ARBEITSKREIS MEDIZINISCHER ETHIK-KOMMISSIONEN

IN DER BUNDESREPUBLIK DEUTSCHLAND

- DER VORSTAND -

Statement of the "Permanent Working Party of Research Ethics Committees in Germany" concerning the Public Consultation Paper: Assessment of the Functioning of the "Clinical Trials Directive" 2001/20/EC of the European Commission.

The Permanent Working Party of Research Ethics Committees in Germany (PWPREC) appreciates the initiative of the European Commission (EC) to consider 'various options for further improving the functioning of the Clinical Trials Directive (CTD) with a view to remedy shortcomings and unintended negative consequences while taking the global dimension of clinical trials into account.'

All Medical Research Ethics Committees (REC) which are involved in the assessment of clinical trials in Germany (n = 53) are members of PWPREC. The board of PWPREC has circulated the Public Consultation Paper (PCP) to all its member RECs and asked for comments.

Our statement mainly focuses on issues that are highly relevant to RECs. We use the notation of the PCP to ease understanding.

Major comments

The PCP discusses many important issues but does so in a biased way. Although ethical issues get attention it is evident that its major concern is to speed up the process of getting a clinical trial approved at almost all costs. The 'bad guys' are the National Competent Authorities (NCAs) and the RECs and to 'prove' their point the PCP publishes questionable data.
One example: The PCP states that there are about 1900 RECs involved in the assessment of clinical trial applications in the EU. The cited reference does not support that number, e.g. Italy alone contributes 1065 ECs, and the ICREL-report mentions that many of these Italian Ethics Committees are rarely (or even less than once per year) involved in the assessment of clinical trials.
With regard to further references to the ICREL-report one has to keep in mind that the response rate to the ICREL questionnaire was just 7.34%. Such a low response rate does not allow for any valid conclusions.

It would be very helpful if the terminology used would follow the accepted standards of science.
Currently the usual word choice of the EC often causes confusion, e.g. the word trial should only be used for experimental research and designs like the randomized trial. Non-experimental research should be called a study. Non-intervention in the EC terminology refers to specifications in the study protocol concerning the therapy/treatment, the diagnostic work-up, and the monitoring/follow-up of the study participants, whereas in the scientific literature the term non-interventional study covers all observational studies, e.g. cohort study, case-control study, cross-sectional studies, although all these study designs standardise diagnostic

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work-up and if appropriate, the follow-up. A study should be called interventional only if the treatment is specified in a study protocol.

The short title 'Clinical Trials Directive' is often misunderstood in the sense that the CTD covers clinical trials of all kinds. To avoid such a misunderstanding it should be changed to Clinical Drug (or Medicinal Product) Trials Directive.

The Note for Guidance: Good Clinical Practice(GCP), both of the EU (1991) and of the EMEA/ICH (1997), asked that it should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. One has to keep in mind that there are many studies and trials that do not intend to do so. The legislation of many MS has however adopted the GCP–standard for basically all drug research (with the exception of non-interventional studies) thus there is a conflict with the constitutional right of freedom of research. The public consultation should thus result in a rational limitation of the ambit of the CTD to those areas where the rights of the research subjects have to be protected by the EU and the data are intended to be submitted to NCAs or to the EMA.

3.4 Options to address the issue as regards the assessment by ECs.

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, and the health care systems in the EU member states are too different to allow for a uniform regulation of ethical issues.
It is an accepted task and responsibility of the RECs to provide public assurance that the rights, the safety and the well-being of human subjects involved in a trial are protected. To accomplish this task the REC has to respect the hard and soft laws and regulations, and the cultural traditions which are present in its ambit.
As standardised procedures will influence the perception of a REC's tasks and its performance any regulation of the work of RECs falls within the ambit of the member states. The principle of subsidiarity requires that there is an evident need for the European Commission to intervene. However the PCP does not provide any substantive evidence that such a need exists. Finally we doubt that there is any conclusive evidence that there are procedural best practices which equally apply in all member states.

