements related to their specific characteristics and the protection of their health and well-being” (Committee on the Environment, Public Health and Food Safety, Amendment 18, Recital 10a (new)).

the effectiveness can be measured only against difficult-to-define parameters of efficacy. This can result in studies for these patients being rejected on the basis of insufficiently high rates of incidence, or on the basis of difficult ex ante assessment of the efficacy parameters.

#### *2.1.1.4 Risks arising from the differentiation between different types of study*

The clear differentiation reflecting the level of risk between the different types of trial, “clinical trials”, “low-intervention clinical trials” and “non-interventional trials” should also be helpful, even if the proposed amendments from the ranks of the European Parliaments recommend a non-specific and therefore less-clear division based on the level of risk of the intervention rather than by the type of study.<sup>72</sup>

The distinction between “clinical trials”, “low-intervention clinical trials” and “non-interventional studies” provided for in the Draft Regulation should be retained. In contrast to the proposal by the EP Committees on the Environment,

Public Health and Food Safety and on the Internal Market and Consumer Protection, this distinction creates a clear demarcation in each case, which is not the case in the committees’ proposal. This could lead to the welcome further streamlining of the administrative procedures and a further reduction in the time allotted for the assessment and approval of the studies for low-intervention clinical trials being dropped due to insufficient clarity of distinction. In contrast to the Draft Regulation, non-interventional studies could be included in the regulation.

#### *2.1.2 Group benefits and the benefits to others of research on vulnerable patients*

##### *2.1.2.1 Deterioration of the level of protection for vulnerable patients*

##### *Undesirable research on healthy children*

Unlike the German Medicinal Products Act, the Draft Regulation permits the principle of research with group benefits without restriction. In Germany, the applicable legislation for medicinal products permits medical product research offering only potential group benefits on minors only if particular criteria are met; in particular, the threshold of “minimal risks and burdens” may not be surpassed.<sup>73</sup> Research offering potential group benefits alone are necessary in paediatrics, for instance in order to ascertain normal values or to determine correct dosages.

On the one hand, the Draft Regulation, unlike the Medicinal Products Act, does not differentiate between healthy and sick patients below the age of consent. On the other hand, it can be interpreted as meaning that in the case of research offering only potential group benefits, the group can be either the group of patients suffering from the same disease or the age

<sup>72</sup> “Given that low-intervention-risk clinical trials have only a very limited and temporary adverse effect – if any – on the subject’s health, ...” (Committee on the Environment, Public Health and Food Safety, Amendment 9, Recital 9).

“It is preferable to define the second category of research in terms of the level of risk to the subject rather than the type of intervention. This is in line with the main aim of the proposal for a regulation, namely to develop a risk-based approach. The provisions of the regulation should also be brought into line with those of the Oviedo Convention, ratified by a number of EU Member States, Article 17 of which establishes the concept of ‘minimal risk’” (Committee on the Environment, Public Health and Food Safety, Amendment 58, Article 2 – paragraph 2 – point 3 – introductory part). ‘minimal-risk clinical trials’ (Opinion of the Committee on the Internal Market and Consumer Protection, Amendment 3, Recital 9) pose only a low risk (Opinion of the Committee on the Internal Market and Consumer Protection, Amendment 6, Recital 11) (The amendment seeking to replace the term ‘low-intervention clinical trial’ with the term ‘minimal-risk clinical trial’ applies to the whole text. If it is adopted, changes will have to be made throughout.) It would be better to define the second category of research by the level of risk incurred by the subject rather than the type of intervention. This reflects the main objective of the draft regulation, which is to establish a risk-based approach. Furthermore, the regulation should be brought into line with the provisions of the Oviedo Convention. Article 17 of that convention, which has been ratified by several Member States, contains a definition of the term ‘minimal risk’ (Opinion of the Committee on the Internal Market and Consumer Protection, Amendment 29, Article 2 – paragraph 2 – point 3 – introductory part).

<sup>73</sup> For this and other requirements, compare Section 41 para. 2 No. 2 AMG.

group.<sup>74</sup> Since the Draft Regulation permits the principle of research offering only group benefits without limitation, this also applies for healthy minors.<sup>75</sup> The level of protection for minors would be reduced.

#### *Clinical studies in emergency situations*

Irrespective of the presence of potential benefits to the individual, Article 32 of the Draft Regulation permits the carrying out of clinical studies in emergency situations. As a consequence, this means that clinical medical product trials in emergency situations, sometimes offering only potential group benefits or potential benefits to others, can be carried out. This is ethically problematic, since in emergencies the ability to express consent or opposition to (continued) participation in a clinical trial may be absent and the legal representative not available. Consequently, in this situation a decision by proxy must be made by the doctors. They can base this only on the well-being and presumed wishes of the patient. If there is no direct individual benefit available, the willingness of the patient to (continue to) participate in the clinical study cannot be assumed. This is why the German Medicinal Products Act rightly demands that there be a direct benefit to the patient in this case.<sup>76</sup>

#### *The inclusion of incapacitated adults*

In Article 30, the Draft Regulation permits – in contrast to the current legal situation in Germany<sup>77</sup> – provided that certain

provisions have been met, the inclusion of incapacitated adults in studies where the only benefit is to the group.<sup>78</sup> This regulation is to be welcomed, since research which offers potential group benefits only on incapacitated adults seems reasonable in research into dementia, for example. However, this applies only if the criteria for “minimal risk and minimal burden” are met, and not if the level of risk is defined to be as low as possible, as in the text of the Draft Regulation.

#### 2.1.3 Lack of legislative stipulations on providing information

In a departure from German law, the draft permits the provision of information to trial subjects to be undertaken by a person who is not a qualified doctor.<sup>79</sup> The requirement for this to be undertaken by a doctor only is a particular feature of German law; the Draft Regulation, by contrast, follows Directive 2001/20/EC and the relevant international rules which do not place limitations on the person who provides the information. Unless there is a legislative stipulation of the prerequisites which a person who is not a doctor must meet in order to undertake this task, this, however, raises the question of how proper and effective information can be given about the risks, the burdens and any potential benefits if the person providing the information does not have the expert training and experience necessary for this task.

74 Art. 32 para. 1 point f of the Draft Regulation states: “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.”

75 This deviates from Section 40 para. 4 of the AMG, which stipulates a “personal indication”.

76 German law permits adults who are fundamentally capable of giving informed consent to participate in studies, even if it is not possible to obtain their consent because of a concrete emergency situation (Section 41 paragraph 1 sentence 2 AMG). In this case, the study must promise direct potential benefits to the individual.

77 In contrast to the previous legal situation in Germany, this would place children and incapacitated adults on an equal footing: The AMG in fact precludes studies which offer only potential group benefits for permanently incapacitated persons. This equality is definitely to be welcomed, since there is no ethical justification for treating incapacitated adults differently from children to be found anywhere in the EU.

78 Ultimately, Art. 30 point h contains two versions: In principle, it renounces the principle of direct individual benefits for incapacitated adults. In the event, however, that the study does not pose any risk to health, it incorporates the right to waive the requirement for direct potential benefits to the individual, with potential benefits to others accepted as sufficient justification, which, according to Art. 30 point f, must be potential group benefits.

79 Art. 28 para. 1 point d of the Draft Regulation; according to Section 40 para. 2 AMG, the relevant information must be provided by a doctor or, in the event of a dental trial, by a dentist.

#### 2.1.4 Statements regarding consent

##### 2.1.4.1 *Exceptional provisions for studies in emergency situations*

The special regulations for the conduct of clinical trials in emergency situations in Article 32 of the Draft Regulation reasonably allow for a general exemption from the requirement for obtaining prior consent, which the AMG has until now explicitly accorded only for patients capable of giving consent.

In the interests of providing particular protection for patients in emergency situations, as previously mentioned, a subsidiarity provision is needed. It is true that Article 32 para. 1 point d of the Draft Regulation stipulates that the applicable research must relate directly to the medical condition which renders obtaining prior consent and providing prior information impossible.<sup>80</sup> However, only a subsidiarity provision would exclude the possibility of clinical studies on emergency patients still being undertaken when studies with those capable of giving informed consent in a non-emergency situation would suffice to achieve the objectives of the study.

In emergency situations it is possible that incapacitated persons can be included in clinical trials of medicinal products without giving consent after prior information if this does not entail more than minimal risk or a minimal burden.<sup>81</sup> In the case of incapacitated adults, this must, according to the Draft Regulation, be linked to a direct potential benefit to the individual,<sup>82</sup> whereas

for minors a direct potential group benefit suffices.<sup>83</sup> There is no ethical justification for this contradictory regulation, namely treating incapacitated adults differently from minors throughout the EU.

Under the conditions named above it would appear that a clinical trial of medicinal products on incapacitated persons including minors is permissible without the prior explicit consent<sup>84</sup> of the affected party or their legal representative and without consent being obtained after prior information. The protection of patients in emergency situations is, in fact, limited to the right to object.<sup>85</sup> Article 32 of the Draft Regulation does not only dispense with a need for prior information, but also with de facto consent.

