COMMENTS ON THE PUBLIC CONSULTATION DOCUMENT
REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION. SANCO/C/8/PB/SF D(2011) 143488

Preliminary appraisal: A single submission would greatly reduce the administrative work of sponsors for submission of documentation to the Member States concerned. Consultation item no. 1: Do you agree with this appraisal? Please comment.

French academic sponsors wish to know how the single submission mentioned above will be implemented compared to VHP procedure that is already in place and works well?

This single submission should be in place as soon as two Member States are involved in a trial. A single "EU Portal" administered by the European Medicines Agency is an interesting approach for multi-national trials but it should remain an **optional choice** for the sponsor as this option will increase the workload for academic sponsors that often conduct uni-national trials.
Moreover, the scope of the Clinical Trials Directive is only on medicinal product for human use and academic sponsors are often conducting other therapeutic trials (e.g. therapeutic strategies comparisons, radiotherapy, surgery, transplantation, transfusion, physical therapy, psychotherapy, diagnostic studies, physiopathology studies…) for which there is no European harmonization. For all these reasons, it is therefore essential to preserve a National Competent Authority.

Preliminary appraisal: A separate assessment would insufficiently address the issue set out above: The difficulties created by independent assessments would remain. Consultation item no. 2: Do you agree with this appraisal? Please comment.

For multinational trials, it is necessary that all the concerned National Competent Authorities should talk to each other before raising questions to the sponsor. This is the current role of the VHP working group.
In the sponsor's point of view, it is really important that a clinical trial is conducted under the same conditions within the Member States involved and this fact could be challenged if independent and individual assessment is carried out by each Member State

Preliminary appraisal: A central assessment is not appropriate for clinical trials approval and would, as regards clinical trials, not be workable in practice for the following reasons:
• This option would insufficiently take account of ethical, national, and local perspectives. For these aspects, a parallel, national, procedure would have to be established in any case.
• The sheer number of multinational clinical trials per year (approx. 1 200) would make centralised assessment very difficult. To this would add all substantial amendments of the clinical trials.
• The involvement of all Member State is not needed, as very few clinical trials are rolled out in more than five or six Member States.
Moreover, a Committee structure requires frequent meetings with a robust supporting infrastructure. The costs (and, consequently, fees) involved would make this mechanism unattractive for academic researchers.
Consultation item no. 3: Do you agree with this appraisal? Please comment.

The respective roles of the National Competent Authority and the Ethics Committee, regarding the assessment of a trial, should be harmonized within Member States. These roles can not be left to the discretion of each state. However, it seems necessary that each Member state keeps its own ethics committee's opinion.
A central assessment of the Clinical Trial Application by all the Member States would generate costs and delay the time of instruction. This option seems unappealing if applicable to all clinical trials that why Option 1.3 is preferred. Option 1.3 should also guarantee short delays to keep European research attractive.

To establish the scope of the CAP one has to have clarity of the three areas which are considered in a clinical trials application:
a) The risk-benefit assessment, as well as aspects related to quality of the medicines and their labelling. This includes the following:
– Acceptability of the clinical trial in view of all anticipated benefits, compared to risks and inconveniences for trial subjects (including control groups), taking account of
. the characteristics of and knowledge about the investigational medicinal product,
. the characteristics of the intervention compared to normal clinical practice;
. the design of the trial;
. the relevance of the trial, including the credibility of the results;
– compliance with the requirements for manufacturing and importation of the medicinal products intended for the clinical trial;
– compliance with the requirements for labelling of the medicinal products intended for the clinical trial;
– completeness and adequateness of the investigator's brochure.
b) Ethical aspects related to informed consent, recruitment and reward. This includes the following:
– completeness and adequateness of the information submitted to obtain informed consent;
– arrangements for rewarding and compensation of investigators and trial subjects;
– arrangements for the recruitment of trial subjects.
c) Local aspects related to suitability of sites, the investigator, and national rules. This includes the following:
– suitability of the investigator;
– suitability of the clinical trials site;
– adequateness and completeness of the insurance or indemnisation covering the investigator and sponsor;
– compliance with the applicable rules on personal data protection.
Only the aspect under point a) would be suitable for the CAP. In particular, the aspects under b) and c) are not suitable for the CAP as they relate to ethical issues (as is the case for b) or to local expertise (as is the case for c).
Consultation item no. 4: Is the above catalogue complete?

