The Permanent Working Party of Research Ethics Committees in Germany

Comments 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

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. These comments submitted here have been seen and approved by all members.

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 statement we focus on those issues only which are in the ambit of RECs.

The title of the revised Directive should properly clarify its legal scope. To this end the title should be: (Clinical) 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 and competent RECs have to be known and identified beforehand. As most RECs have got layperson members whose proficiency in English may be seriously limited certain 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 materiel in languages they do not need. A binding policy is needed how communication should flow between REC and sponsor in case of an incomplete application, a request for additional information, or an amendment. If the CTD should finally ask for the availability of a single submission a pilot phase is definitely needed.

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: the cultural beliefs, the historical experiences, the legal system (e.g. tort law), the legal practice, the 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 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.

Consultation item no.4

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 too.

Consultation item no.5

We cannot agree 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. 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 too. Thus in many member states these assessments are part of the national legislation, e.g. in Germany. In addition an overlap in the scope of assessment 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, has often got 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 (and the majority of the 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.

All tasks and obligations of RECs should remain outside of the CAP.

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 got 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 two MS only.

Consultation item no.8

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

Consultation item no.9

There is little doubt that the CTD has introduced a considerable bureaucratic burden for trials without taking into account the risk profile of the medicinal product and the vulnerability of the 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 at all 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 approved already or not. When a drug has been approved already, one can assume that the benefits exceed the risks, whereas if the drug has not been approved one does not know. Therefore we recommend to differentiate between approved drug (use) and non approved 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 approved drugs are available for use anyhow (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 lots of 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 approve such trials. We understand the reasoning of the EC that 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 highly 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 risk, which is discernible from routine health care. If there are no standardised 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 which carry no extra study-related risk for the 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 one has to realize that quite a few 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 guidances, and detailed guidances is immense and almost unmanageable. Thus we recommend restraint.

Consultation item no.14

We prefer the option of removing insurance/indemnisation requirements under the condition that low risk and low burden are assessed by a REC. The option of having the MS to provide for an indemnisation of damages during clinical trials could be considered as an incentive for a careless trial conduct as the harm has to be compensated by a third party.

Consultation item no.16

The specific provisions of the additional protocol to the Convention on Human Rights and Biomedicine concerning biomedical research of the Council of Europe should be adopted. A distinction of risk and burden in trials with and without a potential direct benefit for the particular research subject is mandatory. To limit the already mentioned complexity of laws and regulations governing medicinal product research we seriously ask to abstain from creating a new text but to refer to the Council of Europe's additional protocol.

Consultation item no.17

We agree with this appraisal.

Consultation item no.18

The responsibilities and the position of RECs should be exclusively regulated by national law of the MS also in the future.

In our view the requirements for safety reporting has 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 the SUSARs only of the trial 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 the SUSARs evidently exceed the risks of the disease or of therapeutic alternatives. The current regulation of SUSAR reporting to RECs pretends a level of patient safety that is not justified by the reality. 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 the reporting requirements to the NCA as the NCA 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. Independent of this the sponsor has to inform the competent REC of new aspects regarding the risk/safety relation of the investigational drug which arise from his continuous evaluation of all reports about adverse events and adverse reactions.