##### 2.1.4.2 *Disregarding the autonomy of minors and incapacitated adults*

The autonomy of minors, incapacitated persons and patients in an emergency situation is accorded too little importance in the current formulation of the Draft Regulation. Thus the Draft Regulation states that the explicit wish of the affected minor will be taken into consideration<sup>86</sup> and that of an incapacitated person considered<sup>87</sup> and that in emergency situations the investigator must not be aware of the subject having previously expressed any objections to participating in a clinical trial.<sup>88</sup> This is counter to applicable law in Germany. The German Medicinal Products Act particularly relates the consent by the legal representative to the supposed will of the minor or, where certain conditions are met provides

80 The German Medicinal Products Act stipulates in concrete terms: "If, in an emergency situation, consent cannot be obtained, treatment which is necessary without delay to save the life of the person concerned, restore good health or alleviate suffering can be started immediately. Consent for continued participation must be obtained as soon as it is possible and reasonable," thereby linking the measures to direct individual benefits. The Draft Regulation does not do this.

81 Art. 32 para. 1.

82 Compare Art. 30 para. 1 point h of the Draft Regulation: "there are grounds for expecting that participation in the clinical trial will produce a benefit to the incapacitated subject outweighing the risks or will produce no risk at all."

83 Art. 31 para. 1 point h of the Draft Regulation: "some direct benefit for the group of patients is obtained from the clinical trial."

84 Art. 32 para. 1 point c of the Draft Regulation states: "the subject has not previously expressed objections known to the investigator", but this does not include explicitly asking whether the potential subject has any objections.

85 Art. 32 para. 1 point c of the Draft Regulation: "the subject has not previously expressed objections known to the investigator".

86 Art. 31 para.1 point c of the Draft Regulation.

87 Art. 30 para.1 point c of the Draft Regulation.

88 Art. 32 para.1 point c of the Draft Regulation.

for compulsory consent by the minor him/herself.<sup>89</sup> Contrary to the provisions of the Medicinal Products Act, the investigator is not obliged to comply with the decision of a minor, insofar as the latter is capable of understanding and expressing their will, and is not required to actively seek to determine the supposed will of the minor.

#### 2.1.5 Unauthorised investigational medicinal products

The Draft allows the possibility of an investigational medicinal product which has not been authorised in a particular Member State, but which is authorised in another Member State, being used as the control medicinal product in the course of a clinical trial in the first-mentioned Member State. The problem is largely, but not completely alleviated by Article 8 para. 2 point a of the Draft Regulation, in which deviation from national standards of treatment is explicitly stated as a reason for refusing approval for a study.

The use of an unauthorised control medicinal product<sup>90</sup> can result in a significantly higher risk to the safety of the subjects, since some medicinal products require significant experience on the part of the prescribing doctor to ensure tenable safe use, which would not be available in a Member State where the product is not authorised.

### 2.2 EU-wide harmonisation of the protection of clinical trial subjects (B)

As already mentioned, the Regulation will become legally binding throughout the EU without requiring implementation by national legislators. In contrast to Directive 2001/20/EC, it does not simply set out a minimum standard – to the extent covered

by its provisions – but will bring about an absolute harmonisation. However, as a consequence, this means that currently applicable national standards providing a higher level of protection will be undermined.

### 2.3 The role of the Ethics Committee (C)

#### 2.3.1 Renunciation of the principle of separation between the pharmaceutical authorities and the Ethics Committee

An important innovation in the Draft Regulation is the renunciation of the principle of a compulsory separation between the pharmaceutical authorities and the Ethics Committee.

According to the concept of the Draft Regulation, it falls within the regulatory scope of the Member State to determine whether an autonomous, independent Ethics Committee is required. Admittedly the Draft Regulation defines the committee responsible for carrying out the assessment in Article 9 in a manner which corresponds to the usual definition of an Ethics Committee. It thus establishes a committee “like an Ethics Committee” whilst allowing greater independence for its members, even if it declines to apply the term.

In the proposed amendments of the EP Committee on the Environment, Public Health and Food Safety the Ethics Committee is defined as conforming to the Declaration of Helsinki<sup>91</sup> and independent.<sup>92</sup>

<sup>89</sup> Compare also Section 40 para. 4 No. 3 of the German Medicinal Products Act.

<sup>90</sup> In the case of a medicinal product which is not authorised for this particular indication alone, the following statements do not apply.

<sup>91</sup> “Authorisation for conducting a clinical trial by the concerned Member State shall be granted only after examination by the ethics committee concerned in accordance with the World Medical Association’s Declaration of Helsinki” (Committee on the Environment, Public Health and Food Safety, Amendment 79, Article 4 a (new)).

<sup>92</sup> “Ethics committee: an independent body in a Member State, consisting of health-care professionals and non-medical members including at least one well-experienced, knowledgeable patient or patient representative. Its responsibility is to protect the rights, safety, physical and mental integrity, dignity and well-being of subjects and to provide public assurance of that protection in full transparency. In cases of clinical trials involving minors, the ethics committee shall include at least one healthcare professional with paediatric expertise” (Committee on the Environment, Public Health and Food Safety, Amendment 64, Article 2 – paragraph 2 – point 10 (new)).

This, however, particularly raises the question – which is not answered by the Draft Regulation – of how the general independence of the committee from the political level postulated in Article 9 can and should be ensured. However, the autonomy and independence of the Ethics Committees is a significant basic requirement for public trust in conducting clinical trials. An actual or a perceived connection between the Ethics Committee and the pharmaceuticals authorities or industry can lead to a loss of trust among the public.<sup>93</sup>

In Germany an independent Ethics Committee is required to monitor, among other things, the procedure for providing proper information and the consent of participants in clinical studies given following this.<sup>94</sup> Experience to date has shown that the Ethics Committees have regularly called for improvements to be made: Fewer than 5% of clinical studies are approved at the assessment without modifications. The improvements required almost always relate to the text of the information provided to patients. The elimination of the independent Ethics Committee could result in the loss of this critical authority and as a consequence study subjects may be given insufficient information.

The loss of an independent Ethics Committee can, furthermore, lead to a re-

duction in the safety of clinical trial subjects. According to current legal requirements the independent Ethics Committee is required to carry out the assessment of the criteria for inclusion or exclusion as well as the individual criteria for aborting the trial. Experience has shown that this frequently leads to these points being amended.

The assessment of the ethical aspects is no longer comprehensive, but is limited to “consent after proper information”. The EP Committee<sup>95</sup> on the Environment, Public Health and Food Safety has also criticised this as inadequate. The basic principles of promoting the well-being, potential benefits and autonomy of the trial subjects and the avoidance or minimisation of harm contained in the frameworks of rules and international conventions mentioned at the start will – in contrast to the current situation – no longer be considered.

### 2.3.2 The setting of deadlines and tacit approval

The different deadlines for clinical trials, low-intervention clinical trials and new therapies provided for in the Draft Regulation are, in principle, appropriate. This is, however, not true of the concrete deadlines proposed: even if an assessment by an Ethics Committee should be received within a limited time frame, some of the deadlines set by the Draft Regulation are too tight<sup>96</sup>. The opinion pronounced by

93 Included in the tasks of the Ethics Committee is sustaining and promoting public trust so that during clinical trials the rights, autonomy, safety and well-being of the trial subjects are assured. (s. ICH-GCP) Reports of irregularities in the allocation and transplantation of organs in Germany have, according to data provided by the German Organ Transplantation Foundation, led to a significant decrease in willingness to donate organs. It would be catastrophic if we were to encounter a reduction in willingness to participate in clinical studies because trust in the seriousness of clinical research was significantly damaged by the abolishment of independent Ethics Committees. This fear affects patients, trial subjects and investigators alike. As a result, clinical research would be weakened, in direct contrast to the legislators' intentions.

94 Statement to the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC. Working party of the German Medical Ethics Committees, 21 August 2012 (available online at: <http://www.ak-med-ethik-komm.de/documents/StellungnahmeEUVerordnungklinischePruefungen.pdf>).

95 “Limiting ethic assessment only to the verification of the informed consent procedure is not enough.” (Committee on the Environment, Public Health and Food Safety, Amendment 107, Article 7 – paragraph 1 – subparagraph 1 – point a).

96 Art. 5 para. 2 Draft Regulation: 6 days for evaluating the scope; Art. 6 para. 4 of the Draft Regulation: 10 to 30 days for Part I, which, for example, should evaluate “risks and burdens” (i.e. carry out a full ethical assessment); according to Art. 7 para. 2 of the Draft Regulation: 10 days for evaluating requirements for obtaining consent (ethical assessment) (Art. 7 para. 1a). A decision on the question whether a trial is low intervention can involve a material assessment which cannot be completed within six days. According to Art. 2 para. 3 of the Draft Regulation, the content of the authorisation and the standard treatment in the Member State must be reported, for example, and the level of risks and burdens for the trial subjects evaluated.

the EP Committee<sup>97</sup> on Industry, Research and Energy, that the time frame must be competitive cannot be reconciled with the time required for the necessary level of diligence in the ethical assessment.