A item regarding the safety long term follow-up of the trial is missing from this list.

Consultation item no. 5: Do you agree to include the aspects under a), and only these aspects, in the scope of the CAP?

The items listed in a) fall under the scope of the CAP, but some comments can be made on:
- the item "*the characteristics of the intervention compared to normal clinical practice*" it has to be underlined that the usual care practices performed within a Member State are better known by the National Competent Authority and the Ethics Committee than by the CAP.

- The item "*design of the trial*" should be clarified. If this item includes the assessment of the methodology of the trial, this should be done by the Ethics Committee instead of the CAP.
- The risk/benefit evaluation in the trial should also be done by Ethics Committee

Moreover, the request regarding the labelling of the medicinal product(s) in all the local languages during the initial Clinical Trial Application submission should be removed. Only one labelling example should be sent.

Disagreements amongst Member States about the assessment done under the CAP (ie the aspects listed in point 1.3.1.a) could be resolved in the following ways:
• an individual Member State could be allowed an 'opt out', if justified on the basis of a 'serious risk to public health or safety of the participant';
• the Member States concerned could vote on the issue and decide by simple majority; or
• the matter could be referred to the Commission or the Agency for a decision at EU level.
Consultation item no. 6: Which of these approaches is preferable? Please give your reasons.

It is necessary to clarify the deadlines for each option.
None of the proposals is entirely satisfactory, but the first proposal can allow the sponsor to initiate a study, except in the countries concerned.
Option 2 is not wished as a vote could introduce a bias in the evaluation and could interfere with the conduct of the Protocol in countries where the local law imposes more stringent criteria than those of the protocol submitted.
The setting of a commission in *Option 3* could delay the trial.

As to whether the CAP should be mandatory or optional, three possibilities could be considered:
• CAP is mandatory for all clinical trials. (This would mean that the provisions on authorisation in the Clinical Trials Directive would be replaced);
• CAP is mandatory for all multinational clinical trials. (This would mean that the provisions on authorisation in the Clinical Trials Directive would be maintained only for single-country clinical trials); or
• CAP is optional. (This would mean that sponsors could continue to refer to the national procedures laid down in the Clinical Trials Directive).
Consultation item no. 7: Which of these three approaches is preferable? Please give your reasons.

The CAP procedure should remain optional as the implementation of the CAP can be lengthy and expensive and could penalise the academic sponsors.
The academic sponsors led many uni-national trials or other therapeutic trials that are not in the scope of the EU directive and that the reason why it is therefore essential to preserve a National Competent Authority.

A type A trial could be defined as '*a clinical trial which, on the basis of the following criteria, poses only minimal risks to the safety of the trial subject compared to normal clinical practice:*
(*a) The safety profile of all investigational medicinal products used in the trial is sufficiently known. This shall be the case if the investigational medicinal products used in the trial are:*

- either authorised in a Member State concerned in accordance with Directive 2001/83/EC or Regulation 726/2004, and used within the authorised indication; or
- part of a standard treatment in a Member State concerned.
(b) The interventions in the trial do not pose more than insignificant additional risk to the safety of the trial subject compared to normal clinical practice in a Member State concerned.'

Consultation item no. 8: Do you think such a pre-assessment is workable in practice? Please comment.

Procedures for the risk evaluation of clinical trials seem useful, appropriate and easy to implement for academic sponsors.
The sponsor should be responsible for the pre-assessment of the protocol before being validated by the National Competent Authority (NCA) and the Ethics Committee (EC) in the country, as compared to the usual practice of the country. The authorization/approval procedures and delays (NCA and/or EC) should be also based on a risk-Based Approach of the trial.
Academic sponsors agree with tacit approval within 60 days.

Preliminary appraisal: Rather than limiting the scope of the Clinical Trials Directive through a wider definition of 'non-interventional trial', it would be better to come up with harmonised and proportionate requirements which would apply to *all* clinical trials falling within the scope of the present Clinical Trials Directive. See in particular points 2.2 to 2.5.
Consultation item no. 9: Do you agree with this appraisal? Please comment.

