



Comments of the German Medical Association

To the Consultation Paper of the European Commission of 09/02/2011
on the 'Clinical Trials Directive' 2001/20/EC

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Preliminary remarks

The following Comments of the German Medical Association (GMA) pertain to the Consultation Paper of the European Commission for the revision of the 'Clinical Trials Directive' (CTD) 2001/20/EC of 9 February 2011 (SANCO/C/8/PB/SF D(2011) 143488), hereinafter referred to as the 'Consultation Paper'. It refers to the specific issues raised in the Consultation Paper and retains the order, numbering and phrasing used therein.

They are based on the responses of members of the German Standing Conference of Directors and Chairs of the Ethics Committees of the State Chambers of Physicians, composed of the Ethics Committees of the State Chambers of Physicians, and collaborating with the Ethics Committees of other organisations, to a written survey.

The GMA also submitted its comments to the European Commission's public Consultation Paper on the Assessment of the Functioning of the 'Clinical Trials Directive' 2001/20/EC of 9 October 2009 (ENTR/F/2/SF D(2009) 32674). At that time, we stated that in Germany, implementation of Directive 2001/20/EC in national law had occurred in conjunction with improved protection of study participants and that the basic ethical prerequisites for the execution of pharmacological clinical trials had improved. Particular mention was made of the increased level of protection afforded by the harmonisation of safety standards in so-called treatment-optimisation studies with medicinal products used within the the scope of their approved indication, the implementation of parallel assessment procedures with separate applications for evaluation by the competent authority and the Ethics Committee, and the creation of universal quality standards through the legal establishment of defined grounds for denial of an authorisation request and the possibility of revocation or withdrawal of an approval or favourable opinion by the competent authority or the responsible Ethics Committee.

The German Medical Association expressly welcomes the consultation and discussion process initiated by the European Commission on the revision of the Clinical Trials Directive based on the experience gained since the adoption of Directive 2001/20/EC and is grateful for the opportunity to submit its comments and suggestions in the framework of the public consultation process. The GMA also welcomes the fact that responsibility for the revision process for the Clinical Trials Directive has been assigned to the Directorate General for Health & Consumers (SANCO).

1.) Consultation Item No. 1:

Do you agree with this appraisal? Please comment.

Regarding Consultation Item No. 1, the Consultation Paper assumes that additional (administrative) costs are incurred by sending largely identical documents to multiple Member States. Secondly, the Consultation Paper assumes that different interpretations of the Clinical Trials Directive in different Member States could result in divergent and in some cases conflicting results.

The German Medical Association reiterates its response to the consultation process for the Clinical Trials Directive of 2009/10, where it stated that differences in the documents to be submitted frequently arise due to the different conditions in the respective national health systems and legal systems. Harmonisation of these differences currently is not being sought. Therefore, a "single submission" must be configured in such a way that these necessary differences are given due consideration in the application process.

This applies, in particular, to the documentation needed by the Ethics Committees for their assessments. On page 4 of the Consultation Paper, it is stated twice that "ethical issues clearly fall within the ambit of Member States", once with the addendum "and should remain there". Thus, it is mandatory to embed any such harmonisation regarding ethics committee practices in the scope of advising clinical trials in the national legal and values system.

The German Medical Association further submits the following comments on 'single submission':

Germany has experience in establishing a single electronic portal for the submission of clinical trial applications for medical devices. In May 2010, a national portal for single submission of clinical trial applications for medical devices to the competent national authority and the Ethics Committee was established. In our experience, this portal did not meet all expectations. For example, the electronic procedure did not reduce the administrative burden but rather, shifted costs to the national competent authorities and ethics committees. We also found that the electronic submission portal reduced the possibilities for flexible, non-bureaucratic and quick error correction. As a result, the post-processing and amendment time and burden for the sponsors has increased.