It is impossible for an Ethics Committee – and sometimes also the applicant – to carry out its task responsibly and properly in every case within too short a time frame.<sup>98</sup> In particular, the very short time allocations proposed by the European Commission lead us to anticipate that possible necessary cross-border discussions may not occur. As already mentioned by the EP Committee<sup>99</sup> on the Environment, Public Health and Food Safety, the regulation on deadlines also has particular significance because tacit approval is widely assumed once the deadline for approval has expired. It must also be stated that competitiveness<sup>100</sup> and incentive mechanisms<sup>101</sup> have no role to play in connection with ethical assessments. This entails significant endangerment of the safety of trial subjects. Furthermore, it is not clear whether the deadlines are measured in calendar or business days.<sup>102</sup>

97 “The timing between submission and decision must be competitive” (Opinion of the Committee on Industry, Research and Energy, Amendment 37, Article 14 – paragraph 3 – point a).

98 Excessively short deadlines may also mean that they can no longer be met by Ethics Committees/Committees with voluntary members. This may lead to volunteers withdrawing their membership. This would mean a loss of important factual expertise for the review of studies in exchange for increased bureaucracy.

99 “The concept of tacit authorisation should apply automatically” (Committee on the Environment, Public Health and Food Safety, Amendment 7, Recital 8). The proposal for a regulation is based on the principle of tacit approval introduced by Directive 2001/20/EC. This principle must be applied in order to ensure compliance with the time limits, which is a prerequisite not only for prompt access to innovative treatment, but also for the safeguarding of the competitiveness of European clinical research (Committee on the Environment, Public Health and Food Safety, Amendment 112, Article 7 – paragraph 3 a (new)).

100 “The timing between submission and decision must be competitive” (Opinion of the Committee on Industry, Research and Energy, Amendment 37, Article 14 – paragraph 3 – point a).

101 “The concept of tacit approval will provide a real incentive for those authorising trials to do so on time” (Committee on the Environment, Public Health and Food Safety, Explanatory statement, Approval times).

102 The problem will be significantly exacerbated if the deadlines are measured in calendar days.

### 2.3.3 National language

All documents including the summary, informative documents and documents for obtaining consent can be provided in a language which is not the national language of the trial country or which does not include a language spoken in one of the test regions.<sup>103</sup> According to Article 26 of the Draft Regulation, every participating country is entitled to demand that documents be provided in its national language.

Article 26 para. 2 of the Draft Regulation also explicitly states that the expectation that, for example, documents in English will be accepted does not apply for documents intended for trial subjects. It can therefore be inferred that the Draft Regulation also assumes that each participating country will demand at least that part of the application intended for the trial subjects will be provided in its national language. This view is also shared by the EP Committee<sup>104</sup> on the Environment, Public Health and Food Safety.

If, however, the Member State does not demand this, it can mean that neither the summary nor the informative documents nor the documents for consenting to participation in a clinical trial are available in its national language or in all recognised national languages or in the languages of significant minorities. Experience has shown that the informative and consent documents regularly need to be

103 Art. 26 of the Draft Regulation, regulation on language: “The language of the application dossier, or parts thereof, shall be determined by the Member State concerned. Member States, in applying the first paragraph, shall consider accepting, for the documentation not addressed to the subject, a commonly understood language in the medical field.”

104 It should be left to Member States to establish the language requirements for the application dossier. To ensure that the assessment of the application for authorisation of a clinical trial functions smoothly, Member States should work towards accepting a commonly understood language in the medical field as the language for the documentation not destined to the subject, such as the Patient Information and the Informed Consent Sheet (Committee on the Environment, Public Health and Food Safety, Amendment 31, Recital 21).



amended during the assessment and approval procedure.<sup>105</sup> Moreover, they must be thoroughly checked from the language point of view to ensure that all study subjects or those responsible for them are able to understand them.<sup>106</sup> Neither of these goals can be achieved if the aforementioned documents are not required to be available in the national language or languages of a particular Member State or of an affected region for assessment by the Ethics Committee.

#### 2.3.4 Division of the assessment report

The proposal includes a division of the assessment report.<sup>107</sup> From the regulatory framework it is clear that the local Part II of the assessment report must routinely be finalised before the Ethics Committee has the draft of Part I of the report. This division makes the ethical assessment of the whole application more difficult, since the results of Part I should naturally have some influence on the ethical assessment.

### 2.4 The procedure for arriving at consensus across the EU states (D)

Additional points of criticism relate to the division of labour and the procedure for arriving at consensus between the reporting country and other Member States affected.

#### 2.4.1 Points of criticism on the division of labour

The assessment of tenability for all participating countries is undertaken solely by the relevant authority within the re-

porting Member State. This is intended to simplify the process, but also has some undesirable consequences. The sole and comprehensive decision-making power of the reporting Member State extends – counter to what the Draft Regulation attempts to suggest – to central ethical aspects, namely the appraisal of the balance of risks to benefits, whilst the influence of the other participating states is largely limited to the assessment of the information provided and the local trial sites. The remaining grounds for refusing participation, according to Article 8 para. 2 of the Draft Regulation, are extremely restrictive and do not include important points of view. This problem is further exacerbated by the fact that this material principle of mutual recognition is not supported by adequate institutional protection. The free choice of reporting Member State open to the applicant described later further exacerbates this problem.

The other participating Member States are thereby almost completely excluded from the final ethical assessment of the clinical trial of medicinal products. Nor are the affected Member States allowed to ask questions themselves. Their involvement is limited to passing comments to the reporting Member State, which this must then “duly” consider. The concept of “due consideration” includes the possibility of ultimately taking no account of the points of view put forward. This creates the risk that ethical aspects which are put forward by the non-reporting Member State are not sufficiently brought to bear.

The non-reporting Member States are bound by the assessment of the reporting Member State, unless the limited conditions set out in Article 8 para. 2 subpara. 2 of the Draft Regulation apply. These do not, however, include a different ethical assessment by a participating Member State.

<sup>105</sup> Response to the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC. Working party of the German Medical Ethics Committees, 21<sup>st</sup> August 2012 (available online at: <http://www.ak-med-ethik-komm.de/documents/StellungnahmeEUVerordnungklinischePruefungen.pdf>).

<sup>106</sup> Ibid.

<sup>107</sup> The division is into a Part I and a Part II. The division is ultimately based on (too narrowly understood) local or ethical aspects and those that can be assessed on a union-wide cooperative scale.

This ultimately introduces the principle of EU-wide mutual recognition of medical standards, although there are good reasons to assume that these standards in fact differ greatly.<sup>108</sup>

#### 2.4.2 Points of criticism on the procedure for arriving at consensus

The procedure for arriving at consensus among EU Member States proposed in the Draft Regulation does not take adequate account of the possibilities presented by modern communication technologies. The fact that there are electronic media such as the Internet, telephone and video conferencing to facilitate faster communication between nations, which in some cases are also more reliable than the post, is not explicitly taken into account in the Draft Regulation. Thus the opportunities to increase the rights of the EU Member States to participate in the assessment of the application without complicating the approval procedure have not been fully exploited.

### 2.5 Miscellaneous (E)

#### 2.5.1 Ensuring funding

The necessity for the sponsor to provide funding has been dropped. This meets the demands of non-commercial clinical testers, in particular those from the field of academia. However, it must be ensured that an alternative provider for finance for the study and any after-care required is found. The proposal does not address this. Without adequate financing throughout the trial the safety of the trial subjects and the success of the study may be endangered.

<sup>108</sup> In this context, the cultural and legal differences between what is medically allowed and what is not allowed in the different Member States which arise in the ethical assessment should be pointed out. The following examples demonstrate considerable differences in social acceptance and legislative provisions as encountered in the various Member States: assisted suicide, surrogate motherhood, pre-implantation diagnostics, research using human embryo stem cells, regulations for organ removal and online prescriptions for drugs. In some states, decisions are completely utilitarian in nature. As a result, the Member States have in the past arrived at completely different ethical decisions on questions of what is medically acceptable.

#### 2.5.2 The problems of cross-border studies

In cross-border medical products studies, the organiser of the clinical trial can nominate any Member State as the reporting country. This enables the trial organiser to select a reporting Member State with lower standards where they can expect to encounter a less critical attitude.

