Comments of the University-based Network of Coordinating Centers for Clinical Trials (KKS Network), Germany, on the Public Consultation Paper of the European Commission on the Functioning of the Clinical Trials Directive, issued 09th of October 2009

General Comments:

The Network of Coordinating Centers for Clinical Trials (KKS-Netzwerk) in Germany is committed to the safety and welfare of the patients during the conduct of clinical trials but also during their treatment in usual care. For this reason, we welcome the step forward in the quality of clinical trials which has been established with the implementation of Directive 2001/20/EC. But for the same reason we welcome the initiative of the European Commission to look at provisions which hamper clincal research i.e. in the field of academic research and which - by hampering this research – also hamper the safety of patient treatment. The consultation paper is a step towards saving the positive provisions of the Directive on the one hand and on the other hand changing those parts of the Directive and the implemtning texts which have turned out to be counterproductive.

The KKS network very much appreciates the proposals for solutions provided in the consultation paper concerning the difficulties and unnecessary provisions / administrative burden involved in the implementation of the so called Clinical Trials Directive 2001/20/EC in the different Member States. We thank the European Commission for carefully listening to the problems identified by the different stakeholder groups during discussion processes during last two years and for taking them seriously.

Being part of the “non-commercial” party of the clinical trial community, we anyhow would not support the introduction of a set of two different standards for the conduct of clinical trials (commercial – non-commercial), but favour to introduce a risk-based approach in European legislation for clinical trials. Furthermore, if the future shows that the envisaged changes in the Directive and the implementing texts have led to further harmonisation between Member States and to a reduction in unnecessary administrative burden, we would recommend that the legislation for the conduct of other clinical trials (e.g. with medical devices) would also be harmonised accordingly in a second step.

We thank the European Commission for the possibility to comment on the consultation paper, the comments are provided below. As quantification regarding the different aspects has already been provided in the initiatives which form the basis of the proposals this has not been repeated here.

Consultation item 1:

Yes. The standards for the conduct of clinical trials have been raised since the implementation of the Directive. Sponsors have introduced internal audit procedures and increased monitoring. With this it is possible to introduce corrective measurements, which might become necessary already during the conduct of a clinical trial. This has led to an increase in patient safety and protection of patient rights, as a potential risk for the safety of patients in the trials and their rights can already be identified during the conduct of the trial.

Furthermore, as there has been a lot more education with respect to the conduct of clinical trials, the awareness concerning the requirements involved in the conduct of clinical trials has raised. The protection of trial participants is also improved as with the enforcement of GCP rules it is less likely that patients participate in a trial unsuitable to produce valid results.

MULTIPLE AND DIVERGENT ASSESSMENTS OF CLINICAL TRIALS (KEY ISSUE N°1)

Consultation item 2:
Yes, the description is correct.

Consultation item 3:
Yes, the description is correct. I. e. for clinical trials with high patient numbers which aim at optimising the treatment with licensed medicinal products the costs have increased tremendously, i. e. because of the administrative processes, the need for monitoring etc.

Quantification should be available through the ICREL project.

Consultation item 4:
Figures should be available via the ICREL-Project.

Which option is preferable?
NCA:
We would prefer the option of a community-wide streamlining of the process, as it is always difficult to rely on a voluntary procedure. Furthermore, if a trial is conducted in several European countries the possibility exists that one MS participates in the voluntary procedure and the other MS does not. This would only lead to more confusion and complexity.

Within the options provided for a streamlined process, we would in the long term prefer to have an option for a centralised procedure with one point of contact for all multinational studies which are conducted in at least two Member States in the EU. As not all competent authorities might already be prepared for this, at least in the middle term a mutual recognition procedure with only one set of documents needed for the application procedure for the clinical trial with defined timelines for the procedure and clear, unambigious descriptions of responsibilities would be preferable. One could discuss whether a procedure which involves two Member States (Rapporteur and Co-Rapporteur) in the assessment process would be preferable to a procedure which involves only one Member State, at least in the beginning. Furthermore, all participating MS should be involved at one point of the assessment procedure to solve questions beforehand. There could be a transition time where both options could be run in parallel and it should be the decision of the sponsor whether a mutual recognition procedure or a centralised procedure is chosen.

