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Comments of Finnish Medicines Agency, Fimea on the European Commission's concept paper regarding the revision of the "Clinical Trials Directive" 2001/20/EC

The Clinical Trials Directive (CTD) sets out rules for the authorisation and regulatory follow-up of a clinical trial with the objective to protect clinical trial subjects and to ensure that the results are credible.

In Commission's concept paper, a considerable attention is focused to the assessment of multinational trials. The present legislation does not provide for a mechanism whereby the application for the clinical trial is submitted jointly to all Member States (MS) concerned as a single submission.

This, however, is not a major problem since, in year 2009, a total of 80 % of the trials were performed in one Member State only (see Table 3 of the consultation paper). Only 20 % of the trials were multinational and only 9 % were performed in more than 4 MSs. Thus, the present mechanism with national applications, serves well for 80-90 % of the applications. There is no need to radically change the system.

Legislation and application procedures are harmonised in the EU in accordance with the present CTD. Detailed guidance on the application format and documentation to be submitted is published. Exchange of information between the MSs is facilitated by a European database, EudraCT. All other information, which is not entered to the database, can be exchanged at the substantiated request of any MS. There are thus no obstacles for a harmonised co-operation within the present system.

For multinational trials, country specific procedures and adjustments can never be avoided: ethics committees work independently at national level, site specific arrangements must be processed individually in each country and, informed consents must be adapted to meet the needs of local requirements and local language. It is very unlikely that a multinational trial can be started in various MSs at the same time. Thus the need of a simultaneous processing of the application is of minor importance. However, if considered important, the present system allows a simultaneous application process too.

In general, there is no need to build overlapping procedures for multinational trials by copying systems from the marketing authorisation processes. This would create delays to the application process and limit the flexibility of sponsors to plan individual country specific timetables. This would also expand administrative work of competent authorities leading to a need of additional resources and resulting in additional costs.

A practical approach to support multinational trials could be adopted within the present directive by a mutual agreement of following practices:

MSs will exchange information via the EudraCT effectively by carefully keeping the content of the database updated by all the MSs concerned.

In a multinational trial, the sponsor and a national competent authority could agree that an assessment report is prepared by the agency and this report would be available to other possible MSs, where the trial is planned to be conducted. The availability of an assessment report allows a

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rapid national processing of the application. On the other hand, it still allows the possibility to pose relevant questions if important aspects are detected. This would be a flexible, economic and rapid way to enhance the application process, and it can be executed within the present legislation.

In the following pages, consultation items of the Commission's concept paper are commented in detail.

1. Cooperation in assessing and following up applications for clinical trials

1.1. Single submission with separate assessment

Item no. 1: Commission's preliminary appraisal: A *single submission* would greatly reduce the administrative work of sponsors for submission of documentation to the Member States concerned.

Single submission would reduce only a minimal fraction of administrative work of sponsors of multinational trials. For mononational trials (80% of the applicants) no advantages can be seen, it would create an additional step to the process. This would be only detrimental for academic investigators.

If applied to multinational applications only, there would be two overlapping systems to be supported by the competent authorities. This would give an unclear picture of the EU system and increase costs and work load without offering a significant benefit.

Item no. 2: Commission's preliminary appraisal: A *separate assessment* would insufficiently address the issue set above: the difficulties created by independent assessments would remain.

Separate assessment is not an issue. There is no demonstration that independent assessments would create difficulties. In all scenarios, 80 % of the trials are performed in one country only and thus assessed independently. Also central or coordinated assessment procedure of multinational trials must contain a possibility for an independent assessment to each CMS.

1.2. Single submission with subsequent central assessment

Item no. 3: Commission's preliminary appraisal: A *central assessment* is not appropriate for clinical trials approval and would not be workable in practice.

Commission's preliminary appraisal and the reasons presented are correct.

1.3. Single submission with a subsequent "coordinated assessment procedure" CAP

Commission's 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.

CAP does not offer any advantage to the present system. Since 80 % of the trials are mononational, it could involve only 20 % of the applications. The CAP would create a cumbersome structure which would contain all the elements that already exist. Even in coordinated assessment procedure, each concerned MS should be able to influence to the result. This means that national independent assessment must be performed in each CMS in any case. The work load of CMS does not decrease and the work load of the reporting MS increases. This creates additional costs and delays in the process.

To obtain a "single decision" per MS, the application must be processed in the local ethics committees anyhow.

1.3.1. Scope of the CAP

Item no. 4: Is the above catalogue complete?

Only the risk-benefit assessment and the aspects related to quality (manufacturing) would be suitable for the CAP.
It is unclear if CAP would bring added value to the application process.

Locally must be processed:

Labelling (language)
Importation of the medicinal products
Informed consents (language, local circumstances)
All ethical aspects (recruitment, rewarding, compensations)
Suitability of the investigator(s)
Trial site(s)
Insurance
Local laws on data protection
etc.

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

All aspects under a) cannot be included in the scope of CAP (see above). CAP offers no major advantage to the application process. It increases work load and delays.

1.3.2. Disagreement with the assessment report

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

None of these approaches is optimal. CAP does not offer such advantages that it should be created.