#### 2.5.3 Factually flawed formulations

In describing the anticipated gain from the study, the regulation proposal (like the German Medicinal Products Act) uses some incorrect terms, as demonstrated, above all, by the inappropriate term *benefits*.<sup>109</sup> Correct would be the use of terms such as *potential* or *possible benefits*. It is naturally a basic principle of clinical studies that the effects of the medicinal product and therefore the benefits it confers cannot be predicted with accuracy, otherwise a study would be neither necessary nor justified. It is therefore not factually possible to know or predict in every case the “therapeutic benefits” (Draft Regulation), “direct benefits” (AMG<sup>110</sup>) or “advantage” (Draft Regulation). Likewise, it cannot be known before the start of the study whether the medicinal product will save the life of the affected person, restore their health or alleviate their suffering. These terms are therefore not factually justified. By contrast, the study plan – where possible even on the basis of statistics – must, without exception, be designed to demonstrate potential or possible benefits.

<sup>109</sup> Art. 28 para. 1 point a of the Draft Regulation “The anticipated therapeutic and public health benefits justify the foreseeable risks and inconveniences”; Art. 30 para. 1 point h of the Draft Regulation: “there are grounds for expecting that participation in the clinical trial will produce a benefit to the incapacitated subject”; Art. 31 para 1 point h of the Draft Regulation: “some direct benefit for the group of patients is obtained from the clinical trial.” The Medicinal Products Act likewise refers exclusively to “direct benefits” or a requirement “to save the person’s life, to restore health or to alleviate suffering”.

<sup>110</sup> In Section 41 para. 1 sentence 1 of the Medicinal Products Act the impossible demand is made: “The use of the investigational medicinal product is indicated according to the findings of medical science in order to save the person’s life, to restore health, alleviate suffering”. A benefit – not a potential benefit – is described.

#### 2.5.4 Lack of differentiation between healthy study subjects and patients

The Draft Regulation does not differentiate between a healthy volunteer<sup>111</sup> and a patient, although this distinction is of fundamental importance for the ethical assessment.

#### 2.5.5 Provision for representation in lieu of the sponsor being established in the EU

Article 70 of the Draft Regulation requires the sponsor to have only a “contact person” in the EU; it is no longer a requirement that the sponsor be established in the EU.<sup>112</sup> This is untenable, since a contact person cannot reliably ensure in every case that urgent safety measures required by the authorities will be implemented immediately.

#### 2.5.6 Limitation of the guarantee of the right of access to legal redress

As a result of the approval procedure, for which the – at times foreign – reporting state is responsible, legal action in the case of misconduct or negligence must be taken against the Member State or its authorities (insofar as this is permissible under the law of the Member State). This significantly restricts the guarantee of the right of access to legal redress and its application for German citizens.<sup>113</sup>

#### 2.5.7 Problematic recommendations in the EU report

##### *Abandonment of the requirement to obtain consent*

In the European Parliamentary Report dated 7.6.2013, some new recommendations were adopted which are in part

problematic. Particularly worthy of mention is Amendment 167 for a new Article 29 para. 3a, which, for particular constellations, seeks to abandon the requirement to obtain consent and to replace it with a mere right to object to participating. This provision is in clear contravention of customary principles.

##### *Orientation exclusively by age*

Article 2 (16) of the Draft Regulation describes as incapacitated, among others, a person who, according to the laws of the Member State concerned, is not old enough to give or refuse consent after receiving proper information. Orientation based solely on age and not on the level of comprehension of which the person is capable contradicts various legal systems (including the German one) in which the definition of a minor is determined by age limits, but in which minors are seen as capable of giving informed consent<sup>114</sup> under certain circumstances. So, for example, the Medicinal Products Act does not accord minors capable of giving informed consent a full right to give consent, but rather a right to refuse consent.

<sup>111</sup> Preferred for Phase I studies.

<sup>112</sup> “Where the sponsor of a clinical trial is not established in the Union, that sponsor shall ensure that a contact person is established in the Union.” In principle, that means that a “post office box” within the EU is sufficient.

<sup>113</sup> How is a citizen of a state to file and successfully pursue legal action abroad? He will be faced, among other things, with a foreign language, foreign legal system and a foreign venue.

<sup>114</sup> Compare, for example, Section 228 of the German Criminal Code where the ability to give informed consent is linked to the natural ability to comprehend and determine for oneself rather than to age.

### 3 Recommendations (Full version)

The intention of the Draft to harmonise, shorten, simplify the procedure and render it more cost-effective is to be welcomed. Equally to be welcomed is the compliance with the general protective rights for adult study subjects capable of giving consent (with the exception of emergency situations), according to which the total anticipated benefits from the study (derived from the benefits to the individual trial subject and the public health/therapeutic benefits) must outweigh the anticipated risks. However, special norms for specific incidence groups should be amended.

Against this background, the Regulation should be modified with respect to the harmonisation and compliance with protective regulations, so that, despite the reduction in administrative requirements and procedural conditions which must be met for approval, the strict requirements for clinical trials on human subjects are maintained. The Draft Regulation should, therefore, be amended so that it does not fall short either legally, ethically or medically of the, to some extent internationally applicable, standards for the protection of all persons participating in a clinical trial of medicinal products – that is to say, including the most vulnerable groups.<sup>115</sup>

The recommended amendments primarily affect (A) the protection of clinical trial subjects, (B) EU-wide harmonisation of the protective provisions, (C) the role of the Ethics Committee and (D) the process for reaching consensus among EU states.

#### 3.1 Protection of clinical trial subjects (A)

##### 3.1.1 The protection of particularly vulnerable clinical trial subjects

As already mentioned by the EP Committee<sup>116</sup> on the Environment, Public Health and Food Safety, the autonomy, well-being and individual benefits of particularly vulnerable subjects, such as minors and permanently incapacitated adults as well as patients in emergency situation, require strict protection.

<sup>116</sup> “Incapacitated subjects, minors, pregnant and breast-feeding women, and where the law of the Member State concerned allows, persons deprived of liberty, as well as subjects with specific needs require additional protection measures. Existing rules and international standards, in particular the provisions of the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research of the Council of Europe should be upheld and integrated into this Regulation in order to guarantee a high level of protection for those subjects with specific needs throughout the Union” (Committee on the Environment, Public Health and Food Safety, Amendment 32, Recital 22).

“A clinical trial on persons deprived of liberty may be conducted only where, in addition to conditions set out in Article 28, all of the following conditions are fulfilled: (a) the national law of the Member State concerned allows research on persons deprived of liberty; (b) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject; (c) no incentives or financial inducements are given except compensation for participation in the clinical trial, which shall be strictly limited to conditions making good the expenses incurred. 2. Informed consent shall be sought from the subject or his or her legal representative as decided upon by the national law of the Member State concerned” (Committee on the Environment, Public Health and Food Safety, Amendment 188, Article 31 b (new)). “A clinical trial on subjects with specific needs may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are fulfilled: (a) it has been assessed and duly justified whether and what specific needs the subject has; (b) the subject has received all relevant information from professionals trained or experienced in working with subjects with specific needs regarding the trial, the risks and the benefits; (c) no incentives or financial inducements are given except compensation for participation in the clinical trial, which shall be strictly limited to conditions making good the expenses incurred; (d) such research either relates directly to a medical condition from which the subject concerned suffers or it is relevant to the population group with specific needs; (e) the clinical trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage, and both the risk threshold and the degree of distress are specially defined and constantly observed; (f) some direct benefit for the group of patients is expected to be obtained from the clinical trial. 2. The subject shall take part in the consent procedure in a manner catering for, where necessary, his or her specific needs, situation and capacity” (Committee on the Environment, Public Health and Food Safety, Amendment 189, Article 31 c (new)).

<sup>115</sup> Compare also the Proposal of the Bundestag parties “EU-wide Regulation on the conduct of clinical trials of medicinal products for human use – ensuring the protection of trial subjects” dated 29./30.1.2013, Drucksache 17/12183 or 17/12184 (available online at: <http://dip21.bundestag.de/dip21/btd/17/121/1712183.pdf>).

### 3.1.1.1 Protection for minors and incapacitated adults

For patient studies where there are individual benefits (including for minors or permanently incapacitated adults), the relative requirement of minimisation with the minimum possible burden and other foreseeable risks stipulated in the Draft Regulation should be retained without amendment – with the exception of emergency situations. Studies in emergency situations should be allowed only where there are direct benefits<sup>117</sup> to the individual patient. The absolute requirement of minimal risks and burdens proposed for emergency studies in the Draft Regulation, i.e. very minor and temporary impairment of the subject's health and well-being, should apply without amendment.

### 3.1.1.2 Need for a subsidiarity provision

It is recommended that the protection of minors, permanently incapacitated subjects and patients in emergency situations is based entirely and ethically on the subsidiarity principle: As already proposed by the EP Committee on the Environment, Public Health and Food Safety, clinical trials of medicinal products on incapacitated patients should be permitted only if studies with persons capable of giving consent are not sufficient to meet the aims of the clinical study.<sup>118</sup> The inability to give informed consent in an emergency situation must be directly related to the clinical condition of the study subject.<sup>119</sup> Likewise,

studies which serve to validate the data collected should be seen as entirely necessary.

