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.

Completely agree.

Regarding the *assessment* of the information, this assessment would be done independently by each Member State, as at present.

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.

Completely agree. It will end-up being the same.

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. 1200) 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.

I agree. However, there should be mechanisms to end up with ethical, national, and local perspectives for international trials. Europe will no longer be competitive. And the procedure could be similar to that of a centralised medicines approval, with one country leading in turn. I would also involve more than six Member States, on a volunteer basis and taking into account the existence of a national steering committee.

Preliminary appraisal: The CAP could offer a sufficiently flexible approach. It allows for a joint assessment without a cumbersome committee structure. It would allow national practice to be taken into account. It would respect that, as a basic rule, ethical issues clearly fall within the ambit of Member States.
Regarding the CAP, four issues need to be considered in particular and shall be discussed in this concept paper:

1.3.1 Scope of the CAP

Consultation item no. 4: Is the above catalogue complete?
It looks fairly complete to me.

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

1.3.2 Disagreement with assessment report

Consultation item no. 6: Which of these approaches is preferable? Please give your reasons.
In my opinion, the preferable approach is number 1 (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'). Voting and having others to decide for your country will not give the Member State enough autonomy and could lead to dysfunctions, and having the Commission or the Agency deciding on every trial would be a pain for the Agency and would become burdensome.

1.3.3 Mandatory/optional use

Consultation item no. 7: Which of these three approaches is preferable? Please give your reasons.
I would maintain the CAP optional. Again, being flexible will produce in everybody a feeling of freedom. With time, an option will become preferable for specific situations.

1.3.4 Tacit approval and timelines

Consultation item no. 8: Do you think such a pre-assessment is workable in practice? Please comment.
It should be. If the medicinal product and the patient population (indication) are identified up-front in the application form, the risk of the trial should be clear to a knowledgeable trimmer. The only thing is to assure that trimmers are knowledgeable of what they are revising.

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

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.

I disagree. I really think that the definition of non-interventional trials should be enlarged. It is very difficult to run epidemiologically sound observational studies (by the epidemiological definition) that are considered Clinical Trials under the above Directive.

2.1.2. Excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive

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.

I agree on that the nature of the sponsor should not be a reason for not applying a rule. Independent researchers also need rules that are clear. My position is not to limit the scope of the Directive, but harmonising the definition of intervention from a methodological point of view, not from a legal point of view.

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

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.

I could not agree more with having one single EU-wide risk-adapted set of rules; however, I am concerned about the final set of rules. There are a wide variety of research designs and not all rules and templates that I have seen so far are flexible enough to account for as many designs as possible. Trying to fit a feasibility study or a qualitative research in a clinical trial template is a nightmare; and what can I tell about the safety reporting of a retrospective case-control "clinical trial".

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

What about on auditing standards? Or on data merging?

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

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.

It could help. I do not know whether it would mess up at the end. I'm thinking that in most instances these "auxiliary medicinal products" will be just variables that are collected as confounding factors.

2.4. Insurance/indemnisation

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?

I am in favour of removing insurance/indemnisation requirements for low-risk trials if any. Actually my position is rather not to call clinical trial to studies where there is no pharmacological intervention.

2.5. Single sponsor

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.

I agree. More sponsors will add a lot of noise. At a European level, only one is advised.

2.6. Emergency clinical trials

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.

I agree. Anything that brings together regulatory framework and methodological texts is welcome.

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

Preliminary appraisal: In view of the jurisdictional limits, particular consideration should be paid to clinical trials in third countries where the data is submitted in the EU in the framework of the authorisation process of

- Clinical trials; and
- Medicinal products.

Regarding the authorisation process for a clinical trial, this is currently addressed in point 2.7.2.4. of the detailed guidance CT-1, which provides that:
'*All studies* [submitted in the authorisation process of a clinical trial] *should have been conducted in accordance with the principles of Good Clinical Practice (GCP).*

To this end, the applicant should submit the following:
— a statement of the GCP compliance of the clinical trials referred to,
— where a clinical trial referred to has been performed in third countries, a reference to the entry of this clinical trial in a public register, if available. Where a clinical trial is not published in a register, this should be explained and justified.'
Regarding the marketing authorisation process of medicines, this is addressed in point 8 of the introduction to the Annex of Directive 2001/83/EC, which provides that:
'*All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. To be taken into account during the assessment of an application, clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.*'
The Agency is currently assessing various actions in relation to the implementation of this provision.
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*.

Consultation item no. 17: Do you agree with this appraisal? Please comment.

I agree, and I really have no further comments.

4. FIGURES AND DATA

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.

I have no further comments.