It is important that in addition to a changed procedure administrative procedures and processes downstream (operated by the different Member States) as well as requirements and timelines during the application and assessment process in the different Member States are harmonised. This is particularly important for a mutual recognition procedure.

Furthermore, i.e. for academic trials it would be very valuable if the sponsor could call upon a the scientific advise of the national competent authorities. We would therefore appreciate if such a pre-application advice could be formally introduced. For all proceses in the application process there should be a waiver for fees for trials from academic sponsors.

We would recommend to introduce such a procedure for all clinial trials, in which at least two MS of the EU are involved. National clinical Trials conducted in only one MS should remain within the sole responsibility of the respective Member State.

EC:

Consultation issue 5:

The most important change would be to have a single application for EC- and NCA-approval at European level which encompasses all the documents needed. This would reduce the administrative burden significantly and would be a huge asset as it would facilitate the appication procedure: it is much easier to produce just one single set of documents than a variety of sets with different contents. At least in the long term it should be possible to make an online application to one single central point of contact with access to the server for national competent authorities and ethics committees (as is the case for clinical trials with medical devices in Germany form march 2010 onwards). As this option would influence only the formal procedure, this should not have any influence on the assessment of ethical issues on national level.

A structured formal process for the exchange between the different national ECs during theapplication process would also be very much appreciated, as this would avoid conflicting statements which would need to result in different versions of the protocol. In this respect one could discuss a process compared to the one established in Germany with one “lead” EC and “involved” ECs which provide the “lead” EC with their advise during the process. In oher words: in the short term a modular concept could be introduced for the EC opinion multinational trials: general aspects of the risk benefit assessment could be implemented in a mutual recognition process; local components as e. g. qualification of trial sites, local “implementation” of a given clinical trial could be managed by the appropriate EC with respect to given deadlines. In order to have a more harmonized procedure for reaching an EC opinion for multinational clinical trials it is necessary to simplify the coordination / adjustment procedures in the MS (with different institutional and legal traditions), which could be based on a more detailed implementing text which could be changed to a regulation.

We agree there must remain a possibilty for a given Member State and EC in that Member State to “opt out” for a vote reached one ethical implications of a clinical trial. But the fact that ethical question remain in the hand of the different Member States should not provide an argument against harmonisation of precedures, requirements and processes.

As there exists overlap between responsibilities of NCA and ECs (the degree of which differs between MS), we would find it useful to distinguish more between the responsibilities of the single parties. This would also help to avoid conflicting statements between NCAs and ECs.

In summary, we would recommend a combination of all three proposals with at least in the short term the single application being the most important to reduce administrative burden.

Practical /legal aspects to be considered:

- Which language will be accepted for application?
- How will EC or NCA-requests for changes be dealt with? - It would be useful that requests for changes during the application procedure will be discussed between ECs and NCAs before providing the final decision to the sponsor.
- In which way can local components (practical aspects / different guidelindes for therapeutic concepts / standards and therapeutic procedures / national state differences) be dealt with with respect to the acceptability of NCA and/or EC authorisation.
- National and even regional law needs to be adapted.
- Timelines need to be fixed.
- How can confirmation of the insurance company be obtained for centralised procedures?

Which parts have to be changed:
Directive 2001/20/EC, article 6 and 7
Guidance document ENTR/CT 2

INCONSISTENT IMPLEMENTATION OF THE CLINICAL TRIALS DIRECTIVE (KEY ISSUE N°2)

Consultation item n°6 and 7:
Yes. The description is correct. However, SUSAR Reports are not only a burden for the competent authorities but also for the ethics committees and the investigators and require an unnecessarily huge amount of ressources.

