

Comment of the Network of Coordinating Centers for Clinical Trials (KKS-Network), Germany

on the

Concept Paper Submitted for Public Consultation on 09/02/2011 Revision of the Clinical Trials Directive 2001/20/EC

The KKS-Network, which is the German network of academic clinical trial units, welcomes the Public Consultation Paper of the European Commission concerning the Revision of the Clinical Trials Directive 2001/20/EC. We are grateful to be able to provide input into the current discussion process. Furthermore, we very much appreciate, that the comments of the academic clinical research community which have been provided in the previous years, have been taken into account when preparing this consultation paper.

General remarks to the Consultation paper:

We would advise to currently stick with the scope of the directive as it is and would only include clinical trials with medicinal products. If – after a period of testing after the implementation of the revised Directive – it has been shown that the new processes work, the scope of the Directive could in a second step be extended to encompass e.g. clinical trials with medical devices, trials with radiation therapy.

The consultation paper in its current form does not stress the procedure of ethics committee approval. In our view it is essential, that this process is included in the thoughts for the revision of the Directive and a possible restructuring of processes to receive maximal benefit of a revision of the directive – e. g. one could think of building up some kind of voluntary harmonisation procedure of Ethics committees of the different Members States. Some of the appraisals should therefore be looked at with respect to the addition of ideas concerning the streamlining of the process for EC-approval.

1. COOPERATION IN ASSESSING AND FOLLOWING UP OF APPLICATIONS FOR CLINICAL TRIALS

1.1. Single Submission with separate assessment

Consultation Item 1

A single submission of the relevant documentation to one single portal would reduce the administrative burden on the sponsor significantly. We would therefore welcome the preliminary appraisal for a single submission of the necessary documentation through a single EU-portal. This should encompass the documentation for application to the Competent Authorities as well as for the submission to the Ethics Committees; the idea of a single portal should be accompanied by the harmonisation of the format and contents of the documents to be submitted to the EC and the Competent Authorities in all Member States. No additional national documentation should be needed.

Furthermore, the formal procedure concerning how documents have to be sent to the portal needs to be defined.

Except for clinical trials which take part only in one country (submission in the language of the Member State concerned), the documents should be sent in English.

Consultation Item 2

Even if a single submission with a separate assessment already would mean a huge asset, i.e. if this would be accompanied by an harmonisation in the documents needed for the trial application in all Member States (s. o.) we agree that a separate assessment would still account for differences in the interpretation of the Directive and furthermore could lead to diverging results of the assessment procedure.

We would therefore support the idea to implement a coordinated assessment procedure for the competent authorities when revising the Directive.

1.2 Single submission with subsequent central assessment

Consultation Item 3

We agree with the appraisal. We do not see that a central assessment would be a workable option at present. We would also have the fear that such a procedure would lead to delays in the approval of clinical trials.

As discussed at the stakeholder meeting already the number of clinical trials to be assessed per year (approximately 1200 clinical trials, not to name the number of amendments to the protocols) shows that such a central assessment is currently not practical. It would have to involve a huge underlying infrastructure, which does not yet exist. This would also mean increasing costs, which is not manageable for academic trials.

Furthermore, most of the trials are not conducted in all Member States so it does not make sense to include all MS in the assessment procedure.

The option could be something to be discussed in the longer term.

1.3. Single submission with a subsequent “coordinated assessment procedure” (CAP)

We welcome a single submission of a harmonised set of documents with a subsequent “coordinated assessment procedure” by the competent authorities as a good option to improve the current process.

We welcome that such a “coordinated assessment procedure” would only include the Member States in which the trial is conducted and that there is the possibility to take account of the local / ethical aspects (which should not mean different documents to be submitted – see consultation item 1). This allows for a joint assessment without needing a “cumbersome” infrastructure, although the structure behind has not been discussed in the paper. The procedure should include concepts of Member States which have proven to be good – e.g. clock stop to clarify items / to ask for more information etc.

Instead of the involvement of all concerned Member States in the assessment procedure of a clinical trial, one could also discuss whether a kind of MR-procedure might be a second option.

A CAP-procedure would only be good and workable, if it does not imply additional burden for the applicant but would lead to quicker and more harmonised process. We therefore find it important to define what would be the “outcome” of the process and what the scope should be. We therefore think it should be defined in the Directive which tasks in the assessment are belonging to the assessment by the CA and which to the assessment by the EC.

