European network of paediatric research at the European Medicines Agency

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Comments on Revision of Clinical Trials Directive 2001-20

On behalf of the European network of paediatric research at the EMA (Enpr-EMA)

1.1. Single submission with separate assessment

Consultation item 1: A single submission would greatly reduce the administrative work of sponsors for submission of documentation to the member states concerned.

This issue is highly relevant to children as the ratio of children to those randomised and completing studies is high when compared with adults. Hence the majority of Phase 3 licensing studies in children will require multi-national studies. This is even more evident in rare disorders of children and is particularly true for trials involving potent biologic agents for which companies are seeking extensions in children.

A single submission could be a first step in diminishing administrative burden if the possibility of one 'central' assessment analogous to the rapporteur/co-rapporteur approach used for handling applications for licensing at EU level were to be explored.

Consultation item 2: A separate assessment would insufficiently address the issue set out above (ie. the assessment would be done by individual member states): The difficulties created by independent assessments would remain

There was strong agreement that this would not have any advantages over the present system.

1.2. Single submission with subsequent central assessment

Consultation item 3: 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 (outlined in document).

Despite the attractions of a central assessment, analogous to the system available for licensing, the majority of Enpr-EMA respondents agreed that at present this would be unworkable in view of national differences in clinical and ethical practice.

If central assessment were to be considered innovative ways of performing the assessment would be required, e.g. web-based review system. A central assessment would have the advantage that assessors could potentially learn from each other. If central assessment were to be explored opt-out options for individual member states would have to be retained.

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

Consultation item 4: 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. Is the above catalogue complete?

It is strongly agreed as this would streamline existing multiple, tortuous and lengthy procedures.

The catalogue does appear to be complete.

Consultation item 5: Do you agree to include the aspects under a), and only these aspects, in the scope of the CAP?

Regarding the aspects discussed under Section a: the problem remains for paediatrics of variation in ethics assessments and regulatory body assessments. This is a particular problem for rare diseases in children where parent/patient involvement could and should inform both regulatory and ethics committees. The recently established Network of Networks (Enpr-EMA) has identified parent/patient involvement as an important issue and for rare disorders a number of specialty European groups exist with strong patient/parent involvement. A centralised procedure could take advantage of such expertise and parental views to inform both regulatory assessment and ethical committee assessment.

Although aspects b and c are the realm of ethics we are aware of initiatives at member state level to streamline ethics committee approval and although ambitious would encourage such harmonisation among member states as they all work on the same principles (e.g. Helsinki).

1.3.2. Disagreement with the assessment report

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

Referral to the Commission or Agency for a decision at EU level for the reasons given in response to question 1 could be a possible solution..

Clinical trials can also be unacceptable despite not being a "serious risk to public health and safety" hence the importance of retaining the option of opt out by individual member states. However moves towards centralised application procedures and gradual confidence building

in the procedure would hopefully reduce the likelihood of such opt outs with time.

1.3.3. Mandatory/optional use

Consultation item no. 7: Which of these three approaches is preferable?

The approach, CAP mandatory for all multi-national clinical trials with provision of clinical trials directive maintained only for single country clinical trials seems preferable. Trials targeted at commonly occurring clinical problems may only require a single national study for licensing as may feasibility or Phase 2 studies. This would also be relevant for PK/PD studies where single country trials may be all that is required. A 4th approach would be to make the CAP mandatory when the trial involves 4-5 or more nations. It is possible that existing national alliances and similar clinical, ethical and legal approaches lead to relatively uniform responses.

1.3.4. Tacit approval and timelines

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

Pre-assessment should be workable as the case for minimal risk would have to be argued cogently by the sponsor and potentially very beneficial for 'low-risk' trials which fall under the clinical trial umbrella but where there is minimal/insignificant patient risk (this is applicable to a number of largely 'observational' biological/ pharmacological studies which do not directly impact on patient treatment). This is also more likely to be relevant to Phase 4 studies but would not be a safe process for new indications, new dosing schedules or extension into younger child age groups. Hence as it stands the pre-assessment described is not complete. The wording should be that the investigational medicinal product is authorised in the age group of the subjects of the intended study.