Our experience with the portal launched in Germany suggests that thorough planning and an extensive pilot phase (> 1 year) with all the stakeholders is essential for a single-submission portal to achieve a significant reduction of administrative workload. An adequately trained staff of sufficient size must be on hand for, ideally, continuous support and maintenance. In addition, detailed guidance on the necessary documentation for a single submission would help keep the rate of inquiries and the revision workload low.

It is required that some of the documents are provided in the language of the respective Member State (e.g. patient information, recruiting materials, patient diaries). Therefore, the submission portal and database needs to be provide, besides a general part, specific parts to which access is provided for the respective Member State. Since personal data are

submitted to the database (e.g. proof of qualification) national data-protection standards are to be met.

As mentioned in the Consultation Paper, the Voluntary Harmonised Procedure (VHP) has provided the option for parallel submission of clinical trial applications for authorisation in all participating Member States on a voluntary basis for some time now. However, this voluntary instrument has only been used by the applicants on a rather small scale. This raises the question of whether the EU administrative effort needed for the establishment of a single application portal would be commensurate with the anticipated benefits, particularly since 78 % of all clinical trials performed in the EU are conducted in a single-country setting (cf. Table 3 in the Annex to the Consultation Paper).

2.) Consultation Item No. 2:

Do you agree with this appraisal? Please comment.

Different assessments by Member States usually stem from differences in their respective legal frameworks, ethical opinions or medical standards. Assessment differences between Member States must thus not necessarily be related to the authorisation procedure, but rather to divergent ethical opinions. Plans to harmonise the Clinical Trials Directive in terms of the assessment of contents must take into account that each Member State has the right to apply higher standards of health care and to provide for higher national levels of protection for the safety of study participants as it deems appropriate. These givens are best served by a 'separate assessment'.

From the perspective of the German Medical Association, a proviso that the respective competent authority and ethics committee are permitted to make their own assessment and decision at the national level still is absolutely necessary (see also our response to Consultation Item No. 1).

Incidentally, the low acceptance of the harmonised authorisation procedure available through the VHP may be taken to indicate that the "difficulties created by independent assessments" represent a smaller obstacle than is often claimed.

3.) Consultation Item No. 3:

Do you agree with this appraisal? Please comment.

We agree with this appraisal. Separate assessments are essential to ensure compliance with ethical, national and local views on clinical trials, for example, in terms of national differences in the standard of care. Therefore, assessment and decision by the competent authority and the ethics committee of the respective Member State still are absolutely necessary.

The safeguarding of the clinical trial subject's protection is a key issue in the assessment and authorisation of clinical-trial applications (cf. recital 2 of the Clinical Trials Directive). The procedures for applications must conform to the Union's norms and standards, their implementing and supplementing national norms as well as the ethical opinions of the individual Member States. It is possible that the national provisions on the protection of clinical trial subjects are more comprehensive than the provisions of the Clinical Trials Directive (cf. Art. 3(1)).

We also share the concern that the complexity of the central assessment process could particularly discourage academic researchers, e.g. for reasons of cost.

4.) Consultation Item No. 4:

Is the above catalogue complete?

5.) Consultation Item No. 5:

Do you agree to include the aspects under a), and only these aspects, in the scope of the CAP?

We provide a joint response to Consultation Items No. 4 and 5 for tangible reasons.

(a) RE: Scope of the CAP

The German Medical Association expressly welcomes the statement in the preliminary appraisal of Section 1.3 of the Consultation Paper, which states that the establishment of a single submission process should hold to the basic rule that ethical issues fall within the jurisdiction of the Member States.

In Article 2(k) of the Clinical Trials Directive, an Ethics Committee is defined as:

"an independent body (...) whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection".

In this context, the German Medical Association doubts whether the procedural separation between the aspects under a) on the one hand and the aspects under b) and c), as proposed in the Consultation Paper, could be maintained on substantive grounds.