3.4.1 One-stop shop for submission of assessment dossier.

Although the concept of a one-stop shop sounds compelling, there may well be considerably less advantages than expected at first glance, and more obstacles to overcome.
First of all there are highly detailed legal and regulatory requirements in Germany which documents have to be submitted to the RECs (see the German GCP-Ordinance). These requirements of the GCP-O are of course based in large part on the CTD but also on the national legal regulations (e.g. drug laws, liability laws), legal practice and experience with clinical trials. In addition the German GCP-Ordinance clearly defines which documents have to be submitted specifically to the NCA and which to the RECs. Most probably such

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requirements, but partly different ones, exist in other countries too. Beyond that, this concept might interfere with Article 5(3) of the German Constitutional Law in terms of an unnecessary and inappropriate restriction of constitutionally guaranteed freedom of research in the academic field. Thus a single dossier for all EU member states poses serious problems.
Second there are single centre studies where only one REC has to be consulted. What are the advantages for the investigators in such a situation to submit their dossier to a central European data bank?
The introduction of a one-stop shop may cost considerably more than expected if the additional resources that are needed by all those who are involved in the process are properly calculated. Thus we recommend to prepare a sound calculation of costs first.
Finally clinical trial dossiers contain highly confidential information. However electronic transmissions via the internet are far from being safe and confidential.
In conclusion based on the arguments outlined above the plan of one central one-stop shop within all EU member states either for RECs or even for the NCAs is clearly rejected.

3.4.2 Strengthening networks of national Ethics Committees involved in multinational clinical trials.

Since 1983 the RECs in Germany have increasingly strengthened their cooperation. Since many years all 53 RECs are member of PWPREC. Although the RECs have different responsible bodies like universities, medical associations or the state government, considerable standardisation and harmonisation of procedures and workflows have been achieved. All RECs use the same application forms, letter templates etc. There is even a consented recommendation for the structure and content of the written patient information which is needed for the informed consent procedure. Since 2008 PWPREC offers regularly continued education seminars for members of RECs. There is a webpage (www.ak-med-ethik-komm.de) which provides transparency and access to all relevant documents and to the minutes of its semi-annual meetings.
The Federal Government which evaluated the effects of the Directive in Germany in 2008 highly appreciated the work of PWPREC and stated that the implementation of the CTD into German Drug Law and the GCP-Ordinance was successfully handled by the RECs and that the work of PWPREC was highly instrumental in this result.

We appreciate any promotion of a closer communication with our European counterparts to learn about their views and experiences. There are considerable doubts however that a direct cooperation of RECs of different countries within the process of assessment of requests for clinical trials applications makes sense:
First of all, the deadline for issuing the judgement of the competent REC is comparatively short in Germany: 30 calendar days for mono-centre studies and 60 calendar days for multi-centre studies. Most RECs – most probably not only in Germany – work on an honorary basis and meet about once a month. It is difficult to imagine how a 'close cooperation' with a couple of RECs in other member states should work, given these time constraints. One should not forget the language problem either. In addition the legal requirements, cultural habits and preferences, and medical expertises vary so much in Europe that it is difficult to imagine that there will be relevant additional value. To give just an example: Given the German history the willingness to accept trials with non-competent patients is definitely highly limited. The same is true – to a

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somewhat lesser degree – with placebo-controlled trials. Finally the prevailing case law demands highly detailed information of the patients about inherent risks of treatments, even if they occur very rarely. These national peculiarities have to be known and respected by the competent REC and cannot mediated by cross-national cooperation. The RECs have to respect the international and national laws, regulations, the legal practice and the cultural attitudes and beliefs.

3.4.3 Clarifying the respective scope of assessment of NCA and Ethics Committees

In our experience the scope of assessment by the NCAs (in Germany the BfArM and the PEI) and by the RECs has been satisfactorily clarified by the 12th and 15th Amendment of the German Drug Law (of 2004 and 2009) and the GCP-Ordinance. Again we think that the subsidiarity principle has to be adhered to and the EC should only act if there is evidence that intervention is needed. In addition an overlap in the scope of assessment is not necessarily a disadvantage: The assessor of the NCA, who is not necessarily a medical doctor, has certainly got a different view of the clinical part of a trial protocol, compared to an active clinician who is member of a REC. Only an active 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.

Summary

In Germany all RECs are members of PWPREC. There is an extensive communication resulting in highly standardised and harmonised procedures. A one-stop shop for submission of assessment dossiers will not work given that the national requirements for documents and records differ due to different national laws, jurisdiction and prior experiences. Communication among RECs of different member states should be promoted, and a certain amount of harmonisation on a voluntary basis might be achievable. Any attempts to limit the independence of RECs have to be avoided however. At least in Germany there is no need for the EC to clarify the respective scope of assessment by the NCA and the RECs. All ethical and moral issues that pertain to the independent REC's approval of a clinical trial application should remain under the sole jurisdiction of the individual member states.

