Revision of the "Clinical Trial Directive" 2001/20/EC

Comments to Concept Paper submitted by the European Commission
for Public Consultation
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In general, Roche supports the comments and suggestions provided by EFPIA on the concept paper presented by the European Commission. The following comments are of particular interest to Roche and have been prioritized accordingly.

Consultation Item 1:
Single submission of documents to an EU Portal with separate assessment

"A single submission would greatly reduce the administrative work of sponsors for submission of documentation to the Member States concerned?"

Do you agree with this appraisal? Please comment.

Roche very much welcomes this proposal and considers the EU Portal would be a major step forward which should be achieved by the new Directive. To be successful, such a system should at least meet the following conditions and details should be vested in further legislation and guidelines after appropriate stakeholder consultation:

1) Submissions must be possible in a confidential and secure mode. Content and format of submissions both for clinical trial applications and ethics committees must be standardized.

2) The portal should encompass all important communication between the sponsor and the competent authorities and ethics committees.

3) Additional clarification would be necessary that the submission to the EU-Portal supersedes any national submission independently of the authorisation system which will finally be chosen. The future procedure should exclude any additional national submission.

4) Clarification is needed that not only the initial application will be channeled through the EU Portal, but also subsequent amendments. As a consequence, all documents related to the application should be submitted through the EU-Portal, independently of the type of clinical trial (academic trials, commercial sponsor trials) and the type of authorisation.

5) We see benefits in having the possibility to submit not only risk-benefit assessment documents (Point 1.3.1a of COM Consultation document) but also documents concerning local aspects and ethics committees (Point 1.3.1b and c) to the EU Portal. We particularly welcome the clarification by the Commission during the stakeholder meeting that submission of all documents related to clinical trials (i.e. both those submitted to competent authorities and ethics committees, including amendments) would be handled through the EU Portal. Future legislation should be clear on this.

6) For multinational companies it is important that the main risk-benefit documentation (Section 1.3.1.a of COM Consultation) for a clinical trial can be submitted in the English language (e.g. protocol, investigator brochure). While it is understood that the language regime is subject to Member States jurisdiction in the case of a national authorisation system, clarification would be extremely important for pharmaceutical companies. Such clarification could, for example, take place in detailed technical requirements, either in the form of detailed guidelines or delegated acts.

Consultation Item 2:
Separate vs. single assessment

"A separate assessment would insufficiently address the issue set above: the difficulties created by independent assessments would remain."

Do you agree with this appraisal? Please comment.

Roche fully agrees with this assessment. We would like to complement this point with a description of criteria which are of key importance for the setting up of a successful future assessment and authorisation system from the perspective of an innovative pharmaceutical company:

1) A one-stop shop is needed for submission (see point 1.1.) and all communication between the sponsor and national authorities and ethics committees should be coordinated by this portal.

2) There is only one set of requirements for submission of an application in the EU. Requirements are clear and cannot be amended by Member States, except for those falling under Member States' competence (e.g. indemnity/ insurance documentation as outlined in Section 1.3.1b and c of the COM Consultation document); the requirements for risk-benefit documentation and assessment should be fully harmonised within the EU, preventing Member States from adding their own rules. Instead of vesting requirements in guidelines, they should be exhaustively regulated in legislation.

3) The assessment and the subsequent step of authorisation should take place within the maximum timeframe defined in legislation (for both together: maximum of 60 days), incentives for a faster process should be put into place.

4) The system allows and promotes further reduction of timelines (< 60 days) for assessment, in particular for innovative products and Phase I trials.

5) For multinational clinical trials applicants should receive only one consolidated list of questions within a defined timeframe. This should apply to initial submission and any subsequent amendments.

6) The application assessment should be linked with preceding scientific discussions (scientific advice, paediatric investigation plan) so as to make processes easier to predict.

7) Sequential assessments of different studies within a clinical trial program should be streamlined on the basis of a risk-assessment and thus lead to fast-track authorisations.

