ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC

PUBLIC CONSULTATION PAPER

Leem contribution (February 2010)

Consultation item 1: Can you give examples for an improved protection? Are you aware of studies/data showing the benefits of CT directive?

In France, a legislation protecting patients was already in place before the CT Directive (loi Huriet-Sérusclat), so we can't give examples of patient protection improvement.

But, in some European countries where no regulation on patient protection was existing, this CT Directive improved patient's protection and gave assurance to sponsors that their multinational trials will be sound, ethical and acceptable in a marketing authorization application (application of GCP, sharing of safety data between national competent authorities).

Consultation Item 2: Is this an accurate description of the situation? What is your appraisal of the situation?

Yes, it is an accurate description.
The question is mainly oriented on the evaluation of a clinical protocol but also applies to other parts of the submission, for example the IMPD evaluation.
Regarding the protocol, this is an accurate description and it results very often in national adaptation of the protocol of a multistate study: submission of country specific amendements. This can create national bias.
For EC, this is a problem for development studies but also for post-marketing commitment studies which study plan is approved upon marketing authorization process and hence not flexible.

Consultation Item 3: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

Yes, it is an accurate description of the situation in terms of workload increase, cost increase, timelines increase for the implementation of a trial.

It's difficult to quantify the impact, but in companies implemented in France, all functions involved with the initiation, conduct and oversight of clinical trials have been impacted. There has been increased consumption on resources in all these functions, including regulatory affairs, clinical operations, clinical trial supplies, compliance and pharmacovigilance.

Consultation Item 4: Can you give indications/quantifications/examples/ for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further details?

For a commercial sponsor, the best procedure is a procedure where the clinical trial application dossier has the same content whatever the member states involved and enabling a single list of question.
It is essential to have ONE dossier with the same content for all members states, to have the possibility of ONE electronic submission.

As most of EU trials are performed in one member state, the current national procedures should be kept.

For multinational trials, the VHP option, set up by the CTFG has to be promoted. An accurate assessment should be done by the CTFG and published. Others members states (for example Italy) should be included in the process.
Roles, responsibilities, timelines, ways of communication between members states and sponsors should be clearly defined. The procedure for the evaluation (who, how) should be clearly defined and published .
An "arbitrage procedure" should be set up.

According to the results of the assessment of this VHP procedure, another option could be discussed. In this case, we will recommand the EFPIA position for a Community CTA review of trials as a complement to the present regulatory framework.

Consultation Item 5: Can you give indication/quantification/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?

Option 3.4.1:
Ideally, one stop shop should be set up for the full ethical submission as Ethics is a multinational concept and only documents that could have national specificities because of language (national summary, patient information leaflet and informed consent) should be submitted to national Ethics Committees. This option doesn't seem realistic.
Electronic submission would be more convenient with access for NCA and NEC (similar to Italian OssC database).

Option 3.4.2:
As for CA where an assessment at community level is envisaged, it would be interesting to have one NEC "rapporteur" +/- "co-rapporteur" at European level. It would decrease workload and considerable useless paperwork (majority of ECs are overloaded). It would also avoid disparity/cohabitation of several documents versions in case of amendment approval/refusal.

At least, there should be no more than one EC per country as in France. Working at a multicenter EC level in some countries is almost impossible. For example in Italy, initial submission to a satellite EC and coordinating EC cannot be performed in parallel: satellite EC will only consider the submission after coordinating EC has given its opinion. Similarly there is no possible submission in parallel for amendments. This leads to different versions of a protocol in a same country.

It is necessary to have a single European format for the EC submission, with a single electronic submission. For the patient information leaflet, at least one national format and ideally one European format.

Option 3.4.3:
Respective scope of assessment of NCA and Ethics Committees must absolutely be clarified. This option should be implemented independently of options 1 or 2.
In France the system in place is working quite well. Scopes of assessment of EC and NCA are well defined, except for protocol amendment and investigator brochure modification. The dossier is submitted to only one EC and its opinion is valid for all the study centers opened in France.

Consultation Item 6: Is this an accurate description of the situation? Can you give other examples?

Yes, it is an accurate description of the situation.

4.1.1 Example 1: substantial amendments: It would be helpful to add a classification of substantial amendments with examples as it is done by Afssaps in France, this will decrease inconsistencies, workload for sponsors and NCA and NEC.

