Response to the European Commission Public Consultation on the Review of the Clinical Trials Directive (Directive 2001/20/EC)

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These views are an individual response based on experience from the RESPECT project and from working with CT paediatric participants and their families, investigators and sponsors.

1. COOPERATION IN ASSESSING AND FOLLOWING UP APPLICATIONS FOR CLINICAL TRIALS

1.1. Single submission with separate assessment

Consultation item 1.
Do you agree that a single submission would greatly reduce the administrative work of sponsors for submission of documentation to the Member States concerned?
Agree. A single submission would greatly reduce the administrative work of the sponsors as long as all information requirements are met with a single application. However, a substantial problem arises if there are divergent and conflicting points of view from the different member states. If there are separate assessments, different sets of information or files would still need to be provided for different assessment authorities. The administrative burden is then, in part, transferred to the EU portal but they would still need to refer back to the sponsor and therefore the sponsor would continue to have these administrative tasks. However, this process would lead to eventual harmonisation.

Consultation item 2 Do you agree that a separate assessment would insufficiently reduce the amount of administrative work of sponsors?
Agree. However, this additional burden may be desirable from a patient perspective. Patient organisations are more effective at the national level. The patients' voice is heard more loudly at the local level. Separate assessments may have advantages where the patients' perspective cannot be easily taken into consideration at the European level.

1.2. Single submission with subsequent central assessment

Consultation item 3 -
Agreed. This option does not sufficiently take into consideration the local and patient perspectives.
The number of multinational clinical trials would entail a very large administrative support system at the EU portal. Although it may be possible that not all member states would be needed to make all decisions a central assessment could cause problems and delays if a trial is expanded to an additional state, or where a new trial using the same substance is applied for in different states. In these cases where a different combination of states is needed to make a decision then the procedure for all states has to be repeated. A different set of committee members might possibly arrive at different conclusions.

1.3 Single submission with a subsequent 'coordinated assessment procedure'.

1.3.1. Scope of the CAP

Consultation item 4
Is the catalogue complete?
No, the aspect of taking into consideration the patients' views is both an ethical point and a local issue which needs to be included. The following points need to be incorporated in the catalogue.
Follow-up procedures – how long after the trial will the participant be monitored?
Incorporation of the patients' perspective – how will this be achieved/monitored?
Compliance with GCP and monitoring of GCP
Adequacy of legislation relating to insurance cover of the patient/participant.
Adequacy of the insurance cover of the patient/participant.

Consultation item 5
Do you agree to include the aspects under a), and only these aspects, in the scope of the CAP?
Agree. Only (A) however:
1) Where the patients' views are to be taken into consideration it is important that they have input in terms of the trial design and the relevance of the trial. It needs to be considered how this will be incorporated into the CAP.
2) Assessment has to be weighed against normal clinical practice and it is only at the local level that this can be assessed adequately as clinical practice can vary across borders and within states. A single representative from a state may not have adequate knowledge of local clinical conditions at all the study sites. In other words there is a danger that the CAP may not be able to adequately judge 'normal clinical practice'.

1.3.2. Disagreement with the assessment report

Consultation item 6
Which of these approaches is preferable?
The 'opt out' option would the only one acceptable when considering that people's health and possibly lives are at stake. If the individual member states believe there are 'serious risks' it would be unacceptable (and unworkable) to force those states to agree.

1.3.3. Mandatory/optional use

Consultation item 7
Which of these three approaches is preferable?
CAP should be mandatory for all in order to simply the system. However, in the first instance the CAP should be optional to allow for a transition period and to not overburden the system at the outset.

1.3.4. Tacit approval and timelines

Consultation item 8
Do you think such a pre-assessment is workable in practice?
A pre-assessment would be workable if this information is available. However, there would be cases where there could be different opinions on the safety profile of the IMP. How would these disagreements be resolved?
The states must have sufficient confidence that this is done in a way that is judged appropriate and adequate. Patients' input on the sufficiency of the safety profile would also be important; this would have to be built into the pre-assessment.

