UZ/KULeuven Reply to Public Consultation Paper on the 'Revision of the "Clinical Trials Directive" 2001/20/EC'

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Introduction.

Within our university and university hospitals, clinical trials represent an important part of our research activities in the biomedical field. Currently, we have around 2000 active clinical trials running in the hospital and around 500 trials are in the contracting phase. In 2010, 893 new study protocols were submitted to the Clinical Trial Center (CTC) of UZ/KU Leuven. Of these, 530 were academic (non-commercial) and non-sponsored trials. The others were either commercial trials or academic trials for which an external funding (such as an 'unrestricted grant') was provided.
These numbers however should be interpreted with caution since the Belgian Law of May 7th 2004 related to experiments on human people has a broader scope than the Clinical Trial Directive 2001/20/EC, including e.g. prospective observational trials and trials with medical devices.

We also refer to our earlier contribution UZ/KULeuven Reply to the Public Consultation Paper 'Assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC (Entr/F/2/SF D(2009) 32674).

Consultation item no. 1 - 5:

In principle we agree with a single submission and a Co-ordinated Assessment Procedure (CAP) for the assessment of the risk/benefit ratio as well as the aspects related to the quality of the medicines and their labeling (keeping all other assessments local).

Consultation item 6:

A comment on the order of the bullet points: the "opting out" of a Member State (MS) should not mean that such MS should no longer participate in the vote. So the vote should always take place *first* between the Member States concerned for a specific study. In case of approval (simple majority after vote of all concerned Member States) a Member State can than "opt out", based on their appreciation of the risk/benefit ratio.

Consultation item 7:

We believe that a CAP can only work if it is made mandatory for all multinational trials, regardless of the type of Sponsor.

Consultation item 8:

To find a balance between due assessment of high risk trials (which should not be approved implicitly) and a too heavy procedure for low risk trials, the proposed *pre-assessment*, estimating the risk of the trial, seems very useful, as long as stable and objective criteria can be applied. Nevertheless, the concerns expressed in our answer to consultation items 11-12 should be taken into account. A risk estimation should not lead to a situation whereby Member States can evade actual harmonization.

Consultation item 9:

Since the current Belgian legislation includes prospective observational (i.e. non-interventional) trials, we already have the problem that the aimed harmonization of the Clinical Trial Directive doesn't cover this type of studies. Therefore, we certainly agree with the proposal of keeping all clinical trials under the scope of the Directive. Regulation would probably even be better to solve this.

Moreover, as already mentioned in our previous reply, we still considerthat the 'borderline' between an interventional and an observational trial is insufficiently defined in the current Clinical Trials Directive. As a non-commercial Sponsor, UZ/KU Leuven hosts a lot of trials falling within this grey zone.

Consultation item 10:

We fully agree with this appraisal: the type of sponsor should not influence the requirements for the trial. Quality assurance of all aspects of the trial (including the medicines), safety of the subjects and reliability of the trial data should be guaranteed, independently of the Sponsor.

Consultation item 11-12:

The principle of risk-adapted rules seems logical, but the practical assessment of the actual risk of 'trial subject safety compared to normal clinical practice', and even more of the 'risk to data reliability and robustness' might become very difficult. This could imply that an assessment of risk, followed by an adaptation of the rules for the clinical trial in function hereof, again results in a non-harmonized procedure (see also our answer to item 9, namely the current difficulties in the interpretation of 'non-interventional'). Therefore, this assessment of risk should be based on a very uniformly defined and unequivocally interpreted 'checklist' or definition.

As for the other aspects, this also depends on what will be decided concerning consultation number 9. If, as in the Belgian Law, non-interventional trials would also be included under the scope of the Clinical Trial Directive, rules for the risk assessment of these trials would probably be based mainly on the integrity of the data.

Consultation item 13:

We agree with the proposed appraisal.

Consultation item 14:

- The first proposed policy option implies that for a category of "low-risk trials" (but see above on the interpretation of "risk") there would no longer be harmonization because only national legislation will determine whether insurance is required. Moreover, a qualification as "low risk" could apply both to an interventional and an observational trial where only the former falls under the scope of the current directive. As we suppose this is not the intention, clarification maybe needed here.

- The implications of the second proposed policy option is difficult. Would the purpose be that a subject can always claim damages in the first instance of the Member state, which can then in turn recover the damages from the Sponsor? Or would the Member state ultimately be liable in any case?

Consultation item 15:

As to the concept of a "single Sponsor", there is currently confusion concerning the meaning of the words "*organization* which takes responsibility for the initiation, management and/or financing of a clinical trial". Some seem to think that this applies to a consortium, by which a "multiple sponsorship" is *de facto* organized. Regardless of the outcome, there is a strong need for clarification here, especially in the context of multicenter multinational academic trials.

Generally we fully agree with the appraisal that option 1 (single sponsor) including the two provisions is the best option. However, it is not fully clear what is meant with the clarification in the first bullet point. Will it be stated that being "the Sponsor" under the Directive does NOT imply being liable in every Member State concerned? Will there be any harmonization on who is liable then?

The second bullet point is particularly important in the Belgian context where prospective non-interventional trials also fall under the scope of the trial legislation.

Consultation item 16:

This issue has been dealt with in Belgian law. To our knowledge, there are no real problems in this respect.

Leuven, May 12th 2011