Furthermore, there are aspects in the assessment conducted by ethics committees which could also be considered to be done in a coordinated procedure of the ECs of different Member States – may be in the first instance on a voluntary basis.

We would plea that the CAP and the assessment by the ethics committees can run in parallel as it is currently the case. It needs to be defined, though, what process should be followed in case of divergent votes.

1.3.1. Scope of the CAP

- a) Risk-benefit assessment:
- b) Ethical aspects related to informed consent, recruitment and reward
- c) Local aspects related to suitability of sites, the investigators and national rules.

Consultation Item 4

The catalogue seems to be nearly complete; it could be discussed whether the procedure for informed consent in emergency situations should be added under b or a.

Consultation Item 5

We in general agree to include the aspects under a) into the CAP-procedure. But risk-benefit comparison is also one of the most important tasks of ECs - it can not be only mentioned as a task for the Competent Authorities.

Also, we find it difficult to include the comparison to normal clinical practice into the scope of the CAP as this will vary in the different Member States. On the other hand it would be useful to do this, i.e. for paediatric trials where there exists a lot of off-label use which is normal clinical practice.

In the longer term, one should also consider some kind of harmonised coordinated procedure of ECs.

1.3.2. – Disagreement with the assessment report

Consultation Item 6

The first option leaves the most possibilities to the Member States and would therefore as a first step be the best option in our view. It also provides Member States to opt out when they are not convinced of the quality of the clinical trial assessed.

Furthermore, it opens the easiest possibility to include new sites after the trial has already started, if no sites in that Member State are already participating in the clinical trial. It would not be necessary to repeat the whole procedure, the “new” MS could decide to agree with the assessment report (what would mean that – if EC approval is also obtained – that the site could be included) or the Member State could decide to opt out and then no participation is possible. We would find it important to define timelines for this.

Experience of the Voluntary Harmonisation Procedure could be taken into account when structuring the process.

1.3.3. – Mandatory / optional use

Consultation Item 7

In our view it seems to be the best to start with option 3 where the CAP is optional up to the decision of the sponsor. In the midterm, the CAP could be made mandatory for all multinational trials.

However, a single portal and the format of the documentation for assessment should be harmonised independent of whether a CAP-procedure is used or not. This would also make it easier to extend a national trial to other countries. But it should be possible that documentation for national trials can be submitted in national language.

1.3.4. – Tacit approval and timelines

Consultation Item 8

A pre-assessment could be practical but there would need to be a very well defined process to make it not more complicated than the normal procedure. Furthermore, it would also need to involve timelines for ethics committee approval to be of any benefit.

There are some important questions to be answered: Who would perform the pre-assessment? What information / documentation are needed for a pre-assessment and what are the timelines for the pre-assessment? If this is not carefully regulated, it could lead to an additional burden for the sponsor. The procedure involved has also to be set into relation with the time that can be saved via this procedure. A pre-assessment procedure for special types of studies does only make sense when it can be done within 12 up to maximum of 30 days.

Regarding the classification:

- a): “part of a standard treatment in a Member State concerned”: is this feasible and how would standard treatment be defined? – may be this would need to be the case in all Member States concerned if it is under the CAP. It might be helpful for paediatric studies.
- b) What is an insignificant additional risk? – We would prefer to stay in the terminology of the directive, e. g. minimal risk (see: group benefit in clinical trials with children). What is “normal clinical practice”?

A further question is whether the classification does only have influence on timelines. What might be more important for those studies would be a risk adaptation of the requirements involved in the approval and conduct of the trial, as those are connected to costs.

At present, concepts for a risk-based approach are discussed in several groups (see ECRIN assessment; reflection paper to be prepared by the Inspectors working group; ideas developed in the OECD Global Science Working Group to facilitate multinational cooperation in non-commercial clinical trials) – those ideas should be taken into account when drafting a process.

2. BETTER ADAPTATION TO PRACTICAL REQUIREMENTS AND A MORE HARMONISED RISK-ADAPTED APPROACH TO THE PROCEDURAL ASPECTS OF CLINICAL TRIALS.

