REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC
CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

Response

1.1 Single submission with separate assessment

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.

Single submission
Yes, a single electronic submission would greatly reduce the administrative work of sponsors for submission of documentation to the Member States concerned, only if there is no divergence between member states in terms of the documents required to accompany a CTA application.

If the 'EU portal' subsequently 'distributes' the information electronically (and as soon as it is submitted by an applicant), to the Member States concerned, then it is a workable solution. Ideally, there should be no case for 'distribution'. The member state(s) concerned should be able to access an electronic application as soon as the applicant has submitted it via the portal.
If there is any human intervention in the proposed 'distribution' process, this has the potential to greatly reduce any benefits derived from being able to make a single submission due to potentially increased timelines for assessment.

Separate assessment
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.
If a single submission is facilitated via an EU portal, then having totally separate assessments is a regressive step and does not help to achieve the desired efficiencies. A solution must be arrived at which allows the assessment of the common parts of an application centrally. In this regard, every effort must be made to ensure that the application documents required for all member states are identical as far as is possible

1.2. Single submission with subsequent central assessment

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.

Comment
Partly agree. A central assessment should be made possible for the common documents for an application. The rest can be handled nationally although there is no reason why it should not be possible to handle these aspects centrally via the formation of a committee consisting of members from each member state.

- 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.

Comment
The sheer number of trials and substantial amendments is a compelling reason for a common assessment structure to be agreed upon in order that duplication of work is eliminated as far as possible. It is wholly unacceptable to continue wasting valuable time and resources.

- The involvement of all Member States is not needed, as very few clinical trials are rolled out in more than five or six Member States.

Comment
On the surface of it, this sounds like an easy option, but it would mean a lost opportunity in bringing the member states together and facilitating the development of consistently high quality assessment capabilities in all member states. The development of such a capability has the potential to have a very positive impact on the conduct on clinical trials and ultimately, patients.

- 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.

Comment
It is highly unlikely that the costs involved to create and maintain new infrastructure would exceed the costs currently incurred by multiple assessments of each application. In fact, central assessments and the increased use of electronic submissions should drive down the overall costs substantially and make it highly favourable for academic researchers.

1.3. Single submission with a subsequent 'coordinated assessment procedure

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

1.3.1. Scope of the CAP

Consultation item no. 4: Is the above catalogue complete?

No comment

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

The aim should be to create a CAP procedure which includes as many elements of an application as possible. Where there are differences, it is important to establish whether these are of a nature such that it is genuinely not possible to pursue a common approach. National assessment should be restricted only to those areas where there is absolutely no common ground.

1.3.2. Disagreement with the assessment report

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';

Comment

There is a danger that this could become the rule rather than the exception which would in turn undermine the concept of creating a CAP procedure and achieving the desired positive changes to the conduct of Clinical Trials in the EU.

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

Comment

Whilst this is a very tempting option, it is an option which has the potential to create outcomes not always in favour of patients. Outcomes must be decided based on what is in the best interest of patients. Voting has the possibility of delivering a popular outcome rather than the appropriate/desired outcome.

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

Comment:

Referring the matter to the Commission or Agency for a decision brings the added burden of a potential substantial increase in the assessment timelines. This option is viable only if assessment timelines are not increased from the current timelines.

Consultation item no. 6: Which of these approaches is preferable? Please give your reasons.
The third option of referral to the commission or agency is a preferred option, but only if it can be guaranteed that the overall assessment time for applications will not be increased from the current timelines.

1.3.3. Mandatory/optional use
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

Comment
Making CAP mandatory for only multinational trials means employing a two tier system which would not achieve the desired efficiencies and reduced costs to make the EU an environment of choice in which to conduct clinical trials.

- CAP is **optional**. (This would mean that sponsors could continue to refer to the national procedures laid down in the Clinical Trials Directive).

Comment
It seems absurd to create new infrastructure at great cost only to have the system used at will. There is also the danger that there might be an overwhelming number of companies that might not use CAP if it is optional in order to maintain the *status quo*, in which case there would be very little or no benefit from the new infrastructure and systems..

Consultation item no. 7: Which of these three approaches is preferable? Please give your reasons.
The most sensible approach would be to make the CAP mandatory for all trials in order to achieve the desired efficiencies and reduction in costs. However, it might be prudent to initiate the CAP procedure in phases starting with multinational trials to establish how well the process works before extending it to all trials.

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 is not unreasonable that pre-assessment would be workable. The question is whether it would deliver any enhanced benefits over the current system or would it just create extra and unnecessary work for all parties concerned?

- As per the consultation document, tacit approval is the exception and as such, whether or not tacit approval is possible or not does not matter.
- As per the consultation document, timelines of the CAP should not be longer than the timelines currently provided in the Clinical Trials Directive. If e.g. a CAP procedure takes longer than the current system, it cannot be beneficial e.g. in the UK, applications for Type I trials on healthy volunteers are on average assessed within 14 days. Any proposed CAP procedure must take this into consideration. A feature of CAP should be an overall improvement in assessment times, but should not lead to a situation whereby it has a negative impact on member states which already have excellent systems in place delivering consistently good times on assessments.
- Categorisation of trials into Type A, B etc is not desirable as it creates further and unnecessary stratification. The current system operates without stratification and there is no reason why a replacement system cannot not operate in the same manner.

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.
Agree with this proposal

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.
Agree with this proposal

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.
Agree with this proposal

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

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.
Disagree with this proposal. The current definition of IMP should be maintained . There is enough guidance detailing the definition of an IMP. On those occasions where there is any doubt, the applicant should refer to their local competent authority. It is also not a good idea to introduce the term auxiliary medicinal products. Apart from the fact that it is absurd to use the word 'auxiliary' to describe a NIMP, it also has the potential to create further and unnecessary confusion. It is better to retain the current definition of an Investigational Medicinal Product. If a product is not an IMP, then it should be called a NIMP. There is already enough guidance on what constitutes and IMP and a NIMP. There is already draft guidance document for a NIMP dossier. Changing these definitions would be a totally retrograde step and create a waste of time and resources with a defined end benefit not certain.

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.

Option 1 should remain the preferred option i.e. that there should be a single sponsor. Any other options have the potential to create further confusion and greater involvement of company legal departments to establish which sponsor is responsible for a particular part of a trial. This in turn could create greater complexity in contracts on responsibility which might deter a trial from progressing as an inordinate amount of time may be spent on writing contracts.
Other options would be great for job creation, but it is unlikely that they would bring any benefits.

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

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.
Agree with this proposal

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.

At the heart of this change process must be the desire to develop a world class system for the conduct of clinical trials in the EU that can be used as a benchmark for the rest of the world to follow.

Any new systems/processes created should be pragmatic and easy to follow. It should be a primary intention of the revised legislation to eliminate bureaucracy.

Most importantly, the EU member states need to work closely to arrive at a CAP procedure which encompasses the bulk of a CTA dossier. The revised Clinical Trials Directive must have a good balance between protecting patients whilst ensuring that the EU remains favourable region in which to conduct clinical trials.

Rather than reinventing the wheel, it would be prudent to review the existing systems in place in each of the member states and extract the best elements of the current system and then supplement them with additional well designed processes that incorporate the use of e-submissions.

Sincerely

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