Other examples:

- Reporting Rules in Germany, because the definition of „investigator“ is slightly different compared to the Directive which in consequence leads to an increase in administrative burden
- Sponsor: need for one single sponsor of the clincal trial in the EU is implemented in different ways in the Member States
- Possibility for clinical trials in emergency situation implemented in different ways (see key issue 4)
- Manufacturing of IMPs (just recently the law in Germany has been changed to account for the situation of academic clinical trials; this could be used a model for a change on european level)
- Definition of IMP/NIMPs
- Labelling

Consultation item n°8:
To change the Directive into a regulation would have the advantage that no national interpretation is possible, as long as the wording in the Directive is unambigious. But as the

Directive can't include all details for the application procedure and for the conduct of a trial, this option might not really solve the problems encountered.

We would therefore think the option to review the Directive with a view to clarifying provisions and define them well so that they are not open for interpretation might be the preferable option. If the wording in the Directive and the implementing texts (guidance documents) is straight forward and there is also a change to a mutual recognition procedure or even centralised application, a Directive instead of a Regulation could be sufficient.

Practical / legal aspects to be considered:

- Adaptation of the implementing texts.
- Change of national laws.

Reasons fort he divergent applications:
The divergent applications are a consequence of the transposition into national law as well as their application on a case-by-case basis: some rules have been implemented in a different way on national level (e. g. definition of investigator, definition of non-interventional trial; Def. of IMP/NIMP, Manufacturing, rules described in guidance documents) others have been applied differently, e.g. application to ethics committees.

REGULATORY FRAMEWORK NOT ALWAYS ADAPTED TO THE PRACTICAL REQUIREMENTS (KEY ISSUE N°3)

Consultation item N°9:

Examples:

- Clinical trials with medicinal products with marketing authorisation performed in licensed applications, which serve to optimize treatment regimens or compare licensed treatments (CER).
- Definition of non-interventional trials: It might be useful in normal clinical practice to get additional data for the treatment of patients, e. g. via questionnaires or via an additional blood sample for additional central laboratory investigation or an additional amount of blood taken during a normal assessment for pharmakokinetic measurements etc. Such interventions should not automatically make this investigation a clinical trial under the scope of the Directive.

A more risk-based approach is needed in such cases. In these cases the current requirements are too complex with respect to the application procedure and the conduct of the trial. Furthermore, the requirement for an additional insurance cover is questionable.

How should this be adressed?

- Introduction of a risk-based approach in the legislation.
- Change of the definition of interventional trial.
- Directive 2001 / 20 / EC article 2, letter c, article 6, ENTR/CT2: There should be a procedure concerning inclusion of new investigators at an already approved site. For

this, the Directive (article 6 paragraph 3d) should be changed to be consistent with the guidance document ENTR/CT2, in which the role of the ECs is to check the suitability of the principal investigator at a site and not of the whole study team. ENTR/CT2 should refer to new site (not investigator) in paragraph 6 3rd sentence, to make this clear.

Consultation item N°10:

Yes, we agree with the description. In the academic setting it is very often a problem that one university / region /country has to take over the responsibility for the whole trial, even if a lot of responsibilities can be transfered by well-defined and clear delegation of tasks.

Other examples:

- Manufacturing: (Directive 2001/20/EC, article 14, paragraph 2, second bullet point; directive 2005/28/EC article 1 paragraph 4 and article 9, paragraph 2): The conduct of multicentre academic clinical trials is hindered by the rules provided in here, as this allows only the re-labelling and re-packaging of medicinal products for the own institution (e.g. unversity) . This is not practical for all studies which include private clinics and regional hospitals. In Germany there has been a revision of the German drug law recently where this provision has been changed to account for the practical implications.

  Furthermore, in this context the restriction of a facilitated process regarding labelling of marketed products to Member States in which the medicinal product is licensed should be deleted.