### 3.1.1.3 Easier approval for clinical studies on rare diseases

In keeping with the comments by the EP Committees<sup>120</sup> on Industry, Research and Energy, on Civil Liberties, Justice and Home Affairs and on the Environment, Public Health and Food Safety, patient studies with specific medical products<sup>121</sup> should also be explicitly allowed for affected parties with rare diseases if the anticipated limited significance of the study due to low rates of prevalence is counterbalanced by a justified potential benefit to those participating in the study and the group of patients suffering from the same disease. A potential benefit is to be assumed if the investigators have comprehensive experience of the rare disease. Alternatively, the burden of disease, potential benefits-risk analyses, efficacy parameters and other peculiarities of the rare disease should be weighed up in addition to the low rate of prevalence. In the same way, clinical trials for patients suffering from multiple illness-

<sup>117</sup> That a clinical trial of a medicinal product could be conducted in an emergency situation where the only potential benefits are for the group of patients, without there being any requirement that the affected person should receive direct benefits, is in contravention of current German law.

<sup>118</sup> "(h a) the research is necessary to promote the health of the population concerned by the trial and cannot instead be performed on capacitated subject" (Committee on the Environment, Public Health and Food Safety, Amendment 174, Article 30 – paragraph 1 – point h a (new)).

<sup>119</sup> The conditions stipulated in Art. 32 para. 1 point d of the Draft Regulation include the fact that in such cases, the clinical trial must relate directly to the medical condition of the patient: "the research relates directly to a medical condition which causes the impossibility to obtain prior informed consent and to supply prior information."

<sup>120</sup> "Whereas most clinical trials are implemented for the assessment of therapies consisting of large samples of patient populations, this Regulation should not discriminate against patients suffering from rare and ultra-rare diseases and should integrate the specificities of low prevalence conditions when assessing a trial" (Opinion of the Committee on Industry, Research and Energy, Amendment 8, Recital 22 a (new)).

"Many rare and ultra-rare diseases are not yet correctly identified or remain partially understood. In clinical trials associating patients affected by such conditions, the knowledge of these illnesses may be significantly improved by the resulting assessment of data. The reporting Member State must have knowledge of this added value" (Opinion of the Committee on Civil Liberties, Justice and Home Affairs, Amendment 63, Annex 1 – part 2 – point 6 – point 6 a (new)).  
"and the prevalence of the condition, especially for rare diseases (defined as severe, debilitating and often life-threatening diseases which affect no more than five persons per 10 000), and ultra-rare diseases (defined as severe, debilitating and often life-threatening diseases which meet a prevalence threshold of no more than one affected person per 50 000)" (Committee on the Environment, Public Health and Food Safety, Amendment 92, Article 6 – paragraph 1 – point a – point i – indent 3).  
"Assessment report on clinical trials in the field of rare and ultra-rare diseases" (Committee on the Environment, Public Health and Food Safety, Amendment 114, Article 7 a (new)).

<sup>121</sup> These are known as "orphan drugs". From the point of view of definition, it is recommended that a medicinal product be designated an "orphan drug" if it conforms to the EU orphan regulations.

es, where there are very small groups of patients, or those suffering from dementia where the effectiveness can only be measured against difficult-to-define parameters of efficacy should be made possible.

### 3.1.2 Research offering potential group benefits or benefits to others

#### 3.1.2.1 *Appropriate level of protection for vulnerable patients*

Without research being undertaken on healthy and sick trial subjects where there is only a potential benefit for the group or for others, important medical insights could not be gained. From the ethical point of view, such trials of medicinal products are not unproblematic, since they cannot be compensated for by a medical personal interest on the part of the trial subject. In contrast to the statement issued by the EU Parliamentary Committee on the Environment, Public Health and Food Safety (compare footnote 8), they can, however, be legitimated on the basis of a minimal, solidarity-based, obligation to tolerate, enhanced by prior consent, given for minors and incapacitated adults by their legal representative, which is linked to the well-being of the affected party.<sup>122</sup> The strict criteria of the EU Regulation must be the legal basis.

If, however, there is no potential benefit to the individual for particularly vulnerable groups of trial subjects (minors, adults, incapacitated adults, patients in emergency situations), inclusion in research which offers potential group benefits alone can be justified only if there is only minimal risk or minimal burden<sup>123</sup>. Consequently, where

there are no potential benefits to the individual, for particularly vulnerable patients minimal risk or a minimal burden should be stipulated as the threshold (absolute requirement of the minimum). This does, of course, result in a reduction in the autonomy of the legal representatives of incapacitated adults and of children (namely their right to give consent even when there is a high level of risk or burden). However, in the case of a conflict between autonomy and well-being, where there is only a potential benefit to the group, the well-being of the charge must take precedence over the autonomy of the legal representative.

This means that admission to clinical trials of medicinal products for which there are only potential group benefits is also to be recommended for permanently incapacitated adults. As far as minors are concerned, participation should be limited to studies where the risks and burdens are minimal, i.e. very minor and temporary impairment of health and well-being (absolute requirement of the minimum).<sup>124</sup> This would place children and incapacitated adults on an equal footing in Germany, in contrast to the former legal situation. This equality is to be welcomed, since there is no ethical justification for treating incapacitated adults differently from children to be found anywhere in the EU.

Research which offers only potential group benefits should not be permitted for healthy minors.

What should, however, be preserved is the principle underlying the Draft Regulation that a clinical study with subjects capable of giving consent should be possible even where there are no potential benefits to the individuals, only the group or other people, and that this

<sup>122</sup> In the case of minors and incapacitated adults, this applies only for research which offers potential group benefits only.

<sup>123</sup> This differs somewhat from the statement by the Committee on the Internal Market and Consumer Protection: "For example, in cases where the research needs to start without delay and there is reason to expect that the potential benefit to the subject of taking part in the clinical trial outweighs the risks or the subject's participation entails only a minimal risk, it should be possible for the clinical trial to begin without his or her prior consent" (Opinion of the Committee on the Internal Market and Consumer Protection, Amendment 17, Recital 23).

<sup>124</sup> In Art. 30 h the Draft Regulation stipulates a requirement of no risk for participation in studies where the potential benefits are limited to the group. This should be replaced with the protective stipulation "minimal risk/minimal burden".

should not be limited by the requirement of minimal risk, but rather by proportional risk<sup>125</sup> (relative requirement of minimisation).

### 3.1.3 Legislative stipulations on providing information

The provision of proper information should be undertaken only by a doctor or dentist or by a medical expert comparably qualified and certified in this respect.<sup>126</sup> The qualification should be regulated by law, and it should be ensured that the standards are comparable to the provision of information by a doctor. The level of protection for trial subjects should not be reduced thereby. This can contribute to EU-wide harmonisation. This would lift the requirement in Germany for this task to be undertaken by a doctor. The demand for legislative regulation of the qualification and certification of these experts should be seen as an understandable compromise solution. To preserve a national right to insist upon this task being undertaken by a doctor through a general or special opening clause would countermand harmonisation.

<sup>125</sup> Directive 2001/20/EC and the AMG do not provide for a general limitation of studies/investigations where the potential benefits are limited to the group or other people based only on minimal risk or burden, nor do they do so for patients (compare Section 41 para. 1 No. 2 of the AMG for studies involving adults where the potential benefits are for the group). Compare also Section 6 para. 2 of the Protocol to the Convention on Bioethics: Here the issue of a lack of direct benefit is explicitly addressed, but the limit is set not as minimal, but acceptable risk.

<sup>126</sup> For example, a specially qualified study nurse could undertake the task of providing information. The certification ensures that the qualification for undertaking the task of providing proper information is equivalent to that of a qualified investigating doctor. It is, however, questionable whether this solution would gain majority support in Germany. Of course the certification solution could not guarantee the same level of medical qualification as a doctor, which is the main (plausible) argument for insisting this task be undertaken by a doctor. We are not so much concerned with the methods of communication as with the necessary expert knowledge required to provide full and reliable information about the medical factors involved in the risks and benefits. Expanding the circle of authorised persons also contradicts the Law on Patient Rights which recently came into force, Section 630e for example.

### 3.1.4 Regulations regarding consent

#### 3.1.4.1 Fundamental requirement for consent to be given in writing

Consent must be given in writing as a matter of principle. By way of exception, consent given in the presence of independent witnesses – confirmed in writing – is permitted in cases where the patient cannot give his consent in writing.

#### 3.1.4.2 Exceptional provisions for studies in emergency situations

Research into medicinal products in and for emergency situations on temporarily incapacitated adults and on minors should not be inordinately hindered. A clinical trial of a medicinal product should be permitted without the consent of the affected person or their legal representative only if a sudden serious change in the state of their health renders carrying out the legal effective process for obtaining consent impossible. In this case, it must be reasonable to assume that the affected party or their legal representative would wish to give their consent. The investigator must also actively seek to ascertain the presumed will of the temporarily or permanently incapacitated patient.