According e.g. to Article 2 of the Clinical Trials Directive, ethical assessment of a study application by the Ethics Committee is crucial to the protection of clinical trial subjects. In the procedure, this assessment cannot be separated from the scientific assessment of risk and benefit¹. Although a risk-benefit assessment is prepared by carefully weighing the

¹ The relevance and scope of the risk-benefit assessment is correctly paraphrased in Module 2, item 6 as "Research Ethical Considerations" ("Identify and state any possible problems that might occur. Present possible gain in knowledge to be obtained in the trial and its importance, possible risks for injuries or distress for the participants. Present your own evaluation of the risk-benefit ratio."). Compare the recommendations for a

foreseeable risks and anticipated benefits of the investigational medicinal product (e.g., based on evidence from pharmacological and toxicological studies, reports of previous clinical trials, ratings of clinical significance or quality issues), the analysis is ultimately descriptive.

A comprehensive decision on whether a clinical study is acceptable and the benefits justify the risks (cf. Article 3(2)a of the Clinical Trials Directive) can only be made taking into account the national legal and ethical requirements.

Risk-benefit assessment, which Article 6 (3) of the CTD defines as one of the responsibilities of the Ethics Committee, is essentially an ethical issue. It is inextricably linked with other ethical issues, particularly those mentioned under b) (informed consent, recruitment and reward). The necessary interdependence of the scientific and ethical assessments must always be considered when discussing administrative issues. Because the ethical positions of the Member States sometimes differ, valuation questions are not appropriate for a central decision. Moreover, the assessment of risk and benefits can vary greatly depending on national differences in medical standards, e.g. whenever a controlled trial involves a comparison against standard of care (standard of good practice) in a Member State.

In the context of different ethical perceptions in the individual Member States and different conditions for risk-benefit assessments by the ethics committee, it is imperative that the aspects specified in Section 1.3.1a) of the Consultation Paper – with the exception of the review of the requirements for manufacturing, importation and labelling of the investigational medicinal product – also be assessed at the national level by the ethics committees of all Member States involved in a multinational clinical trial. Therefore, these study aspects cannot be handled under a CAP, as is the case for the aspects in Sections 1.3.1b) and c).

The German Medical Association assumes that the European Commission does not intend to change the aspects that Article 6 (3) of the Clinical Trials Directive specifies for consideration by the Ethics Committee, which are exercised at the national level and are not centralised.

Still, the establishment of a CAP could be suitable to reduce the administrative burden and cost of the assessment/authorisation of multinational clinical trials. The following aspects mentioned in Section 1.3.1a) are appropriate for assessment in the scope of the CAP:

- compliance with the requirements for manufacturing and importation of the medicinal products intended for the clinical trial;
- compliance with the requirements for labelling of the medicinal products intended for the clinical trial.

To prevent arbitrary selection, a procedure based on objective criteria should be established for selection of the Reporting Member State.

(b) RE: Single decision as outcome of the CAP

The fifth bullet point on page 4 (Section 1.3) of the Consultation paper lists “a single decision per Member State” which would include the aspects assessed in the CAP, as well as the ethical/local aspects of a clinical trial assessment as an endpoint of the CAP. The wording here does not specify whether this single decision at national level would still allow for independent rejection by an Ethics Committee of a clinical trial application.

To ensure the safety of trial subjects in the EU, the ethics committees must still be permitted to assess the aspects specified in Article 3(3)(a) to (k) and to reject a request for approval of a clinical trial if necessary. Therefore, the concept of a single decision would apply only to the procedure by the national competent authority and ethics committee; it is crucial to ensure that decisions by the national competent authority on the one hand and the ethics committee on the other remain sovereign and authoritative.

The different perspectives on the clinical trial application afforded by the national competent authority and the ethics committee combine towards an effective protection for the safety of study participants.

This does not affect the existing rule under Article 7 of the Clinical Trials Directive, which states that “Member States shall establish a procedure providing, notwithstanding the number of Ethics Committees, for the adoption of a single opinion for that Member State”.