8) Sponsors should be motivated to apply innovative standards in protocol design, trial methodology and trial management through incentives such as expedited reviews and – specifically for academic sponsors – through fee waivers.

9) The concept of "Centers of Excellence" will be further promoted within the EU for defined areas (e.g. cancer, CNS, paediatrics, ageing population). The basis could be a network of experts able to take leading roles in the assessment of clinical trial applications. Companies should have the possibility to propose a Rapporteur / Reference Member State.

10) There is a clear demarcation of tasks between the national competent authorities in charge of assessment of a clinical trial and the Ethics Committees.

11) A central, up-to-date overview of requirements that fall under national competences (e.g. insurance and ethical committees) should be established to allow for sufficient predictability. This could eventually be accomplished by the Commission, EMA or the Heads of Medicines Agencies on the national requirements related to point 1.3.1.b.

12) Flexibility is needed to quickly include additional centers in other EU Member States into an authorised clinical trial in the interest of patients, who may wish to participate in a given clinical trial. A timeframe of 15 days maximum is considered reasonable and justified for assessment and authorisation; in addition, there should be a possibility to refer to documents previously submitted (e.g. via EU Portal) without need to resubmit the same documents.

13) Clear mechanisms would be needed for the decision-making process concerning authorisations and any amendments. For the authorisation process following an assessment through CAP, we assume a consensus agreement should be reached in a similar way as for the decentralised (DCP) process of a marketing authorisation (Article 29 of Directive 2001/83/EC). For amendments, we think a distinction could be made between major and minor changes, whereas for the latter only a notification should be required.

While it is primarily important for Roche that all of these criteria will be met in a future system, we have assessed the two policy options proposed by the European Commission to document our preferences.

In conclusion, we agree that the coordinated assessment procedure ("CAP") as defined in the concept paper would represent an improvement compared to current practice. However, it does not fully address the risk of diverging administrative practices and delays of the assessment and authorisation of a clinical trial.

The risk could be addressed by a centralised assessment and authorisation procedure established at the European Medicines Agency leading to an authorisation in all Member States. Unlike ethical questions, scientific aspects are not a national issue. Good science does not stop at country borders and could thus be assessed by one committee instead of several. This would ensure full harmonisation. The concrete workings of such a committee should be looked at in more detail so as to make it more efficient.

Consultation Item 3:
Centralised assessment

"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.....")

Do you agree with the Commission's preliminary appraisal of this option?

Roche has supported the concept of a centralised assessment of a clinical trial application as an appropriate and efficient approach to address shortcomings of the past and continues to do so. Therefore, Roche does not agree with the Commission' s conclusions and provides the following comments on the Commission's assessment:

1) Roche supports EFPIA' s proposal of a centralised system not as the only but rather an optional approach (i.e. sponsors should be able to choose between the centralised and the national system).

2) A national system of ethic committees has already been established and will continue for any policy option, be it a national or a centralised assessment and authorisaton. Insofar the centralised system is not at a particular disadvantage compared to other models.

3) While indeed most multinational clinical trials include a limited number of Member States, the concept of a central assessment and the Union authorisation would have the advantage that trials can easily be expanded to other Member States while avoiding additional separate assessments or other formal steps.

4) According to an external legal assessment (separate attachment) under a centralised system both the assessment of a clinical trial application and the subsequent step of an authorisation in a centralised system can be delegated to the European Medicines Agency. We would consider this a proportionate approach as, unlike for marketing authorisations, there would be no need for involving the European Commission directly in this process.