The possibility to an opt-out must always exist. Other MSs should not be able to vote that a trial can be executed in another MS against its own opinion. The decision cannot be handed over to Commission or the Agency either.

All these planned procedures result in delays and costs to the process.

1.3.3. Mandatory/optional use

Item no. 7: Which of these three approaches is preferable? Please give your reasons.

CAP mandatory for all trials? 80% of the trials are mononational with no need for CAP. It would increase administrative load and hinder national trials and non-commecial, academic trials.

CAP mandatory for all multinational trials? This would lead to two different overlapping systems in the application process which is not reasonable. This would limit the sponsor's options to perform trials the most suitable way. The agencies would have to build two overlapping systems, one for CAP and one for national trials. This needs resources and causes extra costs. How to manage trials performed also outside the EU?

CAP is optional? This would lead to two different overlapping systems in the application process which is not reasonable.

1.3.4. Tacit approval and time lines

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

Tacit approval is an obligatory/automatic authorisation within 60 days. In practice, this is an exception since the assessment is usually performed in lesser time, and the applicant is informed that there are no grounds for non-acceptance or such grounds are expressed.

In simple cases, the whole process does not take many days. In simple cases, not even assessment reports are necessary. All that is needed is a letter to the applicant stating that the trial can be started immediately.

An additional pre-assessment, as suggested, only increases administrative work load and transit time for the whole process. CAP multiplies the work load and time needed.

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. Enlargening the definition of "non-interventional" trials

Commission's 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.

Item no. 9: Do you agree with this appraisal? Please comment.

The present CTD sets clear requirements to all clinical trials (as determined in the directive). This leaves non-interventional trials out of the scope. Pharmacovigilance directive sets out new requirements to post authorisation safety studies (PASS). All possible new interpretations of the limits of non-interventional trials must be processed in line with the implementation of this directive.

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

Commission's 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.

Item no. 10: Do you agree with this appraisal? Please comment.

This practical approach is already possible and can be applied independently of the type of the applicant. The requirements must always be proportionate to the details and complexity of the trial.

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

Commission's 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.

Item no. 11: Do you agree with this appraisal? Please comment.

The present regulation and guidelines sufficiently cover the problem. Additional rules do not necessarily simplify, clarify or streamline the process.

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

At the moment, the number of clinical trials is decreasing in the EU. It seems that EU is not attractive enough as a good research environment. For academic investigators, the increasing amount of new rules and administrative work has become almost overwhelming. By increasing the amount of rules, after a certain point, the net effect becomes negative since nobody is able to digest all the rules.

For the sake of academic research, efforts should be made to diminish the amount of superfluous rules and administrative work.

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

Commission's 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.

Item no. 13: Do you agree with this appraisal? Please comment

The present CTD already covers the definition of IMP. Auxiliary medicinal products which are used during a clinical trial, but are not investigated, need not to be further regulated.

2.4. Insurance/indemnisation

Commission's preliminary appraisal: Both policy options could be a viable solution.

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

Removing insurance/indemnisation for low risk trials is not a practical solution. It is impossible to give exact rules to classify trials according to their possible risk. There is always a risk for errors which also should be covered in all trials. The insurance company should estimate the risk and proportionate it to the costs for insurance.

Optional indemnisation by Member State is not a proper solution. It is not acceptable that the sponsor takes the risk which is covered by someone else; in this case by the Member State.

2.5. Single sponsor

Commission's preliminary appraisal: In view of the above, option 1 may be preferable (=maintaining the concept of a single sponsor).

Item no. 15: Do you agree with this appraisal? Please comment.

Single sponsor is the only practical solution.

A shared sponsorship, where each sponsor is responsible for a specific task, leads to a situation where nobody will take a full responsibility of the trial.

2.6. Emergency clinical trials

Commission's preliminary appraisal: This could be a viable solution in order to address this type of research and bring the regulatory framework in line with internationally-agreed texts.

Item no. 16: Do you agree with this appraisal? Please comment.

In certain circumstances emergency clinical trials are justified also in situations where informed consent cannot be obtained because of the state of the subject.

The CTD should be amended to make such trials possible, provided that the ethics committee has expressed its positive opinion on the protocol.

3. Ensuring compliance with good clinical practices in clinical trials performed in third countries.

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

Commission's concept paper addresses to an important issue. This, however, does not concern the revision of CTD which is focused on trials performed in EU. EU has no mandate to regulate clinical trials in third countries in general. The only possibility is to put sufficient quality requirements to the data presented in marketing authorisation applications in the EU. This should be regulated in the directive 2001/83/EC, not in the CTD.

EudraCT should not be used to register all possible clinical trials from all over the world. This kind of expansion of the database might impede the development and original use of EudraCT. If a register for global clinical trials is needed, it should be tailored separately.

4. Figures and data

Item no. 17: 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.

In table 3, figures for year 2010 should be presented to obtain latest information on the amount and proportion of multinational clinical trials. It seems that the interpretation presented above the table is not totally correct: the latest figures (2009) suggest that only 20 % of the trials are multinational and only 9 % is performed in more than 4 MSs.

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