Consultation Item no. 1: .A single submission would greately reduce the administrative work of the sponsors for submission of documentation to the Member States concerned. Do you agree with this appraisal.

We agree with this appraisal for both national and multinational clinical trials (CTs). We believe that all necessary applications and notifications of CTs to the Member States concerned (MSC) should be submitted through a central "EU portal". This portal should either directly distribute or provide access to the MSC for further distribution of the information to the concerned competent authority and/or Ethics Committee. It can be proposed that a transitional phase should be allowed were only applications of multinational clinical trials are submitted. There should be an agreement on a single Clinical Trial Application (CTA) dossier for all EU Member States.
We need to uniform requirements for national competent authorities and ethics committees at the European level and avoid as much as possible local requirements. The benefits of this proposal is the reduction of administrative work of sponsors for the submission of the documentation to the Member States concerned.
The EU portal should be simple enough to use for any type of Sponsor, a single EU CTA dossier should be submitted in electronic format and the submission via the EU portal should be mandatory for all CTs. In case of multinational CTs, the applications to all CMS should be simultaneous. The "EU Portal" must allow distributi on of the corresponding documentation to both national Competent Authorities and Ethics Committees.

Consultation Item no. 2: A separate assessment would insufficiently address the issue set out above.
Despite the single submission simplifies the process, the separate assessment would not substantially change the current system and the difficulties created by independent assessments would remain.

Consultation item no. 3: **A central assessment is not appropriate for CTs approval and would, as reg ards clinical trials, not be workable in practice. Do you agree with this appraisal? Please comment.**

A central assessment is not appropriate for for CTs approval, since it seems not to be feasible, nor operational.
The Coordinated Assessment Procedure (CAP) will offer the best option for multinational CTs. Initially the CAP could be optional during an "adaptation period of time" until it is proven that the system is functioning correctly.
Changing the European legal framework must also involve the corresponding changes for all Member States.
New authorization procedures should be viable, agile, and competitive with third countries.
However, there are several difficulties in difficult having a single CTA dossier: 1) specific requirements in some Member States of ethics committees and/or competent authorities. 2) The English language for some countries, and 3) standardization of documents (i.e., subject information sheet, informed consent form). 4) Marked variations in the time needed for the preparation of documents may vary between Member States due to local requirements. This may lead to a delay in obtaining approval in the "quicker MSC" if the principle of sending simultaneous applications to all MSC were applied to the CAP. Moreover, sponsors may decide to exclude some countries unless they improve their procedures.

The following conditions are defined for CAP procedure: 1) simultaneous submission of the CTA dossier that reflects the different requirements for national authorities and ethics committees review at the European level. 2) It should be optional at the beginning, before making it mandatory for all multinational clinical trials. 3) The CAP procedure must become faster to get a clinical trial started.
Local differences in national traditions, therapeutic standards and healthcare systems make the CAP not suitable to a sses: ethical aspects related to informed consent, recruitment and reward, suitability of sites or other local aspects (insurance certificate, data protection).

Consultation item no. 4: Is the catalogue proposed complete?
Yes

Consultation item no. 5: Do you agree to include the aspects under a (the risk/benefit assessment, as well as aspects related to quality of the medicines and their labeling) and only these aspects, in the scope of the CAP?

Yes, we agree with the risk/ benefit assessment. Drug quality and labelling are aspects to be included in the scope of the CAP.
Centralized labeling would be acceptable and convenients, but validated translation would be required by the National Competent Authority.

Consultation item no. 6: Which of these approaches is preferable? Please give your reasons.

It is an non-acceptable option that a Member State participate in a CT that is considered to be a "serious risk to public health or safety of the participant". This should be a "good reason" for the immediate refusal of all the member states. If so, it is clear that both choices (i.e, The Member States concerned

could vote on the issue or the matter could be referred to the Commission or the Agency for a decision at EU level cannot be accepted.

Consultation item no. 7: Which of these approaches is preferable? Please give your reasons.
CAP is mandatory for all clinical trials. This option is not accepted. It seems an illogical situation to evaluate a CT performed only in a single-country by CAP.
CAP is mandatory for all multinational clinical trials. This option got the higher support in the discussion.
CAP is optional. A minority supported this option.

Another option is to propose an "adaptation period" with optional use of CAP, to obtain increasing experience and having enough flexibility to avoid technical issues. After this experimental adaptation period, the mandatory use of CAP would be reasonable for all multinational clinical trials.

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

It is supported this kind of evaluation based in the model performed by the Clinical Trials Facilitation Groups.
Additionally, a clear definition should be provided for "Type A" Studies; Type A trials should be identified by the Spon sor, according to the aforementioned, so a pre-assessment should not be required. If European Authorities dismiss a Type A request, an option to redirect the administrative process to the appropriate type of assessment should be pro vided in order to avoid stopping or delaying the procedure.

Better adaptation to practical requirements and a more harmonized, risk-adapted approach to the pro cedural aspects of Clinical Trials

There is a problem due to the different/subjective interpretations of "insignificant low risk**"**

Consultation item no. 9: 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. Do you agree with this apprais al? Please comment.