5) The Commission mentions a cumbersome committee structure as an argument against the centralised assessment. We understand this argument if the "old model" of existing committees is used. However, we think for the central assessment of clinical trial authorisations, it is worthwhile to explore new models and working methods, including the following elements

    a. in general the concept for a Clinical Trial Committee could follow the model of the Pharmacovigilance Risk Assessment Committee – PRAC - (Art. 61 a of the new Pharmacovigilance Regulation 1235/2010);

b. in particular, Member States should be able to delegate their mandate to another Member State (see model of the PRAC – Art. 61a (2) of new Pharmacovigilance Regulation 1235/2010);

c. as a modification of the PRAC concept, a model of a project/product related composition of a Clinical Trial Committee should be explored;

d. alternatively, specific scientific discussions could take place in specific expert groups following the "scientific advice group" model; this would be efficient insofar as it should allow initial involvement into the discussion primarily by experts of those Member States, in which the trial will be conducted ;

e. the final scientific opinion on the assessment should be endorsed by all 27 Member States;

f. a coordination with other scientific committees of the EMA should be established, however, due to the nature of the topic, the Clinical Trial Committee assessments should not need formal decision making by the CHMP but would rather follow the "stand-alone" model of the Paediatric Committee;

g. the Agency could explore virtual meeting and communication opportunities instead of expensive face to face meetings for the Clinical Trials.

6) Additional possibilities to encourage a fast-track system and provide incentives should be explored.

Conclusion:

Roche concludes that 10 years after the establishment of the national system, despite improvement measures of the recent past, the current system has reached its limits. To meet the objectives on innovation of the EU 2020 Agenda and the Flagship initiatives by the European Commission, a centralised assessment would represent a straightforward approach and could be introduced stepwise. It would allow involvement of the expertise by the Member States and, at the same time, the highest degree of reliability and possibility to have a swift assessment and a subsequent authorisation. A swift approach is of key importance for the European pharmaceutical industry to be able to compete in a globalised marketplace. Finally, we think the EU should take the opportunity to develop new models for increasing its cooperation efficiency through EMA. Roche would appreciate the opportunity of an open dialogue with the Commission and Regulatory Agencies on new models and approaches in this respect.

Consultation Item 4:
Coordinated assessment procedure – CAP

The authors of the concept paper consider three possible areas for defining the scope. These three areas are presented on page 5 of the Concept Paper

The authors of the consultation paper propose that only one area, *"the risk benefit assessment as well as aspects related to quality of the medicines and their labelling'* would be suitable for being within the scope of the CAP.

They consider that the other two areas namely *' ethical aspects related to informed consent, recruitment and reward"* and *'local aspects related to suitability of sites, investigators, and national rule* such as those relating to insurance/insemination or personal data protections matters' are to be fully managed at national level.

Is the "catalogue" outlined on page 5 of the Consultation Paper complete?

Firstly, according to our assessment the catalogue described by the Commission appears to be complete.

Secondly, concerning the assessments and descriptions made in Section 1.3/ 1.3.1 we would like to highlight that, the "CAP" system should only be taken into account if at least all of the conditions we described under 1) can be met. In addition, clarifications would be needed for the establishment of a coordination group, involving at least the Member States concerned with regard to the clinical trial.

Consultation Item 5:
CAP - catalogue of documents to be assessed

Do you agree to include the aspects concerning 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?

We largely agree with the Commission´ s assessment.

However, we have concerns on the Commission´s previous assessment under Section 1.3 that it should be completely up to each Member State to divide the tasks between the competent national authority and the Ethics Committee.

Firstly, we think that the risk-benefit assessment of a clinical trial in preparation of an authorisation should clearly fall under the responsibility of the competent authorities (European or national depending on the system). This point should be clarified in legislation and not leave room for interpretation.

Secondly, we understand that the organization of ethics committees is a national responsibility. While we acknowledge that this system should remain unchanged, we see benefits in aligned remits and an increased consistency and transparency of approaches by Ethics Committees across Europe, such as convergence of considerations on composition and working methods (e.g. interaction between competent authority and ethics committee in case of discrepant views). Irrespective of such an approach each ethics committee should have the right to come to its own conclusion.

We are of the opinion that the ethics committee approval system within the European Union would benefit from support by the Union trough the establishment of collaboration platforms for an exchange of best practices and views. Such a platform could be established by the European Commission in a similar way as this was done for the collaboration of Member States in the area of Health Technology Assessment (EUnetHTA). It would be beneficial if such a network would be vested in European legislation. This would allow for a higher degree of coordination, cooperation and transparency and ensure appropriate funding.