4.1.2 Examples 2: - Regarding SUSARS expedited and periodic reporting rules differ among MSs and although the Eudravigilance database has been set up, the number of reports has dramatically increased whereas the number of trials has not significantly changed since the Directive is in force.

- Reporting of SUSARs: an access to Eudravigilance for ECs would be better (if ECs are reorganized: 1 EC assessing the trial per country);

Other examples:- scope of assessment of NCA and EC is not harmonized in EU (in MS Italy assessment of Quality part of the dossier is done by clinical center). Respective scope of assessment of NCA and Ethics Committees must absolutely be clarified.

- In France, a comparator is defined as IMP. However the main difference between member's states is whether this comparator (when it's a standard of care) should be provided/paid by sponsor.

Consultation Item 7: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

Insufficient patient protection: this item is in contradiction with what is stated in previous paragraphs (§ 2.5)
The risk-benefit balance is not only based on SUSARs, Pharmacovigilance staff analyse other data to establish an accurate balance. Over-reporting and duplication of reports are not a guarantee for safety.

Clinical study costs also increased for commercial sponsor.

Consultation Item 8: Can you give indication/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail? In particular, are the divergent applications really a consequence of transposing national laws, or rather their concrete application on a case-by-case basis.

The most important option to address the issue would be to clarify role and responsibility of NCA and ECs.

Option N°1 is important because these points need to be amended. It can be a first step by decreasing the burden linked to the CTA documentation, amendments and safety reporting. Addition of a provision that MSs can't add CTA requirements will benefit to all.

A regulation may be easier to implement and will avoid country specificities, but will need a full review of the Directive, whereas reviewing the Directive will allow updating only the part that need to be clarified.
In France, the national transposition of the Directive is clear.
If additional items are added to the current directive, regulation could be considered as implementation should be faster.

Consultation Item 9: Can you give examples for an insufficient risk-differentiation? How should this be addressed?

Yes, same documents must be submitted for a phase II and a phase III clinical trial (as an example), no differentiation if the class of product is already well known.

Documentation could be differentiated on study risk assessment.

Consultation Item 10: Do you agree with description? Can you give other examples?

The implementation of a single sponsor per multinational clinical trials is not an issue for industry sponsors.
There is a need to harmonise and simplify safety reports reporting between EU and US requirements

Consultation Item 11: Can a revision of guidelines address this problem in a satisfactory way? Which guidelines would need revision, and in what sense, in order to address problem?

The most important revisions of guidelines which need to be addressed are the content of the clinical trial application, substantial amendments and safety reporting.
For example, content of the dossier must be described in detail in the directive so that it is identical and binding for member states for CA and EC.
IMP/Non IMP definition and labeling should be harmonized.

Consultation Item 12: In what areas would an amendment of the clinical trials directive be required in order to address the issue? If this was addressed, can the impacts be described and quantified?

Areas to amend the CT directive:

- Substantial amendments
- Scope of NCA and EC
- Content of the clinical trials submission
- IMP/NIMP definition
- Clinical supply labelling
- SUSARS reporting

Consultation Item 13: Would you agree to this option and if so what would be the impact?

Regulations should not be created according to sponsor. The objective of regulating clinical trials is to ensure patients protection and obtain reliable data. These are the objectives to be reached. If the current situation is considered as too burdensome for academic and can be reduced still reaching the objectives then should be the same for industry sponsors.

Consultation Item 14: In terms of clinical trials regulation, what options could be considered in order to promote clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants?

This is already addressed in other directives / regulations.
There is a need to increase the dialogue between the different parties involved (EMEA/ NCA, NEC…)

Consultation Item 15: Should the issue be addressed? What ways have been found in order to reconcile patient's rights and the peculiarities of emergency clinical trials? Which approach is favorable in view of past experiences?

In France, it's already authorised and well explained in the French law.

In France : (refer to Code de la Santé Public – Article L1122-1-2): Informed consent must be signed by a family member or a "person of trust". Patient must be informed and his consent requested as soon as possible

Consultation item 16: Please comment? Do you have additional information, including quantitative information and data ?

No specific comment

Consultation item 17: What other options could be considered, taking into account the legal and practical limitations?

No specific comment

Consultation Item 18: What other aspects would you like to highlight in view of ensuring the better regulation principles? Do you have additional comments? Are SME aspects already fully taken into account?

SME aspects seems to be already taken into account