In order to accommodate an acute emergency situation where consent cannot be obtained without delay, in this special case it should suffice for the consent of the patient or his legal representative to be sought as soon as possible after the event (Article 32 para. 2 point a of the Draft Regulation). At the same time, there must be a chance that the life of the patient can be saved, his health restored or his suffering alleviated. Furthermore, there should be no more than a minimal perceptible additional<sup>127</sup> risk or a minimal additional burden to the patient.

<sup>127</sup> Especially in the case of particularly serious diseases or injuries the level of acceptable additional risk / burden can be weighed and measured against the risks of the medical condition and the outcome quality of the standard treatment and the risks and results to be anticipated from the new treatment.

### 3.1.4.3 Taking account the autonomy of minors and incapacitated adults

Minors and incapacitated adults<sup>128</sup> should be involved in the decision to give consent by their legal representative in accordance with their ability to make judgements.<sup>129</sup> If a minor is in a position to evaluate the information and does not consent to participating in a clinical trial, they must be excluded from the clinical trial. As required by German law, in the case of minors who are capable of giving consent, their positive consent must be sought. It is therefore recommended that the EU go beyond the principles for obtaining consent contained

<sup>128</sup> Compare the statement by the Committee on the Environment, Public Health and Food Safety: “A clinical trial on persons deprived of liberty may be conducted only where, in addition to conditions set out in Article 28, all of the following conditions are fulfilled: (a) the national law of the Member State concerned allows research on persons deprived of liberty; (b) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject; (c) no incentives or financial inducements are given except compensation for participation in the clinical trial, which shall be strictly limited to conditions making good the expenses incurred. 2. Informed consent shall be sought from the subject or his or her legal representative as decided upon by the national law of the Member State concerned” (Committee on the Environment, Public Health and Food Safety, Amendment 188, Article 31 b (new)). “A clinical trial on subjects with specific needs may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are fulfilled: (a) it has been assessed and duly justified whether and what specific needs the subject has; (b) the subject has received all relevant information from professionals trained or experienced in working with subjects with specific needs regarding the trial, the risks and the benefits; (c) no incentives or financial inducements are given except compensation for participation in the clinical trial, which shall be strictly limited to conditions making good the expenses incurred; (d) such research either relates directly to a medical condition from which the subject concerned suffers or it is relevant to the population group with specific needs; (e) the clinical trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage, and both the risk threshold and the degree of distress are specially defined and constantly observed; (f) some direct benefit for the group of patients is expected to be obtained from the clinical trial. 2. The subject shall take part in the consent procedure in a manner catering for, where necessary, his or her specific needs, situation and capacity” (Committee on the Environment, Public Health and Food Safety, Amendment 189, Article 31 c (new)).

<sup>129</sup> Compare the statement by the Committee on the Internal Market and Consumer Protection: “The incapacitated subject has received adequate information in relation to his or her capacity for understanding regarding the trial, the risks and the benefits; (b) the incapacitated subject has received adequate information in relation to his or her capacity for understanding regarding the trial, the risks and the benefits from the investigator or his/her representative, in accordance with the legislation of the Member State concerned” (Opinion of the Committee on the Internal Market and Consumer Protection, Amendment 81, Article 30 – paragraph 1 – point b).

in Article 29 and following of the Draft Regulation and stipulate a binding (rather than mere “taking into consideration”) objection by minors capable of forming an opinion. This demand should, reasonably, also apply to incapacitated adults.<sup>130</sup>

Permanently incapacitated adults must under no circumstances be included in a study without prior informed consent being given by their legal representative after receiving proper information.

### 3.1.5 Unauthorised medicinal products

The use of a medicinal product which is not authorised in a particular Member State as a control product should be explicitly forbidden.<sup>131</sup>

## 3.2 EU-wide harmonisation of the protection of clinical trial subjects (B)

Since the planned EU Regulation will be legally binding in the Member States, the provisions and the level of protection for research into medicinal products on human subjects must be consistently high. Lower standards of protection must be precluded. Insofar as existing, more extensive, national protective regulations will no longer apply, the standards imposed should not, as a matter of principle, fall short of the highest national protective standards – in Germany those of the Medicinal Products Act for example. In order to achieve the desirable level of protection, the Draft Regulation must therefore be tightened up. To introduce a helpful opening clause rather than tightening up the Regulation is not recommended in principle<sup>132</sup>. An opening clause would

<sup>130</sup> Likewise Section 41 para. 3 No. 2 in connection with Section 40 para. 4 No. 3 sentence 3 AMG.

<sup>131</sup> In the case of a medicinal product which is not authorised only for this particular indication, this ban shall not apply.

<sup>132</sup> Compare the statement by the Committee on Industry, Research and Energy: “compliance with national law related to ethics.” (Opinion of the Committee on Industry, Research and Energy, Amendment 28, Article 7 – paragraph 1 – subparagraph 1 – point a (new)).



countermand EU-wide harmonisation and would necessitate amendment of the proposed approvals procedure.

In accordance with the recommendation of the EP Committee on the Environment, Public Health and Food Safety, authorisation of medicinal products within the EU for which the studies have been conducted outside the EU should occur only where the same ethical principles have been observed as those enshrined in the EU Regulation.<sup>133</sup>

It is recommended that the strict requirements for research on human subjects be formulated within the regulation itself in order to ensure a consistently high level of protection throughout the EU.<sup>134</sup> If the strict requirements for research on human subjects are not formulated within the Regulation itself, then –

as also proposed by the EP Committees<sup>135</sup> on the Internal Market and Consumer Protection, on Industry, Research and Energy and on the Environment, Public Health and Food Safety – the Regulation should permit individual Member States to introduce higher protective standards than those defined in the Regulation for their own territories<sup>136</sup> (opening clause; e.g. for particular groups such as minors or incapacitated adults). Not least to cover this eventuality, the proposed platform for an exchange between Ethics Committees should be implemented as stated by the EP Committee<sup>137</sup> on the Environment, Public Health and Food Safety.

### 3.3 The role of the Ethics Committee (C)

#### 3.3.1 Autonomy and independence

The existing regulations regarding an assessment by an independent Ethics Committee must be retained in principle and drawn together in a dedicated article.

<sup>133</sup> “Where the clinical trial referred to in paragraph 4 has been conducted outside the Union, it shall comply with this Regulation and respect the ethical principles of the World Medical Association’s Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Human Subjects by the Council for International Organizations of Medical Sciences as regards subject rights, safety and well-being, and the reliability and robustness of data generated in the clinical trial.  
Justification  
Clinical trials in third countries should apply the same standards of safety and protection of patients as in the EU, so that the safety and well-being of subjects always prevails over all other interests. “Equivalence” leaves too much open to interpretation. The ethical principles of the Declaration of Helsinki and the CIOMS guidelines should be respected by all studies, including those conducted outside the EU” (Committee on the Environment, Public Health and Food Safety, Amendment 149, Article 25 – paragraph 5).

<sup>134</sup> The inclusion of special legislative regulations such as radiation protection in Germany for exposure to radiation caused by studies on medicinal products (x-rays, computer tomography) is clearly not regulated. With regard to radiation protection, it follows the opening clause in Art. 87 of the Draft Regulation, which stipulates that any special authorisations in this respect remain unaffected. These have been harmonised by European Union legislation.

<sup>135</sup> “compliance with more restrictive national provisions than those laid down in this Regulation relating to subjects’ protection in clinical trials involving vulnerable persons as defined by national Law” (Opinion of the Committee on the Internal Market and Consumer Protection, Amendment 56, Article 7 – paragraph 1 – subparagraph 1 – point a (new)).

“Where the clinical trial concerns other categories of subjects who are considered vulnerable under national law, the application to conduct the clinical trial shall be assessed on the basis of the national law of the Member States concerned” (Opinion of the Committee on the Internal Market and Consumer Protection, Amendment 69, Article 10 – paragraph 2 a (new)).  
“compliance with national law related to ethics” (Opinion of the Committee on Industry, Research and Energy).

“The regulation proposal must take into account Member States’ diversity in ethical assessment for the protection of the subjects, a principle that is respected by various international instruments e.g. the Declaration of Helsinki and the Oviedo Convention on Human Rights and Biomedicine” (Committee on the Environment, Public Health and Food Safety, Amendment 107, Article 7 – paragraph 1 – subparagraph 1 – point a).

<sup>136</sup> In this context, the cultural and legal differences between what is medically allowed and what is not allowed in the various Member States which arise in the ethical assessment should be pointed out once more. If it is not possible to achieve harmonisation of the Draft Regulation with a high level of protection in place, the alternative opening clause becomes increasingly important.

<sup>137</sup> “In order to bring clarity and consistency into the ethical review of clinical trials, without imposing the burden of full harmonisation, the Commission should set up a platform to encourage cooperation and the sharing of best practices between ethics committees. Participation in this platform should be voluntary” (Committee on the Environment, Public Health and Food Safety, Amendment 27, Recital 14 b (new)).