Consultation Item 6:
CAP - Options in case of disagreement with assessment report

The authors of the paper have proposed that disagreements amongst Member States could be resolved in 3 possible ways as follows:

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';

② The Member States concerned could vote on the issue and decide by simple majority; or

③ The matter could be referred to the Commission or the Agency for a decision at EU level.

Consultation item no 6: which of the approaches (i.e.①, ② or③) is preferable? Please give your reasons.

On this point we have made some assumptions: If a comparable system was chosen as defined in Article 28 of Directive 2001/83/EC, the system would encompass at least the following steps:

Step 1 - Reporting Member State prepares a draft assessment report.

Step 2 - Assessment report is approved by the Member States concerned within a certain timeframe.

Step 3 - Each Member State takes a separate decision on the authorisation.

On this basis, we do not understand whether the disagreements referred to in this point are related to the discussion before approval of an assessment report (process of Step 2) or thereafter (after Step 2 and before or in parallel to Step 3) and clarification would be needed in this respect.

On Point 1) If there was a justified serious risk to public health or safety to the patient we would like to question how another Member State could vote in favor of a positive assessment of a study.

on Point 2) No matter if the vote takes place during the assessment period (Step 1) or after the approval (Step 2), we have concerns that a simple majority vote on a disagreement between potentially a small number of Member States could still lead to authorisation difficulties on the basis of an approved assessment report in practice in the Member States that voted negatively.

On Point 3) A referral to the Agency or Commission is considered to be a lengthy process, which would only be justifiable in exceptional cases, e.g. if there were justified serious risks to public health or safety to the patient.

Therefore, our conclusion is slightly different than EFPIA's conclusion and we are proposing the following:

- Member States should be obliged to resolve any issues during the coordinated assessment process;

- Therefore, an opting out after conclusion on the scientific assessment should only be allowed if a robust and public health based justification is presented on the basis of defined criteria (to be defined in Commission guidelines); the clear limitation of what constitutes a serious risk to public health should automatically limit the number of opt-out cases;

- It is clear that a justified serious risk must be resolved. As Member States concerned could obviously not resolve the issue through discussion, a simple majority vote would always single out the Member State without addressing the issue. Therefore, in order to really address any public health risk a referral to the Commission or the Agency seems proportionate in those exceptional cases. To limit the number of referrals, the concerned Member States could take a decision on submitting a referral to the Agency or the Commission on the basis of a single majority.

- Timelines need to be defined within which any potential problem must be resolved and when a study can be started in a Member State. For instance, there should be a clear time point by when Member States, that have approved the assessment report and authorised the clinical trial, may start the clinical study if the issue has not been resolved.

- Following assessment swift authorisation by the concerned Member States should be the rule; therefore any opting out should not be detrimental to the start of the study in Member States which have a positive opinion on the trial if open issues cannot be resolved within a reasonable timeframe.

- The applicability and practicability of such future provisions should be reassessed by the Commission after a defined period (e.g. 5 years).

Consultation Item 7:
CAP – Mandatory/ Optional Use

Three approaches are proposed as follows:

*① Coordinated assessment procedure mandatory for **all** clinical trials*

*② Coordinated assessment procedure mandatory for **all multinational** clinical trials*

*③ Coordinated assessment procedure **completely optional***

Consultation item no 7: Which of these three approaches (①, ② or ③) is preferable?

Roche disagrees on option No.3. Once implemented in legislation, the CAP should be a mandatory concept for multinational clinical trials. If the CAP was an optional concept this would mean that companies could follow different approaches for a single IMP. For reasons of consistency on clinical trials such an approach should not be in the interest of the majority of regulators and various stakeholders.