Consultation item n°11:

Revision of guidance documents:

No, we do not think that this option could solve the problem. The revision of the guidance documents can contribute to a reduction in the administrative burden but as the guidance documents are not legally binding this is not sufficient. Furthermore - as already mentioned in the consultation paper -, this does not solve the problems connected with items which are regulated in the Directive itself.

Revision of the Directive itself:

In our view this would be the best option, as with this also the problems linked with definitions in the Directive itself could be adressed.

Consultation item 12:

Areas which require an amendment:

- Sponsorship (Rules for the division of responsibilities between countries including liability)
- Application produres (guidance dacouments need to be more unambigious or the application procedures could be defined in more details in a GCP-ordinance)

- insurance cover (to be taken over by the Member States for academic trials)
- SUSAR-reporting
- reporting rules
- definition of non-interventional trials
- requirements for GMP for the IMP in certain circumstances
- Labelling provisions in trials with licensed products which serve for optimizing the treatment of the patient, in which very often just the active pharmaceutical ingredient should be defined as IMP

There is also a need to ensure that the Directive and guidance documents are in line.

Impact of sponsorship rules:
Because there is up to now no real harmonisation between MS, it very difficult for academic institutions to take over the sponsorship for institutions in other MS, if they do not have reliable experts in the other Member States. This leads to the problem, that e. g. universities are not willing to rely on institutions in the other countries, it is sometime very difficult to find a sponsor for an academic multinational trial.

Consultation item n°13:
No, we would not agree to this option. We do not find it useful to introduce two different standards for commercial and non-commercial trials and we also do think that it will not be possible to transport this idea to the public. It has to be taken into consideration, that there are also academic trials which have a high risk (e.g. first in man-studies – FIM; from bench to beside), and it would not be reasonable to exclude those from the Directive. With such an option we all will loose credit.

Furthermore, as this would mean that those trials would have to be excluded from a (unforeseeable) future use in a marketing application, this would lead to the fact that in some cases a trial needs to be conducted twice which is not ethical.

The better option is to reduce administrative burden whereever possible (and a lot of the options in this paper would provide for such a reduction) and to introduce a more risk-based approach. This and an increase in public funding for such trials as well as additional provisions for academic trials (e. g. no application fees or fees for inspections or insurance cover to be taken over by the MS) would solve the current problems better than introducing two different standards.

ADAPTATION TO PECULIARITIES IN TRIAL PARTICIPANTS AND TRIAL DESIGN (KEY ISSUE N°4)

Consultation item n°14:

Consultation item n°15:
Yes, the issue should be adressed. In Germany there exists an example which could be generally applied where a judge could under defined circumstances in an emergancy

procedure designate a legal representative who could provide informed written consent before the randomisation / inclusion into the trial or – where this is not possible – the judge provides the consent for the inclusion into the trial and the legal representative has to provide informed consent after the inclusion /randomisation of the patient ("Heidelberger Modell").

ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES ("GCP") IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES (KEY ISSUE N^{O}5)

Consultation item n^{O}16:
No additional information available.

Consultation item n^{O}17:
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Consultation item n^{O}18:
Adaptation of the prerequisites for participation of adult subjects not able to give informed consent according to the rules for children.
(see directive 2001/20/EC, article 2, letter j, article 3 letter d, article 5, letter a)

There is a huge need for clinical research for this group of patients, i. e. with an ageing society (problems e. g. dementia or psychiatric disorders, to improve the treatment for this group of patients). We do not really understand why the level of protection for vulnerable patient groups like children and adult patients unable to provide informed consent should be different. Furthermore, the Directive does not take into account that patients who might have lost the capability of informed consent during their life can not be included into a trial even if this would be according their putative will.

Participation in clinical trials should therefore be possible under the same circumstances as in children (e.g. if there is a benefit for the group of patients with this indication and if the trial is only involving minimal risk and minimal burden).

On behalf of the KKS Network
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2009/12/21