Additional comments

2.4 Sponsors involved in clinical trials

Individual researchers who act as sponsor and investigator at the same time have been forgotten. But for investigator-initiated trials this combination is typical.

2.4 Authorisation by national competent authorities and Ethics Committees

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The term "authorisation" in connection with Ethics Committees is not correct; it should be deleted in the whole PCP. Ethics Committees are entitled to give a "favourable opinion" as defined in Article 9 of the CTD. This different wording underlines the different positions and responsibilities of the NCAs and of the Ethics Committees.

Item 1

In Germany even before the CTD all clinical trials with drugs had to be seen and judged by a REC prior to its start. The CTD and its implementation into the German Drug Law has certainly formalized and bureaucratised the application and assessment procedures but has strengthened the position of the RECs too. We have little doubt that from a formal point of view the CTD has helped considerably to improve the quality of trial protocols and informed consent forms. However we are not aware of any study that has shown that these improvements resulted in an improved protection of the patients.
Besides the formal requirements of the CTD to be followed by all parties (sponsor, investigator, NCA, REC) there exist examples which indicate an improved protection of the subjects in clinical trials, e.g. in studies with minors or handicapped persons the risks or burden have to be reduced to the minimal possible level or even to an absolute minimal level. This, for example, limits blood collection in placebo-controlled, double blind trials or other protocol-related invasive investigations.

In this context one has to mention that since the implementation of the CTD in Germany only one REC is reviewing the application dossier in detail, e.g. the trial protocol and the written informed consent documents. If this REC fails in its assessment for whatever reason neither the CTD nor the German Drug Law provides any means to correct it. Prior to the CTD all applications for multi-centre trials had been reviewed by at least two RECs which is certainly a safer procedure than the current one.

Item 2

We cannot comment about 'diverging assessments' by the NCAs but we like to emphasize that in Germany the scope of the assessment by the NCAs and the RECs is clearly defined by the German Drug Law and the GCP-O.

Item 3

A non-uniform beginning of a trial in the various member states (MS) is typically due to many reasons, not only 'divergent assessments'. Many pharmaceutical companies obviously experience difficulties regarding harmonisation of their procedures and recruitment of centres. In addition there seems to be a lack of adequately trained staff (at CRO- and sponsor-level) which often causes avoidable delays. We provide two examples which support our assumption:

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One large REC in Germany did the following analysis: mean processing time for multi-centre trial applications (n=160) of the REC from submission dossier in – final vote out: 36 days. Mean waiting time for sponsor's response (if REC asked for additional information): 44 days (range: 13-150).
Very few applications (< 10%) pass the REC without requests for modifications. Many of these could be avoided if staff was better qualified, e.g. very often the written patient information pursuant to the insurance law is not in agreement with the German law.

We did not understand the sentence "This leads to a situation where the time-lag between the finalisation of the clinical trials protocol and the 'first patient in' becomes unnecessarily long." (p. 13). In our understanding a trial protocol can only be considered as 'final' if it has been positively voted by the competent NCA and REC. This sentence is a further example for the biased presentation of the PCP.

The last sentence of this bullet point is misleading: RECs do not want to deny access to new, innovative treatments. However 'new' and 'innovative' does not automatically mean 'effective' and 'safe'. That is why it is the legal and ethical task of the RECs to safeguard the patient's rights and integrity when drugs are used whose effectiveness and safety profile are not known yet.

There is a positive side too from these diverging starting points: first experiences with the new drug and the trial protocol can be gained and in case that there are some serious risks not too many patients have already been exposed.

Item 4

The scientific and ethical assessment of a trial application dossier may indeed differ between MS and rightly so, as the accepted medical standards differ too. Many trials, e.g. in pain, involve a placebo control group. For ethical reasons a rescue medication has to be provided. But the chosen rescue medication may not be the accepted standard in all MS, or an active control might be deemed as inferior in some MS but not in all, e.g. based on national treatment guidelines. It is well known that co-medications vary to a large extent from MS to MS, too. Such co-medications may seriously impact the balance of risks and benefits.

Item 6

We agree with the description of the reporting of SUSARs. In our assessment about 80% of the 'SUSARs' that are reported to the German RECs do not fulfil the legal definition of a SUSAR as they are either not serious and/or not suspected side effects and/or not unexpected. The required causality assessment by a qualified person is often missing too. We have discussed this issue repeatedly with representatives from the sponsors (i.e. the pharmaceutical industry) with very little effect. The current unsatisfactory situation may be due to a lack of qualified staff at the sponsor, and to the practice to minimize liability risks by reporting every adverse event.
The situation concerning 'substantial amendments' is basically similar.