6.) Consultation Item No. 6:

Which of these approaches is preferable? Please give your reasons.

National differences in medical treatment standards must be taken into account when deciding on clinical trial applications so as to avoid equal treatment of essentially unequal conditions. It is crucial that risk-benefit assessment consider the recognised standard of treatment of a given disease, for example, when depriving a patient of a proven therapeutic method. The risk-benefit assessment must therefore remain within the ambit of the individual Member States (cf. our response to Consultation Item No. 5).

Differences in the standard of care in the 27 EU Member States are substantial. A majority vote or a decision by the European Commission or EMA (options 2 and 3) would lead to the introduction of a centralised decision on a clinical trial application (in slightly weaker form) by way of applying the CAP.

7.) Consultation Item No. 7:

Which of these three approaches is preferable? Please give your reasons.

As long as the scope of the CAP extends to the risk-benefit assessment without limitation (cf. item no. 5) and also includes other aspects to be assessed by the national ethics committees, then the German Medical Association cannot support the CAP overall for the aforementioned reasons.

However, if – as suggested – modifications are implemented to take into account national differences and the tasks of the Ethics Committee, Option 3 ('CAP is optional') would be preferable to the German Medical Association.

In accordance with our response to Consultation Item No. 6, it is a prerequisite that different decisions by the respective Member States are recognised.

Even optional use of the CAP should be limited to those clinical trials carried out in at least two Member States (according to the data in Table 3 of the Annex to the Consultation Paper, this applies to 22 % of the trials). This is supported by the principle of subsidiarity of EU law (Article 3b (1) and 3 TEU). On the other hand, the administrative costs for single-country clinical trial applications submitted under the CAP may exceed those of applications submitted in accordance with national regulations. Page 12 of the European Commission's 2009 Consultation Paper ("Assessment of the Functioning of the 'Clinical Trials Directive' 2001/20/EC") listed the administrative costs of clinical trials as one of the main reasons for a possible revision of the Clinical Trials Directive. Therefore, use of the CAP should be limited to multinational clinical trials in the EU.

As stated in our response to Consultation Item No. 5, some aspects of clinical trial authorisation are particularly well suited for a CAP, especially those pertaining to the quality and labelling of investigational medicinal products. The sponsor may not start a clinical trial in a Member State until the responsible Ethics Committee has issued a favourable opinion that includes an assessment of the appropriateness of the risk-benefit ratio.

Furthermore, it is doubtful whether there is sufficient need for regulation to justify introducing a mandatory general European procedure. Significant harmonisation of the decisions of individual Member States on multinational clinical-trial applications has already been achieved by the mere fact that the competent authorities of all Member States are obligated to abide by the European Commission and EMA guidelines as well as the Declaration of Helsinki as amended in 1996 when deciding on an application (cf. Article 288 (5) of the Treaty on the Functioning of the European Union as well as Article 3 (2) and Article 4 of Directives 2005/28/EC).

8.) Consultation Item No. 8:

Do you think such a pre-assessment is workable in practice? Please comment.

(a) RE: Tacit approval

The German Medical Association shares the opinion that a tacit approval is not appropriate. An explicit decision should be made in the interest of both the clarity of a granted authorisation and of the safety of clinical trial conduct.

(b) RE: Timelines

We have no fundamental objections to the introduction of fixed timelines. However, the timelines should be sufficiently long. It cannot be generally assumed that the assessment of amendments will invariably require less time, effort or diligence than the assessment of the original application. Some amendments affect only isolated aspects of a clinical trial, whereas others introduce far-reaching changes in the clinical trial that will necessitate a full re-assessment. It can be shown that short timelines lead to early decisions, but the quality of the decisions may be significantly impaired.

The period of 20 days for the assessment of substantial amendments that was introduced in German law has proved to be insufficient for the assessment of complex amendments. The German Medical Association therefore advises caution in the introduction of shortened timelines for assessing amendments.

