ARBEITSKREIS MEDIZINISCHER ETHIK-KOMMISSIONEN

IN DER BUNDESREPUBLIK DEUTSCHLAND

- DER VORSTAND -

The Permanent Working Party of Research Ethics Committees in Germany

Position Paper concerning the Revision of the 'Clinical Trials Directive' 2001/20/EC Concept Paper Submitted for Public Consultation SANCO/C/8/PB/SF D(2011) 143488 Brussels 09/02/2011

The Permanent Working Party of Research Ethics Committees in Germany (PWPREC) is the association of RECs (i.e. 'single opinion' RECs) in Germany. About 85% of all RECs in Germany are members. The Board of the PWPREC has circulated the Public Consultation Paper (PCP) among all its members and asked for comments. The Board of the PWPREC has approved this Position Paper.

The PWPREC highly appreciates that the European Commission (EC) involves all stakeholders in the discussion about the revision of the Clinical Trials Directive (CTD). In our Position Paper we focus on those issues only which are in the ambit of RECs in Germany.

The title of the revised directive should properly clarify its legal scope. To this end the title should be: Drug (or Medicinal Product) Trials Directive.

Consultation item no. 1

Technically a 'single submission' may seem to be easy but the inherent complexities should not be underestimated. For a multinational clinical trial all National Competent Authorities (NCA) and competent RECs have to be known and identified beforehand. As most RECs have layperson members whose proficiency in English may be seriously limited essential parts of the application have to be in the national language. In Germany the GCP Ordinance requires that all written Informed Consent materials and a synopsis of the trial protocol covering all essential parts of the protocol are provided in German. Thus it may be a quite complex task for the sponsor to submit centrally certain parts of the application in the respective national languages and for the central submission portal to redistribute these, and only these parts, to the competent national RECs. The offices of the competent RECs must definitely not be overloaded with synopses and IC material in languages they do not need. Furtheron the legal requirements concerning the insurance of research subjects and the protection of the research subjects with regard to trial-induced radiation exposure vary considerably within the EU Member States. Again, if there should be a single submission in the future the appropriate information and documents have to be provided Member State-wise. This is a considerable challenge. In

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our experience many applicants even now experience considerable difficulties in getting together the required information and documents for the national application. Thus we doubt that a single submission will greatly reduce the administrative work. A binding policy would be needed on how communication should flow between REC and sponsor in case of an incomplete application, a request for additional information, or an amendment. One should also consider having the option of a single submission only with regard to NCAs but not for RECs as ethical issues are not within the legislative ambit of the EU.

Consultation item no. 2

As ethics are not within the ambit of EU legislation and RECs are independent institutions, uniformity of the RECs' assessments across the EU Member States (MS) cannot be achieved. There are good reasons that all ethical and moral issues in the context of the REC's approval of clinical trials remain under the jurisdiction of the individual EU member states: cultural and ethical beliefs, historical experiences, legal system (e.g. tort law), legal practice, standards of medical care and the health care systems in the EU MS are too different to allow for a uniform regulation of ethical issues.

Consultation item no. 3

We fully agree with the appraisal as stated in the PCP that a central submission with subsequent central assessment is not appropriate, as the RECs' evaluation of the trial application has to be done *within* the EU MS, i.e. decentral. The protection of rights and well-being of research subjects in clinical trials has to take into account national health care and legal systems and ethical perceptions and traditions of the individual MS.

Consultation item no. 4

We seriously disagree with the current categories a, b, and c (see comments under Consultation item no. 5). In principle a catalogue should remain open to add points based on the ongoing experience in assessing clinical trial applications. As RECs we want to stress that not only the written information submitted to obtain informed consent (IC) is important, but the way how IC is asked for and documented, too. In addition, insurance issues and the communication of the conditions precedent and subsequent to liability are highly relevant as well.

Consultation item no. 5

We disagree with the current categories a, b, and c. It is the accepted obligation of a REC to assess the scientific quality of a clinical trial, to evaluate the risk-benefit balance for the individual research subject and, in relation to the relevance of the trial, for the benefit of health care too.

The CTD 2001/20/EU has thus specified in article 6 the tasks of the Ethics Committees, which must not be restricted.

The risk-benefit assessment is essentially an ethical issue. It cannot be separated from other ethical aspects (listed under b), and the necessity for a comprehensive, unified scientific and ethical review must not be ignored when

discussing procedural options. Among other factors, the potential benefit of the IMP for the research subject and the relevance of the trial for science and healthcare are part of the ethical assessment of *beneficence*. The assessment of risks and burdens has implications with regard to *non-maleficence*. Aspects of design (such as inclusion and exclusion criteria, control groups etc.) may be relevant to questions of *justice*. Finally, the risk-benefit ratio has implications for the exercise of *autonomy* and informed consent.