On the remaining Options 1 and 2)

Roche considers it imperative that the future system fulfills the following minimum criteria concerning purely national clinical trials, i.e. clinical trials which are conducted in only one Member State:

- the assessment for national trials will only be performed by the Member State, in which the study takes place;
- no coordination with other Member States is needed in such a case;
- the outcome of the review is made accessible to other Member States;
- the system allows extension of the trial to other Member States following a defined procedure;
- the system should allow Member States to conduct an assessment which is faster than 60 days (as already applied by some countries) and thus incite competition between Member States;

A revised system should definitely be no more cumbersome for purely national clinical trials than the current situation.

We understand that Option 1) offers the advantage of "one system" for the European Union. Clinical trials which are conducted in one country only could constitute a "special case" of option 1) not requiring any type of coordination with other countries. Under this assumption applications for single-country trials under the CAP system should, in practice, be handled as national trials today.

If the above criteria cannot be implemented, Roche gives preference to option 2).

Consultation Item 8:
CAP – timelines for authorisation, pre-assessment

"There should be clear rules on the timelines for the approval of substantial amendments, taking into account that the assessment is limited to aspects of the clinical trial which have been subject to" a CAP.... *"The timelines could be shortened where the risk to trial subject is low and where the assessment in the CAP is limited largely to issues of reliability of data. To this end, these types of trials (hereinafter 'type –A trials') could be identified in pre-assessment."*

The proposed definition of a 'type A' trial is as follows:

"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.'

Do you think such a pre-assessment is workable in practice? Please comment.

Comments on the Commission' s explanations:

1. Tacit approval and timelines

- While Roche would like to challenge the idea of abandoning a tacit approval in general, the company agrees that a tacit approval will be difficult under the CAP. There should be clear maximum timelines for an assessment and subsequent authorisation not exceeding the current provisions (60 days).

- In addition, there should be clear maximum timelines for the authorisation of a substantial amendment. We consider that 10 days for assessment and 5 days for authorisation of an amendment under the CAP could constitute a reasonable approach.

2. Concept of the pre-assessment :

- Roche welcomes the opportunity of a "fast-track" assessment; such a system needs potentially be complemented through a fast-track authorisation system and highlights the need to implement such a system also for innovative products that have not been authorised.

- While the procedural details of the pre-assessment concept are not described, we have concerns that such a process may be cumbersome in itself and therefore we have doubts that such a system will result in actual benefits in terms of review time. In no way such a pre-assessment should add to the complexity of the overall assessment procedure or prolong the overall timelines of an assessment.

- If such a procedure will be installed, we agree that the criteria for the pre-assessment should primarily be risk-based.

3. Definition of "Type A-trial" which are subject to shortened timelines:

- We understand that under the current proposal for a pre-assessment, a fast-track approval would only apply to studies with products that are marketed. Such a limited concept would not meet the needs of an innovative company. This applies even more as in certain regions or countries, even within the EU, an authorisation is possible between 28 and 35 days (e.g. fast track authorisations are possible and applied in practice in Belgium, the UK, Ireland, Germany, Denmark, Austria and Spain). We fear that under a harmonised system, where a fast-track system is limited as proposed by the Commission, the above mentioned current provisions might not be possible any more and such a situation would be difficult for Roche to accept.

- If for "type A trials" reference is made to authorised products, this should not only refer to authorisations in the Union but be extended to authorisations in the ICH regions.

- We understand and agree that in no way patient safety must be negatively impacted through a fast-track procedure. On the other hand, a fast-track procedure should also be possible for other products or situations.

- Finally, we propose that, depending on the outcome of an individual risk-assessment, sequential trials within a clinical trial program should also qualify for a fast-track assessments and authorisation. We are of the opinion that sequential assessments of different studies within a clinical trial program should be streamlined on the basis of a case-by-case risk-assessment and a as such also fall under the category of "type A trials".

Consultation Items 9:
Scope of CT Directive - non-interventional trials

"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 could apply to all clinical trials falling within the scope of the present Clinical Trials Directive. "

Do you agree with this appraisal proposed in the Concept Paper? Please comment.