### 3.3.2 Certification to ensure EU-wide high standards

In order to sustainably increase trust among the public and thereby, in accordance with the intention of the legislators, to strengthen clinical research within Europe, an autonomous, independent Ethics Committee must be fully involved in every Member State concerned.<sup>138, 139</sup> Similarly, in the proposed amendments by the EP Committee on the Environment, Public Health and Food Safety – as already mentioned – the Ethics Committee was defined as complying with the Declaration

of Helsinki<sup>140</sup> and therefore explicitly defined as independent.<sup>141</sup>

An Ethics Committee for every state concerned must also be comprehensively involved,<sup>142, 143</sup> i.e. the principles of promoting the well-being, the potential benefits to and the autonomy of the study subjects as well as the avoidance or minimisation of harm to the individual should be assessed. The training and activities of every Ethics Committee should be regulated by law.<sup>144</sup> The certification serves to ensure harmonisation of the ethical assessment in accordance with the required legal regulation across the EU.

Approving authorities and Ethics Committees should be given sufficient time to carry out careful evaluation and assessment. At the same time, suitable deadlines measured in business days should be set for completion of the trial

<sup>138</sup> Compare, for example, the statements in the Declaration of Helsinki (15) in which an independent assessment by an Ethics Committee independent of any assessment by the authorities is required.

<sup>139</sup> “(14a) ‘Ethics Committee’: an independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and well-being of subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent” (Opinion of the Committee on Industry, Research and Energy, Amendment 16, Article 2 – paragraph 2 – point 14 a (new)).

“Ethics committee: an independent body in a Member State, consisting of health-care professionals and non-medical members including at least one well-experienced, knowledgeable patient or patient representative. Its responsibility is to protect the rights, safety, physical and mental integrity, dignity and well-being of subjects and to provide public assurance of that protection in full transparency. In cases of clinical trials involving minors, the ethics committee shall include at least one healthcare professional with paediatric expertise” (Committee on the Environment, Public Health and Food Safety, Amendment 64, Article 2 – paragraph 2 – point 10 (new)).

“Authorisation for conducting a clinical trial by the concerned Member State shall be granted only after examination by the ethics committee concerned in accordance with the World Medical Association’s Declaration of Helsinki” (Committee on the Environment, Public Health and Food Safety, Amendment 79, Article 4 a (new)).

“The Union should show due respect for human rights, patient safety, and high standards of ethical scrutiny, by reintroducing independent ethics committees in the Regulation” (Opinion of the Committee on Industry, Research and Energy, Short Justification)

“The Union should show due respect for human rights, patient safety, and high standards of ethical scrutiny, by reintroducing independent ethics committees in the Regulation” (Opinion of the Committee on Industry, Research and Energy, Short Justification)

“In the assessment, the view of an independent Ethics Committee shall be taken into account” (Opinion of the Committee on Industry, Research and Energy, Amendment 32, Article 9 – paragraph 3).

<sup>140</sup> “Authorisation for conducting a clinical trial by the concerned Member State shall be granted only after examination by the ethics committee concerned in accordance with the World Medical Association’s Declaration of Helsinki” (Committee on the Environment, Public Health and Food Safety, Amendment 79, Article 4 a (new)).

<sup>141</sup> “Ethics committee: an independent body in a Member State, consisting of health-care professionals and non-medical members including at least one well-experienced, knowledgeable patient or patient representative. Its responsibility is to protect the rights, safety, physical and mental integrity, dignity and well-being of subjects and to provide public assurance of that protection in full transparency. In cases of clinical trials involving minors, the ethics committee shall include at least one healthcare professional with paediatric expertise” (Committee on the Environment, Public Health and Food Safety, Amendment 64, Article 2 – paragraph 2 – point 10 (new)).

<sup>142</sup> “The responsible Ethics Committee shall be involved in the assessment of the information referred in paragraphs 1 and” (Committee on the Environment, Public Health and Food Safety, Amendment 207, Article 40 – paragraph 2 a (new)).

<sup>143</sup> “The decision to authorise the conduct of a clinical trial or a substantial modification thereof can be granted only if the relevant ethical aspects of Part I and Part II have been favourably assessed by the competent body or bodies of the Member State concerned. 2. The conclusions thereof shall be included in the assessment report drawn up in accordance with Articles 6 and 7” (Opinion of the Committee on the Internal Market and Consumer Protection, Amendment 59, Article 7 a (new)).

“In the assessment, the view of an independent Ethics Committee shall be taken into account” (Opinion of the Committee on Industry, Research and Energy, Amendment 32, Article 9 – paragraph 3).

<sup>144</sup> The Ethics Committee can definitely be an authority – albeit an independent one. (compare AMG).

assessment. The deadline for participating Ethics Committees should be short. The different deadlines for clinical trials, low-intervention clinical trials and for new therapies should be retained, albeit with changes to the actual deadlines.

### 3.3.3 National language

In accordance with the amendments recommended by the EP Committee<sup>145</sup> on the Environment, Public Health and Food Safety, written information and the documents for obtaining consent from the trial subjects should, without exception, be provided to the responsible Ethics Committee in its national or regional language in order to reliably ensure the required degree of safety.

### 3.3.4 Adjusting to the division of the assessment report

The results of Part I of the report should be assessed by the relevant independent Ethics Committee along with the application. As already proposed by the EP Committee<sup>146</sup> on the Environment, Public Health and Food Safety, the fact that the local Part II of the assessment report must routinely be finalised before the Ethics Committee has the draft of Part I of the report must be precluded.<sup>147</sup> In this case, the deadlines must be amended accordingly.

In every affected Member State the comprehensive and independent ethical review of the trial plan and the document for obtaining consent after the provision of proper information should be limited to just one independent Ethics Committee. The involvement of other Ethics Commit-

tees for comprehensive assessment within the same Member State should be explicitly precluded. Other committees within a Member State, also referred to as Junior Ethics Committees, taking account of the vote of the Senior Ethics Committee for their country, are required only to assess the suitability of the investigators and the trial sites within their Member State (that is to say, not to undertake a comprehensive assessment).<sup>148</sup> Junior Ethics Committees should not be entitled to register a vote in the meaning intended by the Regulation. Rather, Junior Ethics Committees register their vote with the Senior Ethics Committee.<sup>149</sup>

By contrast, it should be explicitly permitted for Ethics Committees to enter into an ethical discussion about possible ethical or legal concerns based on their considerations for review with the senior Ethics Committee and all other Ethics Committees. A discourse between several Ethics Committees creates a desirable and necessary internal corrective mechanism. In accordance with a recommendation from the EP Committee<sup>150</sup> on the Environment, Public Health and Food Safety, this should set a mutual learning process in motion.

<sup>145</sup> “and presented in a language which is easily understood by him or her” (Committee on the Environment, Public Health and Food Safety, Amendment 34, Recital 24).

<sup>146</sup> “The assessments of the aspects to be addressed in Parts I and II of the assessment report shall be conducted simultaneously” (Committee on the Environment, Public Health and Food Safety, Amendment 106, Article 7 – paragraph 1 – subparagraph 1 – introductory part).

<sup>147</sup> Compare Art. 7 para. 2 of the Draft Regulation.

<sup>148</sup> The recommendation corresponds to the current legal situation, if not the actual practice of all committees: the current procedure for arriving at consensus for various Ethics Committees in multi-centre studies on medicinal products in Germany alone, can, as previous experience shows, be very costly, if every Ethics Committee undertakes a new comprehensive assessment. The costs in terms of bureaucracy and time involved in this can exceed what is possible for universities or hospitals.

<sup>149</sup> This should also apply for study centres which later come under the jurisdiction of a Junior Ethics Committee. Both the vote on the suitability of the investigators and the trial site and any stimulus for discussion should be passed on to the senior Ethics Committee.

<sup>150</sup> “She is also proposing that the Commission set up a platform where ethics committees from across Europe can discuss how they authorise clinical trials and learn to work together and exchange best practice. If ethics committees can together find a more harmonised way of working, both sponsors and patients will be better informed of what to expect” (Committee on the Environment, Public Health and Food Safety, Explanatory statement, Ethics Committees).

For the – where necessary cross-border – discussion,<sup>151</sup> the use of electronic media should be explicitly permitted. In addition, it is recommended that the provisions regarding the procedure for arriving at consensus among Ethics Committees are enhanced along the same lines as the Voluntary Harmonisation Procedure (VHP) developed primarily by the Clinical Trials Facilitation Group.<sup>152</sup> The results of the discussion will be presented by the senior Ethics Committee.

### 3.4 The procedure for arriving at consensus across the EU states (D)

#### 3.4.1 Right of consultation for all Member States involved

The right to consultation in the final ethical and scientific assessment is necessary in all Member States involved. In agreement with the EP Committee<sup>153</sup> on the Internal Market and Consumer Protection, a procedure for arriving at consensus should be established to ensure this goal is met.