It is important to note that the ethical assessment of a clinical trial cannot be procedurally separated from a scientific assessment of risks and benefits and the scientific quality of the trial. Ethical considerations define the questions that the scientific assessment needs to answer. While the risk-benefit assessment needs to be prepared by a careful analysis of foreseeable risks and potential benefits (such as evidence from pharmacological and toxicological assessments, reports on previous clinical trials, an estimation of the clinical relevance, or aspects of quality), this analysis is essentially descriptive. The final comprehensive decision whether a clinical trial is *acceptable* is, however, ethical in nature. Furthermore, to check the completeness and adequateness of the information submitted to obtain informed consent the trial protocol and the investigator's brochure have to be assessed by the competent REC. In many MS these assessments are a part of the national legislation, e.g. in Germany. In addition, an overlap in the scope of assessment by the REC and the NCA is not a disadvantage with regard to the safety of research subjects: The assessor of the National Competent Authority (NCA), who is not necessarily a medical doctor, often has a different view, e.g. of the clinical part of a trial protocol, compared to an active clinician who is member of a REC. Only an experienced physician (many members of the RECs in Germany are active physicians) is able to assess the potential benefits, the risks and the feasibility of a trial protocol, given the eligibility criteria, the investigational and the control treatment, and the setting.

All tasks and obligations of RECs have to remain outside the CAP. In our opinion there is no need for the EU to regulate uniformly the scope of assessment for NCAs and RECs as long as the requirements regarding the careful and complete review of the application and time targets are met. Thus we definitely agree with the statement under 1.3. that …' it would be up to each MS to divide the tasks between the competent national authority and the Ethics Committee.'

The PWPREC is strictly opposed to the concept of a 'single decision' per Member State as mentioned on page 4 of the PCP. As RECs need to be completely independent it has to issue its statements – be it an approval or denial – on its own.

Consultation item no. 7

The CAP should remain optional. Thus it is up to the sponsor to decide which procedure is more appropriate for a given trial, e.g. monocenter trials or trials within one or a few MS only.

Consultation item no. 8

It could be practicable if the competent REC is involved in the pre-assessment. Only the REC should have the right to assess whether there is insignificant risk and burden.

Consultation item no. 9

There is little doubt that the CTD has introduced bureaucratic burden for trials without taking into account seriously enough the risk profile of the medicinal product and the vulnerability of research subjects. This 'one size fits all'-approach is not appropriate. We agree with the assessment of the PCP that the requirements are not risk-commensurate. More precisely, the CTD does not adjust its requirements with regard to the potential risks of a trial. In our opinion it makes a major difference whether a drug has been authorised in the EU already or not. When a drug has been authorised already, one can assume that the benefits exceed the risks, whereas if the drug has not been authorised one does not know. Therefore we recommend differentiating between authorised and non-authorised drug (use) as suggested under 1.3.4. of the PCP. The objectives of such trials are often very important, e.g. clinical endpoint trials. As authorised drugs are available for use anyhow (usually without any special requirements) it is hard to understand why the proper monitoring and documentation of the treatment and its outcomes should be 'penalized' by red tape, insurance, approval by drug authorities and the like. Such trials typically only involve risks which are close or equal to those of usual medical care. We recommend that the NCAs are notified about such trials and that RECs have to review such trials. We understand the reasoning of the EC if such low risk trials were covered by a broadened definition of non-interventional trials the conduct of multi-national studies would most probably not become easier. Thus we prefer to keep these trials within the CTD under the condition that their conduct is made considerably easier in agreement with the plans as outlined in 1.3.4. of the PCP.

At last, a final remark regarding this point. The current regulation is particularly contra-intentional in the areas of drug safety studies. Many drug safety studies need to be done in the 'real medical world setting' to find the inherent risks of drug use under the conditions of routine health care. When there is no intervention concerning the choice of an approved treatment in a study, there is usually no study specific medicinal product risk, which is discernible from routine health care. If there are no standardized specifications of diagnostic work-up and follow-up such a (scientifically invalid) study is considered a non-interventional study, which is not covered by the CTD. Just by adding standards for observation in a study, which carries no extra study drug-related risk for study participants (and may even improve patients' safety) this study is considered a clinical trial.

Consultation item no. 10

Yes, we agree. We are strictly against a risk differentiation based on the status of the sponsor. In the context of so-called academic or non-commercial trials it has to be realized that many of these trials are organized, logistically supported or even funded in part by a pharmaceutical company. The degree

of patient (or volunteer) protection must not depend on the status of the sponsor, i.e. a manufacturer or academic investigator, or on the status of a so called 'non-commercial study'; the only ethically and scientifically acceptable risk differentiation is based on the prior knowledge about and experience with a drug, and on the vulnerability of the patient sample.