We completely agreed with the appraisal, so the scope of the Clinical Trials Directive should not be modified.
However, probably "non-interventional trials" can be replaced by "non-interventional studies" as "trial" implies interventional procedures. It is necessary to review and to clarify the definition of the criteria to define an interventional and a non-interventional trial.
Studies with a lower frequency of the monitoring or low risk procedures are considered as low risk clinical trials (Type A).
An standardized procedure for the classification clinical trials would be welcomed.

Consultation item no. 10: 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 i ndependently of the nature of the sponsor ('commercial' or 'academic/non-commercial'). Do you agree with this appra isal? Please comment.

We completely agreed with this appraisal. There should not be any difference between commercial and non-commercial trials. Patient safety and data quality should be guaranteed by the same legislation regardless of who is t he sponsor of the clinical trial.
However, the directive makes no distinction between different types of clinical trials (early phase, phase IV…), and this should be avoided in the future. General requirements must be establish for all study types (independent of the sponsor or the non-commercial character), but the new directive should consider exceptions to this rules based on the based on the risk of the trial. It would be great to reduce the administrative procedures and burocracy in low risk trials. This would facilitate the non-commercial research.

Consultation item no. 11: More precise and risk-adapted rules for the content of the application dossier and for safety reporting. Do you agree with this appraisal? Please comment.

We agree with the proposal, establishing differences in the process of authorization. We need more detailed rules.

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

In order to define a risk-adapted approach, it would be necessary to consider four critical factors:

1. Investigational Medicinal Product Classification: An individualized assessment should be considered for biotechnology products, gene therapy products, cell therapy products and genetically modified organisms.
2. For medicinal products not included in the previous point, some categories of risk (based on the marketing authorization would be defined: Authorized medicinal product under the authorized conditions, Authorized medicinal product under different conditions of use and Pre-Authorization (different clinical trials should have different requirements: first-in-human studies vs with Phase III)
3. Existence of an "standard of care"
4. Study population: individualized assessment should

Consultation item no. 13: Clarifying the definition of 'investigational medicinal product' and establishing rules for ' auxiliary medicinal products' clarify, and streamline the rules for medicinal products used in the context of a clinical trial. Do you agree with this appraisal? Please comment.

We agree to differentiate between IMP and "auxiliary medicinal product".
We also agreed on the modification of the term IMP provided by the concept paper, but considered that depending on the type and design of the protocol, safety, relabeling, covering and information to be provided about the IMP should be specified, differences should be implemented depending on whether the IMP is an authorized or a non-authorized drug. The IMP should be considered the drug under study, but not all the standard therapy.
Moreover,
differences should be implemented depending on whether the IMP is(are) an authorized or a non-authorized drug (s), taking into account the type and the design of the protocol, safety, relabeling, covering costs.
"Auxiliary medicinal products: it is recommended to specify which kind of treatments should be included in the definition.
Rules to be applied to "auxiliary medicinal product" should be the same applying to authorized drugs in terms of documents, costs covering, information and labelling.

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

Yes, both options are possible**.** But, because not only the drug but the simple fact of a trial being performed is a risk for the subject (voluntarily participating in the trial), we agree that removing insurance is not applicable in any case, even low-risk trials. The only situation for not having insurance would be the case in which the participating institutions certainly already have such a policy covering even the low risk trials.
The proposal should be sent to the European Committee of Insurance in order to know their position regarding these issues.

Consultation item no. 15: Maintaining the concept of a single sponsor is preferable. Do you agree with this appraisal? Please comment.

Against Single Sponsorship even if European requirements for submission are harmonized. It is impossible for an investigator to act as sponsor and assume all responsibilities (insurance, IMP,…), although a partner company would be keen to participate. In the context of independent research, the single sponsor model for the complete EU limits the possibility of implementing contingency plans during the course of the study to complete studies that are not achieving the initial expectations. In the case of independent research it is sometimes necessary to seek for partnerships between centers in order to complete the study, and these centers cannot assume the responsibilities of the other participants and vice versa. Finally, this is an excluding model, as it does not allow multiple sponsorship.

Cons of following Option2: Multiple Sponsorphip makes it difficult to assume all the responsibilities of the sponsor.
For pharmacovigilance it is apparently safer to have a single sponsor in charge.
Multiple Sponsorship would still require always one of them to assume a “coordinating” role and all the responsibilitie s should be clearly determined among them (additional bureaucracy).
If there are multiple sponsors, we would not have to give local explanations that delay the studies.

Consultation item no. 16: Clinical Trials Directive could be amended to the effect that the informed consent and th e information from the investigator may take place during or after the clinical trial in Emergency Clinical Trials. Do you agree with this appraisal? Please comment.

Yes. The performance of an Emergency Clinical Trial (ECT) is considered clinically relevant and its specific regulation should be equally regarded. The IC (Informed Consent) and the Patient Information carried out by the the Investigator can take place after inclusion of the patient in the study when : the study subject is not capable of giving consent; the physical and mental condition of the subject that prevents from providing the IC is a (necessary) characteristic of the study population; due to the emergency situation it is impossible to obtain the IC from the parents/legal representative and/or the study subject has not previously expressed objections know by the investigator