Roche agrees with the Commission' s proposal to leave the definition of "non-interventional trials" unchanged and thus not limit the scope of the Clinical Trials Directive, considering that such trials are currently excluded from the Directive.

We are of the opinion that the Directive should continue not to apply to "non-interventional trials".

Furthermore, we would support a clarification of the definition insofar as the intervention should relate to the investigational medicinal product (IMP). For such studies, which do not include interventions related to the IMP, it should be possible to document the results in a Case Report Format. Such studies should not fall under the scope of the Directive.

Consultation Items 10:
Scope of CT Directive and academic/ non-commercial sponsors

"Rather than excluding clinical trials by 'academic /non-commercial sponsors' from the scope of the Clinical Trials Directive it would be better to come up with harmonised and proportionate requirements for clinical trials. There proportionate requirements would apply independently of the nature of the sponsor ('commercial' or 'academic/non-commercial')."

Do you agree with this appraisal? Please comment.

Roche would not welcome limiting the scope of the Directive but supports the idea of harmonised EU-wide standards. Applying double or different standards for academic/ non-commercial sponsors and commercial sponsors is not acceptable. This is important as results in particular of such academic studies may have an impact on the overall risk-benefit assessment of a medicine.

However, from the question it is not fully clear whether the Commission intends to make academic/ non-commercial sponsors subject to all existing requirements or whether requirements would need to be newly established (possibly on the basis of existing requirements) for all types of sponsors. In any case, requirements should be sufficiently detailed and harmonised without leaving room for interpretation by Member States.

Consultation Items 11 and 12: Harmonisation of rules:

"This approach (more risk adapted rules for the content of the application dossier and for safety reporting) would help simplify, clarify, and streamline the rules for conducting clinical trials in the EU by providing one single, EU-wide, and risk adapted set of rules."

11 - Do you agree with this appraisal?

Roche fully supports the harmonisation of the above mentioned aspects in legislation. The guidelines recently published by the Commission provide important elements which need to be vested in legislation. We support a proposal through technical Annexes which can be changed through delegated acts. These can easily be amended or changed as the environment evolves and as there will be future needs for changes.

12 -Are there other key aspects on which more detailed rules are needed?

Roche considers it important that the new legislation does not leave room for interpretation on any classification of an amendment (major and minor amendments) and the necessary procedures related to any notification (do and tell procedure, tacit approval for minor amendments; 10 days assessment and 5 days authorisation for major amendments).

Detailed rules for safety reporting are needed.

More clarification is needed, through a legal basis for certain guidelines or clarification within those guidelines, that existing technical guidelines are exhaustive . Examples of guidelines which are currently subject to different interpretation by Member States:

- Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials (CHMP/QWP/185401/2004 final)
- Guideline on the Requirements for Quality Documentation concerning biological investigational medicinal product in clinical trials (EMA/CHMP/BWP/534898/2008)

Consultation Item 13:
Definitions/ Rules: "Investigational Medicinal Products" (revised) and "auxiliary medicinal products" (new)

"The combined approach (investigational medicinal product and definition of and rules for auxiliary medicinal product) would help to simplify, clarify, and streamline the rules for medicinal products used in the context of a clinical trial."

Do you agree with this appraisal?

- For such a proposal to be feasible, the future regulatory regime for auxiliary medicinal products needs to be indeed proportionate.
- For the envisaged definition of an investigational medicinal product clarification is needed as what should be considered a "reference" in a clinical trial.

Consultation Item 14:
Insurance/ Indemnisation

Several policy options are proposed:

- *"Removing insurance/indemnisation requirements for low-risk trials: This policy option would remove the insurance requirement for clinical trials which typically pose a low risk for trial subjects ";* or
- *"Optional indemnisation by Member State: This policy option would put Member States under an obligation to provide for an indemnisation for damages incurred during clinical trials performed in their territory, taking account the national legal system for liability. In view of the damages arising today."*

Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

As all countries of the European Union currently have different mandatory clinical trial insurance policies in place it would not be favorable to remove insurance requirements for low risk- trials or to optional indemnify by Member State, but to create single European clinical trial insurance wording through harmonised standards. The Protection of the Patient against insolvency of the Sponsor still should be the leading argument.