2.1. Limiting the scope of the Clinical Trials Directive

2.1.1. Enlarging the definition of non-interventional trials

Consultation Item 9:

We could – under certain circumstances - agree with the appraisal. The trials mentioned are very important and currently are not only suffering from the degree of non-harmonisation, but also from the requirements, which have to be fulfilled (e.g. insurance cover). If those trials are kept under the scope of the directive, a risk based approach for the regulation of those trials is needed. If such an approach would not be followed, those important trials might not be conducted in sufficient number in future because of the financial constraints involved in the requirements.

This would mean if a risk based approach can not be adopted, we would urge that the definition is widened.

2.1.2 Excluding clinical trials by “academic/non-commercial sponsors” from the Scope of the Clinical Trials Directive

Consultation Item 10:

We do not find it acceptable to have two different standards for clinical trials dependent on the sponsor who takes over the responsibility for the trial and therefore agree with the appraisal. The safety of patients should not be dependent of who the sponsor of the trial is. Patients need to be able to rely on that the standards defined are fulfilled when they agree to participate in a clinical trial.

The standard of clinical trials and the quality of conduct has improved since the implementation of the Directive, which should not be forgotten.

What we find important, however, is to implement reasonable conditions / procedures and to reduce administrative burdens wherever possible and to enlarge the financial support for non-commercial (academic) clinical trials. This is especially important for the conduct of large Comparative Effectiveness trials or multinational trials in orphan diseases where there are often only 1 – 2 patients who can be included into the trial per site.

2.2 More precise and risk-adapted rules for the content of the application dossier and the safety reporting

Consultation Item 11:

Yes, in general this appraisal would be of help we would agree. It is important however, that the detailed provisions are binding for the Member States, as the harmonisation will otherwise not be achieved.

Consultation Item 12:

Ethics committee approval (technical / procedural aspects) – need to be binding for the MS Report

2.3. Clarifying the definition of “investigational medicinal product” and establishing rules for “auxiliary medicinal products”

Consultation Item 13:

Yes.

2.4. Insurance / indemnification

2.4.2 Policy options

Consultation Item 14:

A combination of both options seems to be needed:

Policy option 1 should be followed for those trials mentioned (Phase IV) – In Germany the German drug law will very likely be changed accordingly during the next year.

The preferable option, however, would be, that the Member States take over the insurance / indemnification for academic sponsors. This option would only pose a small financial risk on the Member States. This option would also solve the problems for a lot of important paediatric trials in which clinical standard arise often medicinal products used off-label. How this option could be realised would need thorough discussion.

2.5. Single Sponsor

Consultation Item 15:

Yes, we agree with this appraisal, as long as there is true harmonisation of the regulatory framework.

2.6 Emergency Clinical Trials

Consultation Item 16:

We agree with the appraisal in the way that research in such a population should be made possible. We would recommend to implement rules under which such consent could be postponed – there are several examples in the different Member States that could serve as a model (e.g. different models used in Germany; see: FDA Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors; Exception form Informed Consent Requirements for Emergency Research; March 2011).

We would recommend that the process is described in detail so that a harmonisation will take place.

It should be taken into account that for some research conditions no legal representative exists; it is therefore also important to define a procedure for those cases, e.g. whether and also how a legal representative should be appointed.

It is also important to lay down rules how data, which have been collected before a possible non-consent (refusal of consent of the patient) can be used for the analysis of the trial, because this otherwise might lead to bias.

3. ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

Consultation Item 17:

Yes.

4. FIGURES AND DATA

Consultation Item 18:

No

ADDITIONAL GENERAL REMARKS:

The consultation paper is focussing on very high level general aspects, even if those are of more technical nature and more detailed than in the previous consultation. It is therefore important, to involve the stakeholders when drafting the more detailed technical document.

There are aspects not mentioned in the concept paper which need revision. We would therefore very much appreciate, if the following aspects could be looked at when drafting the revised document:

- Manufacturing (article 4, second paragraph, second bullet point / 2005/28/EC; limitation regarding simplified requirements for labelling of IMPs)
- SAE-Reporting - adaptation to the guidance document: Reporting of SUSARs to ECs only in form of line listings twice a year, except in special circumstances; with respect to reporting to the investigator: Clarification that notification is only to the investigator who is the leader of the team.
- Provision of Start of clinical trials in trials with orphan drugs (inclusion of new sites)
- Participation of people not able to give informed consent when there is a benefit for the group of patients that is to be included (adapt to conditions for participation of minors – article 4, recital 4)
- To include changes / requirements for ethics committee approval into the revision process.