(c) RE: Pre-assessment of 'type-A trials'

While a risk-adapted approach to the regulatory process appears attractive at first glance, some details of the proposed 'pre-assessments' are unclear, specifically:

- The criteria for 'insignificant additional risk' and 'normal clinical practice' are not defined well enough to make these determinations in a given concrete case. It is also unclear which authority should make these decisions.

According to Article 6 (3) (a) of the Clinical Trials Directive, it is up to the Ethics Committee to decide "... whether the evaluation of the anticipated benefits and risks as required under Article 3(2)(a) is satisfactory and whether the conclusions are justified". This decision requires a comprehensive assessment of the clinical trial, e.g. compared to the usual standard of care in the respective Member State in that concrete case, and is one of the core responsibilities of ethics committees. It is not clear how an *a priori* classification of a study as a 'type-A trial' could be achieved with reasonable certainty without a careful assessment of risks and benefits as described above.

- Regarding cases where a marketing authorisation for the medicinal product to be assessed has already been issued in a Member State, it is important to remember that the standards for the approval decision may vary in accordance with the medical standards in the respective Member State. Should this criterion be used, provisions should be made to ensure that the assessment takes place within the scope of the indication that the authorisation pertains to. Besides, it must be a prerequisite that a Europe-wide authorisation has been issued on the basis of Regulation 726/2004 or that

the product is authorised in all EU Member States in which the assessment is to be conducted.

- Past experience has clearly shown that – even at the time of their approval – the safety and clinical usefulness of new drugs often have not been fully evaluated in terms of patient-relevant outcomes. Some examples are listed below.
 - Rofecoxib (Vioxx[®]), a drug introduced on the German market as a painkiller in 1999, was withdrawn in September 2004 because of potential cardiovascular risks related to it, which became known after its approval. By that time, the active substance had become one of the best-selling medicinal products. After a critical evaluation of the entire class of drugs, other COX-2 inhibitors were later withdrawn from the market.
 - With the recommendation to suspend the authorisation for rosiglitazone (Avandia[®]), an oral antidiabetic agent from the new class of glitazone diabetic drugs, the EMA ended the reassessment in September 2010 due to the drug's unfavourable risk-benefit ratio (including cardiovascular risks) with the recommendation to suspend the authorisation.
 - The eventful history of metamizol, an analgesic well-known and controversial within the EU for many decades, impressively attests to the great variability in the assessment of its risk potential. It also demonstrates the difficulties in unanimously setting a risk level to drugs with a variable authorisation status.

These arguments and examples demonstrate that, apart from clearly identifiable criteria that already justify a risk-adapted exception for non-interventional trials (Article 2c), there are hardly any clear-cut general characteristics of 'low-risk trials' that could guarantee adequate protection of clinical trial subjects.

9.) Consultation Item No. 9:

Do you agree with this appraisal? Please comment.

We agree with this appraisal and the rationale behind it. Enlarging the definition of non-interventional trials should be avoided for reasons of the safety and rights of clinical trial subjects.

10.) Consultation Item No. 10:

Do you agree with this appraisal? Please comment.

We agree with this appraisal. It is not appropriate to exclude clinical trials from the scope the Clinical Trials Directive based on the nature of the sponsor.

11.) Consultation Item No. 11:

Do you agree with this appraisal? Please comment.

12.) Consultation Item No. 12:

Are there other key aspects on which more detailed rules are needed?

The German Medical Association has no fundamental concerns relating to more detailed regulations for the content of the application documents.

The introduction of risk-adapted guidelines and clinical-trial application dossiers that vary in content and scope depending on risk raise concerns regarding the protection of the rights and safety of study participants. The risk-differentiation of the CTD with respect to safety reporting is appropriate in its current form.

The assessment of risk to trial subjects in the context of a specific trial is one of the most important tasks of the competent authorities and ethics committees. The decision regarding the risks associated with a clinical trial is influenced by many factors in any case and can be made only on a case-by-case basis (cf. our response to the Consultation Item No. 4). Regarding the safety of trial subjects, it would be risky to reduce information or to shorten the time limits for decisions by the competent authorities and ethics committees in advance of an assessment.