The definition of non-interventional studies should be clarified.
The academic sponsors approve the fact that the non-interventional studies could be part of the EU directive only if on a risk-based approach of the trial is retained .i.e. the assessment of the non-interventional studies should be only done by the Ethics Committee to shorten the delays.

Preliminary appraisal: Rather than limiting the scope of the Clinical Trials Directive, it would be better to come up with harmonised and proportionate requirements for clinical trials. These proportionate requirements would apply independently of the nature of the sponsor
('commercial' or 'academic/non-commercial'). See in particular points 2.2 to 2.5.
Consultation item no. 10: Do you agree with this appraisal? Please comment.

Academic sponsors do not wish to be excluded from the Clinical Trials Directive as they conduct independent and good quality research and want to be recognized. A risk-based approach is clearly preferred.

Preliminary appraisal: This approach would help to simplify, clarify, and streamline the rules for conducting clinical trials in the EU by providing one single, EU-wide, risk-adapted set of rules.
Consultation item no. 11: Do you agree with this appraisal? Please comment.

The academic sponsors fully agree with the risk-based approach to regulate clinical trials with appropriate procedures for each category of risk.

Consultation item no. 12: Are there other key aspects on which more detailed rules are needed?

No other key point is needed.

Preliminary appraisal: This combined approach would help to simplify, clarify, and streamline the rules for medicinal products used in the context of a clinical trial.
Consultation item no. 13: Do you agree with this appraisal? Please comment.

The academic sponsors agree with the simplified and clarified definition of the Investigational Medicinal Product.
Regarding the "auxiliary medicinal products", no requirements (traceability and labelling) should be asked if these products have a Marketing Authorisation and is in-label use.

Preliminary appraisal: Both policy options could be a viable solution.
Consultation item no. 14: Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

The academic sponsors agree with the principle of insurance depending on the risk-based approach. Insurance must be mandatory for high risk interventional trials but for non-interventional and low-risk studies, insurance should be removed.
Moreover these insurance rules should be harmonised within Member States.
To this point, it is essential to take into account local regulation and the clinical trial sites in which studies are conducted (eg health institutions are insured for their care activities).

Preliminary appraisal: In view of the above, option 1 may be preferable, provided that:
• it is clarified that the 'responsibility' of the sponsor is without prejudice to the (national) rules for liability; and
• it is ensured that the regulatory framework for clinical trials in the EU is truly harmonised (see point 2.2).
Consultation item no. 15: Do you agree with this appraisal? Please comment.

The two options should be offered to the sponsor.
The Option 2 guarantees the safety of the patient/trial if there is only one clinical trial database and only one safety database.

Preliminary appraisal: This could be a viable option in order to address this type of research and bring the regulatory framework in line with internationally-agreed texts.
Consultation item no. 16: Do you agree with this appraisal? Please comment.

The academic sponsors agree with the proposals of the Clinical Trials Directive. Regarding the informed consent, the Ethics Committee shall give its approval.
The item "the trial subject has not previously expressed objections known to the investigator" may be difficult to check in case of extreme emergency.

Both provisions, as well as implementation work could be further supported and supplemented through the following:
• Codifying, in the revised legislative framework, the provision in point 2.7.2.4. of the detailed guidance CT-1 (see point above); and
• Further supporting capacity building in third countries where the regulatory framework for clinical trials, including its enforcement is weak.

In addition, in order to increase transparency of clinical trials performed in third countries the legislation could provide that the results of these clinical trials are only accepted in the context of a marketing authorisation process in the EU if the trial had been registered in the EU clinical trials database *EudraCT* and thus be published via the public EU-database *EudraPharm*.20
Consultation item no. 17: Do you agree with this appraisal? Please comment.

The academic sponsors agree with these proposals.

The concepts discussed above are based on the figures collected by DG SANCO during the impact assessment exercise. These figures are annexed to this paper. It is crucial that these figures are checked and complemented by stakeholders where possible and necessary.
Consultation item no. 18: Do you have any comments or additional quantifiable information apart from that set out in the annex to this document? If so, you are invited to submit them as part of this consultation exercise.

The summary of the final report should not be structured with the only objective of applying for a marketing authorization (MA). Some items of this report should remain optional as trials not always aim at applying for a MA.