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We doubt that it is a wise decision to get non-interventional trials (better: studies, NIS) covered in the future by the Community legislation on pharmacovigilance. Pharmacovigilance is typically focussed on safety issues, whereas many NIS are not.
As 'current medical practice' varies, and will vary in the future too among the MS, it is only consequent that the borderline between a clinical trial and a NIS is drawn differently in individual MS. To reduce the size of this problem we strongly recommend to modify the current definition of a NIS in the CTD Article 2 (c) 3rd sentence: No *risky or burdensome* additional diagnostic or monitoring procedures shall be applied to the patients and…….

Item 7

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.

Item 8

We do not recommend to adopt the CTD as a Regulation. As has been stated many of the problems seen with SUSARs and substantial amendments are due to conditions which will not be modified by a Regulation. We are also afraid that a regulation will result in a lower level of patient safety than the current level achieved in Germany. What is definitely needed is more qualified staff at the sponsors and more continued education and training.

Item 9

We agree with the assessment of the PCP that the requirements are not always risk-commensurate. More precisely, the CTD does not at all adjust its requirements with regard to the potential risks of a trial. In our

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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).

A drug use is authorized if the approved indication, dosage, and duration of use are adhered to. 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, but that they are not covered by the CTD.

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.

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.

As the most absurd example for the non-sensical and unintended negative consequences of the CTD we received this report from one of our member RECs: About 15 years after the approval of a drug (typically used for senior patients) there was a signal raising the suspicion that the drug may cause an excess mortality. The manufacturer planned a cohort study to check the validity of the signal. Eligible for the cohort study were only those patients who had been treated with this drug prior to approval in phase II and Phase III-studies about 15 years ago. These former trial participants respectively their relatives should be identified by the then investigators and their survival status should be notified, and compared with an appropriate control group. According to the CTD this study was considered by the legal representative in the REC as a trial, as the assessment of the survival status is not part of 'current medical practice'. Thus an insurance was needed although there was no study-related drug administration and many of the former participants were already dead!

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Item 11

With regard to SUSAR reporting see comments for Items 6 and 7. In addition we recommend that SUSARS of drugs which have been approved since a certain time period, e.g. 2 years, should be reported to the NCA only.

Item 13

One should not forget that the scope of the Note for Guidance: Good Clinical Practice for Trials on Medicinal Products in the European Community of the EC in 1991 focussed explicitly on trials and data that were meant for drug authorities. The same is true for the Note for Guidance on Good Clinical Practice ICH Topic E6 of 1997. As many investigator-initiated trials do not have this objective but try, e.g. to optimise the administration of approved drugs in the treatment of cancer , the red tape burden for this type of trials should be reduced. Thus we recommend to add to the definition of a non-interventional study of the CTD …No *risky or burdensome* additional diagnostic or monitoring procedures shall be applied to the patients…. See comments for Items 6 and 9 too.

Item 14

We agree with the objectives of the Pediatric Regulation EC 1901/2006. However more time is needed before a sound evaluation of its implementation can be performed.

Item 15

There is no doubt that patients in medical emergency situations have a right to receive evidence-based medicine of the highest standards, too. We are aware that there are considerable problems in many countries to perform a randomized trial with emergency patients. We do not think that a regulation concerning emergency clinical trials in a uniform manner for all MS will be very helpful at present. We rather think that there is a need for public discussion about this issue in those countries which do not have an appropriate solution yet, so people can raise their concerns. Only then a solution can be found which is acceptable and does not harm the trust of the people in the ethical soundness of experimental therapeutic research.
The Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research contains in its Article 19 a specific provision. In force as an international legally binding instrument of the Council of Europe, this protocol should be listed in an appropriate rank.

Items 16 and 17

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We appreciate the fact that the PCP discusses ethical issues of clinical trials in third countries. As PWPREC has got little experience in this field, and as it is a complex matter, we are hesitant to be very specific. It may suffice to say that we will support any action that will benefit the protection of research subjects in third countries. The EC should help to establish and to sustain qualified and independent RECs wherever they do not yet exist. Qualified and truly independent RECs are the major guarantor that the rights of the research subjects are protected in clinical research.
The already mentioned protocol concerning biomedical research has a specific provision covering research in countries of the 3rd world: Article 29 "Research in States not parties to this Protocol".

Certifying correctness

28 December 2009

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