1. Simplification for multi-national clinical trials within the EU

Currently for each Member State a local policy with country specific limits and wordings is requested which causes an extraordinary effort for the Sponsor as well as for the Insurance Companies handling multinational Insurance Programs. Minimum limits differ from 100'000 Euros per Patient up to 1 Mio Euro per Patient.

A EU Clinical Trial Policy with a general minimum insurance limit needs to be defined. The Policy can be issued by each insurance company registered in the EU for all participating countries. Local mandatory Reinsurance like the "Probandencover" in Germany should be abolished or harmonised.

2. Risk level differentiation

The EU wording should reflect the different risk levels of clinical trials as this is already in place in some countries. To simplify the application process for clinical trials, the wording should consider a specific risk spectrum. The categories could be low, medium and high risk. From Clinical trials which typically pose a low risk for clinical trial subjects see point 1.3.4 of the concept paper to sophisticated biopsies or other maximal invasive methods.

3. Acceptance by Ethic Committees

Once being approved to be the EU Clinical Trial Insurance Policy, Ethic Committees should be obliged to accept the Policy and certificates issued hereunder. Actually Sponsors face time consuming discussions with Ethic Committees regarding Clinical Trial insurance even if certificates are issued by local insurers.

Consultation Item 15:
Single sponsor concept

"In the view of the description option 1 (maintaining the concept of a single sponsor) 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"

Do you agree with this appraisal proposed by the authors of the Concept Paper? Please comment.

Roche supports the concept of a "single sponsor". We are concerned that a "multiple sponsors" concept could result in a more complex system with limited benefits in only few circumstances while for the large majority of clinical trials the single sponsor concept has proven to be useful in the past.

In addition, and on the Commission' s consideration we have the following comments:

- We consider it important that some tasks and responsibilities of a sponsor can be delegated within a company or to external entities as long as delegated roles and responsibilities are unequivocally defined in a contract between the partner(s). Any future system should continue to allow such delegation.

- Studies with collaborative groups (which may involve multiple stakeholders e.g. academics and eventually be identified as commercial entities) have increased over the past years. For the cooperation between pharmaceutical companies and such groups it is important that such flexibility concerning the delegation of tasks will be maintained.

- We understand the current wording of Article 19 of Directive 2001/20/EC on the civil and criminal liability of the sponsor is already clear today.

- For reasons of transparency of sponsors becoming active in the EU it may be of added value if the EMA or the Commission or the Member States under the HMA prepared an exhaustive overview of implemented provisions concerning responsibilities and liability rules of all Member States affecting sponsors and made this overview publicly available.

- We agree that a further harmonisation of technical requirements on clinical trials (Section 2.2 and Consultation Items 11 and 12) would implicitly lead to more clarity for sponsors concerning their responsibilities and expectations by competent authorities concerning the supervision of sponsors.

Consultation Item 16:
Emergency Clinical Trials

It is proposed to amend the Clinical Trials Directive to the effect that the informed consent and the information from the investigator may take place during or after the clinical trial under certain conditions outlined on page 14 of the Concept Paper.

"This could be viable option in order to address the type of research and bring the regulatory framework in line with internationally-agreed texts."

Do you agree with this appraisal? Please comment.

We understand and support the Commission's approach. While the issue seems to be primarily a point for healthcare professionals, the pharmaceutical industry could equally be affected by the problem.

Consultation Item 17:
Clinical Trials in Third Countries

The authors of the Concept Paper refer to the criteria applicable to determine that the results of trials performed in third countries are acceptable to support applications for marketing authorisations filed in the EU and in particular to relevant provisions contained the Annex to Directive 2001/83/EC and in CT-1[1]

They mention various actions undertaken by the EMA in relation to the implementation of this legislation and propose:

1) *"Codifying in the revised legislative framework, the provision in point 2.7.2.4* of CT-1 " i.e.
"All studies 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."