13.) Consultation Item No. 13:

Do you agree with this appraisal? Please comment.

We agree that clarification of the terms 'challenge agent', 'background treatment' and 'rescue medication' is necessary. In the Consultation Paper, a concrete proposal is made based on references and cross-references between Directives 2001/20/EC and 2001/83/EC, and the term 'auxiliary medicinal product' is introduced. At first glance, it is not clear how this approach might simplify the existing rules. Instead, it would be preferable to incorporate a comprehensive definition in a revised version of the Clinical Trials Directive.

In doing so, it must be ensured that the medicinal products to be used as background treatments or rescue medications ('auxiliary medicinal products') in a clinical trial are subject to the provisions of Directive 2001/83/EC, i.e. that the safety and efficacy of these substances has been determined by the competent authorities. The authorisation of a medicinal product must be a necessary prerequisite for the use of the medicinal product as a background treatment or rescue medication, since only for authorised products sufficient data are available to allow for an adequate risk-benefit assessment and an effective planning of study design.

Especially in the case of 'challenge agents', the problem may arise that these substances are not approved for the indication for which they are used in a clinical trial. In this case, the required effect and its safety profile should at least have to be described in the authorisation process.

14.) Consultation Item No. 14:

Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

It is hardly possible to define, in general terms, which types of trials could be classified as 'low-risk'. Previous attempts at a definition do not seem to provide an adequate protection of trial subjects in all circumstances (cf. Section 1.3.4, Consultation Item No. 8). Therefore, a complete removal of insurance/indemnification requirements for trials presumed low-risk would not be appropriate. Instead, we recommend maintaining the current general insurance/indemnification requirements for all clinical trials.

The focus of these reform efforts is on lowering the costs of insurance. However, the existing requirements of the Clinical Trials Directive already allow sufficient latitude for risk-adapted assessment of insurance premiums. The possibilities for conducting risk analyses between sponsor and insurers are not yet being utilised to an optimal extent.

Moreover, the German Medical Association expressly opposes leaving the decision of whether a clinical trial is to be insured up to the Ethics Committees.

15.) Consultation Item No. 15:

Do you agree with this appraisal? Please comment.

We agree with this appraisal. Adherence to the concept of a single sponsor for clinical trials in the EU serves to ensure the safety and protect the rights of trial subjects.

16.) Consultation Item No. 16:

Do you agree with this appraisal? Please comment.

The ethical standards in the aforementioned international texts are not accepted in all EU Member States, particularly in relation to studies involving persons unable to give consent. Conversely, some Member States deliberately provide a more stringent standard or a higher level of protection of trial subjects. In particular, several Member States have not signed or ratified the 'Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine'.

To prevent instrumentalisation of a person unable to consent, it must not be possible to dispense with the requirement of informed consent in an emergency unless there is a reasonable chance of rescue, recovery or relief for the individual patient. There must be a chance of individual benefit. The following conditions should also apply:

- The benefit exceeds that of a tried and tested treatment

- The participant or his/her legal representative has not previously expressed objections known to the investigator
- The informed consent would have to be obtained from the trial subject or his/her legal representative as soon as possible.

The decision to conduct clinical trials in emergency patients must be made in accordance with the applicable national laws of the respective Member States. After revision of the Clinical Trials Directive, the option to include a person in an emergency situation in a clinical trial without the prior consent of his/her legal representative should not be allowed if it undermines the otherwise applicable ethical rules of the affected Member State.

17.) Consultation Item No. 17:

Do you agree with this appraisal? Please comment.

We agree with this appraisal.

18.) Consultation Item No. 18:

Do you have any comments or additional quantifiable information apart from that set out in the annex to this document? If so, you are invited to submit them as part of this consultation exercise.

We do not have any additional comments.