#### 3.4.2 Adjustments to the procedure for arriving at a single opinion

The procedure for arriving at consensus should explicitly allow the use of elec-

tronic media as well as permitting queries made by means of these media. In addition, it is recommended that the provisions regarding the procedure for arriving at consensus among the EU states during the assessment – with the involvement of the independent Ethics Committees – are likewise enhanced along the same lines as the Voluntary Harmonisation Procedure (VHP) developed primarily by the Clinical Trials Facilitation Group.

- (1) Any comments received by the reporting Member State should be included in the report. Only the reporting state is entitled to ask questions of the applicant.<sup>154</sup>
- (2) Variations in the decision must be justified by the reporting Member State.
- (3) In the event that the senior independent Ethics Committee of a Member State justifiably<sup>155</sup> comes to the conclusion that the balance of benefits to risks is untenable, the Member State in question should – as already recommended by the EP Committee<sup>156</sup> on the Internal Market and Consumer Protection – have the opportunity to refuse to authorise the part of the clinical trial that was to take place on its territory. Before doing so it should have attempted to reach a common

<sup>151</sup> “In order to bring clarity and consistency into the ethical review of clinical trials, without imposing the burden of full harmonisation, the Commission should set up a platform to encourage cooperation and the sharing of best practices between ethics committees. Participation in this platform should be voluntary” (Committee on the Environment, Public Health and Food Safety, Amendment 27, Recital 14 b (new)).

<sup>152</sup> For this a mutually acceptable position is arrived at in shared discussion between representatives of the Member States concerned (e.g. via telephone or video conferencing). The reporting Member State functions as a coordinator in this decision-making process. The so-called VHP was mainly developed by the Paul Ehrlich Institute (Federal Agency for Sera and Vaccines and for Biomedical Medicinal Products) and has been exemplarily and successfully tested in more than 80 applications.

<sup>153</sup> “The role of the reporting Member State and of the Member States concerned should be clarified in order to avoid duplication of assessment. Therefore, the authorisation procedure should also include a joint assessment phase during which the Member States concerned have the possibility to submit comments on the initial assessment report communicated to them by the reporting Member State. This joint assessment should be carried out before the reporting date and allow sufficient time for the Reporting Member State to incorporate comments from Member States concerned” (Opinion of the Committee on the Internal Market and Consumer Protection, Amendment 7, Recital 11 a (new)).

<sup>154</sup> “The reporting Member State, and only the reporting Member State, may, between the admissibility date and the assessment date, request additional explanations from the sponsor, taking into account considerations that it has, as well as considerations communicated by the other Member States concerned, as referred to in paragraph 5” (Committee on the Environment, Public Health and Food Safety, Amendment 102, Article 6 – paragraph 6 – subparagraph 1).

<sup>155</sup> “And shall document them in the assessment report. If the assessment report of the reporting Member State deviates from the considerations of the Member States concerned, the reasons for such deviation shall be stated in the assessment report” (Opinion of the Committee on Industry, Research and Energy, Amendment 26, Article 6 – paragraph 5).

<sup>156</sup> “Where the Member State concerned disagrees with the conclusion of the reporting Member State on the basis of points (a) and (b) of the second subparagraph of paragraph 2, the clinical trial shall not take place in the Member State concerned” (Opinion of the Committee on the Internal Market and Consumer Protection, Amendment 61, Article 8 – paragraph 2 a (new)).

solution – where necessary by taking advice from external bodies such as the EMA (European Medicines Agency).<sup>157</sup>

- (4) As already regulated in the Draft Regulation,<sup>158</sup> this should also apply if the clinical trial falls short of the standards of care in a participating Member State.
- (5) In the event that the Ethics Committee of the reporting Member State comes to a negative assessment in the benefits-risks analysis, the clinical study as a whole shall not be approved.

### 3.5 Miscellaneous (E)

#### 3.5.1 Ensuring funding

The abandonment of the requirement on sponsors to provide funding is to be welcomed as this promotes opportunities for long-term non-commercial studies. However, the sponsor must be obliged to provide full details of how the study is to be financed and of the after-care for the subjects.<sup>159</sup>

<sup>157</sup> “In the event of disagreement on other grounds, the Member States concerned shall attempt to agree on a conclusion. If no conclusion is found, the Commission shall take a decision on the conclusion after having heard the Member States concerned, and, if appropriate, having taken advice from the European Medicines Agency. Justification: The decision of the reporting Member State is binding for the others. It could happen that a reporting Member State supports a clinical trial while the authorities and ethics committees of the majority of the concerned Member States do not. Even if the authorities and ethic committees work together to find agreement, there must a solution to resolve conflicts. The Commission is accountable to scrutiny by the EP and Council, so is better authorised to take such a decision than the reporting Member State. As it is foreseen only in extraordinary circumstances, the additional time needed is acceptable” (Committee on the Environment, Public Health and Food Safety, Amendment 119, Article 8 – paragraph 2 – subparagraph 3 a (new)).

“In order to help the reporting Member State and the Member States concerned to provide a well-informed assessment of the application, the reporting Member State should consult the Scientific Advice Working Party of the EMA (Europ. Medicines Agency) which is better placed to provide the necessary Expertise” (Committee on the Environment, Public Health and Food Safety, Amendment 114, Article 7 a (new)).

<sup>158</sup> Art. 8 para. 2 point a of the Draft Regulation.

<sup>159</sup> “Information on the financing of the clinical trial shall be submitted” (Committee on the Environment, Public Health and Food Safety, Amendment 286, Annex I – part 16 – point 61 a (new)).

#### 3.5.2 Clarification of the problem of cross-border studies

In order to reduce the possibility of avoiding higher standards by selecting a reporting Member State with lower standards, the Member State with the highest number of participants should be the reporting Member State.<sup>160</sup>

#### 3.5.3 The use of factually correct formulations

Where factually appropriate, the term benefits should be replaced with the term potential benefits.

#### 3.5.4 Differentiation between healthy study subjects and patients

Where appropriate, a distinction should be made between a healthy volunteer and a patient, since this distinction is of fundamental importance for the ethical assessment.

#### 3.5.5 Necessity of the sponsor being based in the EU

In order for urgent safety measures required by the authorities to be implemented immediately, it is essential that the sponsor be based in the EU.

#### 3.5.6 No limitation of the guarantee of the right of access to legal redress

A significant restriction of the guarantee of the right of access to legal redress and its application is totally unacceptable.

<sup>160</sup> It must be considered in this that at the start of a study, there may still be some uncertainties in the planning. The total number of participants is still not completely known at the start of a study, sometimes a single-centre study is planned, which is later extended to become a multiple-centre study.

### 3.5.7 Consideration of problematic areas in the EU Report

#### *Adherence to the requirement to obtain consent*

The proposed amendment 167 for a new Article 29 para. 3a, which, for particular constellations, seeks to abandon the requirement to obtain consent and to replace it with a mere right to object to participating, should not be implemented.

#### *Taking account of national legislative provisions*

The definition of incapacity and the resultant legal representation<sup>161</sup> should be left to the Member State on the basis of Consideration 22 of the Draft Regulation.

#### *Selecting a head of the clinical trial for each Member State*

For each participating Member State, a head of the clinical trial (coordinating investigator) must be named in the application for approval so that any necessary measures to avoid risks can be communicated and implemented with proper medical skill without delay.

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<sup>161</sup> “Therefore, this Regulation should be without prejudice to national provisions which may require that the consent of more than one legal representative of a minor is required” (Opinion of the Committee on the Internal Market and Consumer Protection, Amendment 16, Recital 22).

## VI. Methodology

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### 2 Experts

This statement has been reviewed by seven independent scientists. The following people have reviewed the text:

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The academies would like to sincerely thank the experts for their many suggestions for improvements, which were discussed and incorporated as far as possible by the working group.

### 3 Proceedings

This response was produced using a written circulation procedure. After completion by the working group, the draft text was submitted to the expert reviewers. Their comments, along with the proposed amendments from the EP Committees which were produced in the interim, were taken into account in the final version.

The response was adopted by the relevant committee on 19<sup>th</sup> December 2013.

## VII. Abbreviations

*The abbreviations are listed below in alphabetical order*

AMG	Arzneimittelgesetz (German Medicinal Products Act)
Art.	Article
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
CIOMS	Council for International Organizations of Medical Sciences
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
DIR	Directive
Draft Regulation	Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC
EC	Ethics Committee
EMA	European Medicines Agency
e.V.	eingetragener Verein (registered association)
EP	European Parliament
EP Committees	European Parliamentary Committees
EU	European Union
ex ante	based on prediction and extrapolation from earlier studies
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ML	Member of the German National Academy of Sciences Leopoldina
MS	Member State
Para.	paragraph
PEI	Paul-Ehrlich-Institut (Federal Agency for Sera and Vaccines and for Biomedical Medicinal Products)
Sen EC	senior Ethics Committee
SME	Small and medium-sized enterprises
VHP	Voluntary Harmonisation Procedure
WHO	World Health Organization



## VIII. Acknowledgements

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