Consultation item no. 11

There is certainly a need for more flexibility and thus to be able to respond faster once a deficiency has become obvious or new scientific advances have been achieved. We agree as long as the rules in the Annex are an advice and not an obligation.

Consultation item no. 12

We understand that there is a need for European standardization and harmonization of the rules governing medicinal product research to allow for the conduct of drug studies across Europe without undue difficulties. But even now the multitude of regulations, directives, notes for guidance, and detailed guidance is immense and almost unmanageable. Thus we recommend restraint.

Consultation item no. 13

We did not identify a problem with the definition 'investigational medicinal product'. The test substance, the active comparator and placebo are investigational medicinal products but not auxiliary medicinal products. While we agree that a clarification is needed with regard to challenge agents, rescue medication and background treatment, the proposed system of references and counter-references between Directives 2001/20/EC and 2001/83/EC and the introduction of an additional term (auxiliary medicinal product) do not help to simplify the rules for medicinal products. A clear definition within the CTD, expressly exempting challenge agents, rescue medication and background treatment as long as they have already been authorized for marketing in the EU, respectively that their safety profile is well known (challenge agents), seems preferable.

Consultation item no. 14

We prefer the option of reducing insurance/indemnisation requirements under the condition that low risk and low burden are assessed by a REC, and that the medicinal products are used within their authorized directions for use. Of course there has to be an insurance for harm that happened culpably in such cases, e.g. a general liability insurance as it is in Germany mandatory for physicians. The CTD should allow for a risk-adjusted insurance for studies with a very low but a still existing risk, too.

The option of having the MS to provide for indemnisation of damages during clinical trials could be considered as an incentive for a careless trial conduct as harm has to be compensated by a third party.

Consultation item no. 16

To limit the already mentioned complexity of laws and regulations governing medicinal product research we seriously ask to abstain from creating a completely new text. Thus we suggest that in such trials the assessment of risk and burden should follow e.g. the provisions of the 'Convention on Human Rights and Biomedicine' and its 'Additional Protocol concerning Biomedical Research' of the Council of Europe. A distinction between risk and burden is mandatory for trials with and without a potential direct benefit for the particular research subject. In this context we would like to stress that in some MS, e.g. in Germany , the legal options to include patients who are unable to provide informed consent are more restricted (due to specific historical experiences) than in other MS. The new CTD should allow for such a higher level of protection.

Consultation item no.17

We agree with this appraisal.

Consultation item no. 18

In the future, responsibilities and the position of RECs should be exclusively regulated by national law of the MS, too.

In our view the requirements for safety reporting have to be reconsidered, as outlined in our response (Item no.6) to the first public consultation of October 2009: The major problem with the current regulation of SUSAR reporting with regard to patients' safety is that the competent REC receives SUSARs only for those trials it has approved, and that it does not have any access or right to get informed about efficacy/effectiveness data. Thus a REC can only act appropriately if SUSARs evidently exceed the risks of disease or therapeutic alternatives. The current regulation of SUSAR reporting to RECs pretends to have a level of patient safety that is not justified by reality. Moreover, even 10 years after the CTD many sponsors do not follow the definition of SUSAR but are reporting either adverse events or expected reactions. Most RECs in Germany are not in a position, and do not intend, to actively monitor the safety data of all clinical trials in their field of responsibility. Thus it might be advisable to concentrate reporting requirements to the NCA as it oversees all trials of a certain drug and for all indications. A further option is to promote the use of Data Safety Monitoring Boards which are quite often established for long-term clinical trials. Their impact on safeguarding patients' integrity needs to be evaluated. However, the competent REC should receive a SUSAR- and safety-summary as they need to learn from experience. Independently of this the sponsor has to inform the competent REC of new aspects regarding risk/safety relations of investigational drugs which arise from the sponsor's continuous evaluation of all reports about adverse events and adverse reactions.

Annex – key figures 7.3 Number of incidences/level of damages

Finally we would like to comment on the statement of the "German KKS Netzwerk" of about only three minor liability cases in the last ten years: The "Insurance Working Group" of PWPREC organises annual meetings with

the insurance companies which are involved in the so called AMG-Versicherung, (drug trial insurance) and has been informed that every year about 80 - 100 new liability claims are under investigation. When liability is accepted in most of these cases the sum was low but in some very few cases an amount > 100 000 € has been balanced in recent years.

Certifying correctness

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