2) *"Further supporting capacity building in third countries where the regulatory framework for clinical trials, including its enforcement is weak"*

3) The authors of the Concept Paper also propose that *"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."*

Do you agree with these 3 proposals? Please comment:

While Roche agrees with the concept of the three proposals made, we ask the Commission to consider the following points:

- On the third point instead of requesting registration in the EudraCT database, we would propose to accept registration in a WHO certified registry and ClinicalTrials.gov in addition. This means that reference to entries in such certified registries should also be acceptable in an application for a marketing authorisation.

- We understand that any future requirement on GCP in third countries may trigger additional inspections/ compliance check by EU authorities in third countries. We assume this could lead to increased activities by authorities and an increased administrative burden for companies. To avoid duplication of work and ensure efficient use of resources by regulators, industry and all participants in a clinical trial we would welcome initiatives for enhanced cooperation of different regions on inspections.

[1] Communication from the Commission (2010/C 82/01)

- Finally, we would like to remind that with the MRA between the EU and Switzerland both parties had expressed the intent to expand the MRA on mutual recognition of results on GMP inspections to GCP inspections. We did not see that work has moved forward in this respect. On the other hand Switzerland remains to be a country actively conducting clinical trials.

Consultation Item 18
Figures and Data

We would be grateful if you could provide recent information on

- **Time /resource required prior to the initiation of multinational clinical trials in all concerned Member States**
- **Resource required e.g. to file /clear protocol amendments in multinational trials, time needed to implement these changes.**

Recent and precise figures and data illustrating the issues which the revision of the clinical trial legislation should address will be very welcomed.

On point 6 of the Annex of the consultation document we have explored the following data:

	Total for a CT in 1 country	Total for a CT in 3 countries	Commission estimate
Initial submission	101 h	159 h	40 h
Follow-up information	27 h	49 h	16 h
Amendments	16 h	38 h	10 h

Explanation:

The time needed for the sponsor to comply with administrative requirements of an average clinical trial application has been estimated by assessing the number of man-hours spent on both a central (headquarters) level and an affiliate level. It has been calculated that the total number of man-hours spent on the submission of a CTA is more than double the Commission's estimate for a single-country trial. For a multinational trial, which would particularly benefit from a successful revision of the clinical trial directive, this number is even higher: for instance, the time spent on the submission of a trial conducted in three EU member states is estimated to be almost four times the Commission's estimate. The man-hours spent on follow-up information and amendments are also significantly higher.

We are concerned that the compilation of country-specific documents at both a headquarters and affiliate level is one of the key factors contributing to these high estimates. Other factors include the following:

- Lack of alignment in the timelines for follow-up information.
- Translation activities for some member states.
- Local ethics approval issues requiring HA communication.
- Notarized documents needed in some member states.
- Planning and coordination for the alignment of different elements, such as labeling information, the quality IMP documentation and the investigator's brochure (we acknowledge that the preparation of the content of these documents is not included in these estimates, yet there are also administrative efforts required for the preparation of these documents).

It must be underlined that these numbers reflect an estimate of an average trial. The actual time for a submission can vary greatly depending on the type of study, the availability of any previous CTAs with the same IMP, the involvement of new countries, etc. The time spent on follow-up information can also vary, depending on whether questions or requests for information from multiple countries are similar and whether the timelines are aligned.

The recommendations elsewhere in this consultation document would reduce the time for various steps, thereby also lowering administrative costs. For instance, the time spent on an initial submission may be lower due to increased harmonisation of requirements and consequently less man-hours spent on an affiliate level. Resolving the current lack of alignment between member states in the follow-up information stage, could also reduce costs at both headquarter and affiliate level.

With the assumption that all submissions can be made through a central EU portal, as suggested in the consultation paper, the preparation time of a multi-national trial in any future CTA system is similar to that of a single-country trial in the current system. Therefore, our estimations show that 35 to 50% of preparation time and related administrative costs could potentially be saved in such a future system.