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

Consultation item 9
Harmonised and proportionate requirements for all CTs
Agreed. Trial subject protection should be of the highest importance in all states. Expanding the definition of a 'non-interventional trial' would undermine harmonisation across Europe. A single approach, if this can be agreed and monitored would fulfil the idea of harmonisation.

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

Consultation item 10
- *requirements for CTs independent of the nature of the sponsor.*
Agreed. It is too difficult to say if a commercial interest is involved or not. A comprehensive approach would be simpler and easier to administer.

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

Consultation item 11
– precise rules would simplify clarify and streamline CTs
Agreed. If the contents of the dossier can be harmonised and safety reporting standardised, it would reduce time spent in preparing multinational studies, however there is an initial problem of clinical units not being used to the reporting procedures if these have differed from standard procedures. Unanimous agreement with all states would need to be in place before this was enacted.
Risk judgement compared to normal clinical practice will be complicated by differences in normal clinical practice carried out within Europe. This would need to be carefully assessed and studied.

Consultation item 12
– other key aspects on which more detailed rules are needed.
A key aspect missing is the patient input to the trials – how will this be standardised across Europe?

A single submission with a single assessment is unlikely to further patient involvement unless patients for each condition are organised at the European level. A more comprehensive structure with monitoring of representativness would need to be installed before a single assessment process could adequately incorporate the patients' perspective. It is difficult to imagine how a patient representative at the European level would be able to adequately represent patients at a local level who may not be formally organised or not organised at all.

An issue to be investigated is how to establish a patient representative who will represent patient organisations that may not be organised at a European level, and represent patients in states where the patient organisation is inactive or absent and in cases where the patient is poorly represented or not represented.

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

Consultation item 13

A combined approach would help to simplify and streamline the rules.

A clarified definition of IMP is useful and rules for 'auxiliary medical products' would be beneficial. In terms of explanatory power, a simplified approach with clear boundaries between concepts would be welcome.

2.4. Insurance/ indemnity

Consultation item 14

Which policy option is favourable in view of legal and practical obstacles? What other options could be considered? Too difficult to determine risk in all cases. Even low-risk trials must have insurance / indemnity. The second option is preferable where member states are under an obligation to provide for indemnity for damages.

2.5. Single sponsor

Consultation item 15

- Option 1: (maintaining the concept of a single sponsor) may be preferable

Multiple sponsorship would lead to further confusion.

2.6. Emergency clinical trials

Consultation item 16

IC may take place during or after the CT under certain conditions. This is a viable option bringing the regulatory framework in line with internationally- agreed texts.

No, a patient should only be included in a trial if there are grounds for assuming that the direct benefit to the patient outweighs the risks as is stated in the directive. The objective here should be primarily to ensure the safety of the patient and not to be in line with other documents. A rule could be constructed that in such cases where the patient is not capable of giving consent and where the patient's legal representative is also unavailable then the decision must be made in writing by two doctors one of whom is not involved in the research and the decision is made on the basis of what is best for the patient. The doctor should also be held accountable for their actions in the case that the inclusion proved not to be in the patient's best interests or the patient later objected to inclusion.

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

Consultation item 17

Concerning data submitted in the EU - Do you agree with the appraisal

Yes, codifying the legislative framework will make compliance easier and provide for greater possibilities of adherence. Capacity building through training in EU GCP should be required and reported. Inclusion in the EudraCT and publication via EudraPharm should be requirements.

4. FIGURES AND DATA

Consultation item 18

Do you have any comments or additional quantifiable information apart from that set out in the annex to this document?

In order to determine where the problems arise with administrative burden it would be necessary to have more detailed information. This would need to include information about the trials that did not proceed including those that were withdrawn. We need to see these figures broken down into age groups, disease, high/low risk CTs, type of trial, etc. It is also important to see more details of the SUSARs and the claims made if a pre-assessment of risk is to be made in the future.

(correction to table 1 – should say presumably say that these are trials performed and not 'applied for' in the title and first box. There are missing data in table 3)

It is also necessary to see more details concerning paediatric trial applications and waivers. There may be additional administrative burdens involved with paediatric trials and perhaps paediatric trials need to be looked at separately from trials on adults.