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 No. 9: Rather than limiting the scope of the CTD 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 CTD.

Agreement with this appraisal. The present position is particularly difficult for investigators as national competent authorities and ethics committees can vary in their interpretation of the clinical trials directive. It would be better to deal with such issues in the same way as for clinical trials.

However it might be appropriate to exclude trials that are really without risk e.g. randomization of existing therapies that are used in parallel at present and nobody knows what treatment is best.

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

Consultation item no. 10: Rather than limiting the scope of the CTD, 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.

Despite the anxiety expressed below, the majority of members agree in principle with the appraisal as it is important to encourage and promote collaborative studies across member states.

The majority view is not to exclude academic studies from the EC clinical trial directive although care should be taken to not directly impose the same stringent requirements on these trials. As many studies are funded by local, national and European funding bodies, budgets to do these studies are usually much lower than available to the pharmaceutical industry. If the same stringent requirements are to be imposed on these studies, the risk is that only drugs relevant to the industry will be studied in the future. As is clear from pediatric investigation plans submitted, many drugs important for children will be understudied, such as for example the treatment of pain.

A framework should be developed that can guide academic researchers to design studies as optimally as possible, while not overburdening them. In this regard the framework currently being developed in the Netherlands, may be a useful exemplar.

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

Consultation Item No. 11: 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.

Agreement with the preliminary appraisal. This is relevant to children particularly those involved in PK/PD studies using routinely used medicines currently being used off-label. Opportunistic taking of samples from already placed intravenous lines or use of micro-sampling techniques and sparse sampling methods are relevant here. It would be up to the sponsor to argue the case as to why this is should be viewed as monitoring existing clinical practice and likely to have a significant benefit for those involved without incurring any or minimal risk.

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

No additional issues were identified other than those already in place.

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

Consultation Item No. 13: This combined approached would help to simplify, clarify and streamline the rules for medicinal products used in the context of a clinical trial.

In agreement. This is highly relevant to children's cancer trials when many "background" drugs are used. The significant advances in children's cancer survival were achieved by incremental approaches to existing management protocols by investigating the additional benefit or otherwise of variations in dose schedules of established products or the addition of

new drugs. An insistence that all drugs being used in such trials are labelled as investigational products is creating a significant additional burden and currently limiting studies in children.

Furthermore this item does not appear to have sufficiently considered the problems of paediatric medicines, where the current established practice, and consequently the reference treatment may be off-label or unlicensed.

2.4. Insurance/indemnisation

Consultation Item No. 14: Both policy options could be a viable solution. Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

Both options could be implemented. Removal of insurance/indemnity requirements for low-risk trials is attractive but may be difficult due to differences in interpretation of requirements between member states.

2.5. Single sponsor

Consultation Item No. 15: In view of the above, option 1 may be preferable, provided that 1) it is clarified that the "responsibility" of the sponsor is without prejudice to the (national) rules for liability; and 2) it is ensured that the regulatory framework for clinical trials in the EU is truly harmonised.

Agreement with this appraisal. A single sponsor can only be responsible if protocols are rigorously followed by local lead investigators and who will continue to be responsible for any medical mishaps incurring in their patients recruited to the relevant study.

2.6. Emergency clinical trials

Consultation Item No. 16: This could be a viable option in order to address this type of research and bring the regulatory framework in line with internationally-agreed texts

Agreement with this appraisal. This is highly relevant in paediatric emergency medicine and in neonatal and paediatric intensive care. Any major problems with such proposed trials would be identified at assessment regulatory level and ethics committee level. In the text describing this issue reference is made to parent's legal representative in case of adults. This of course also applies to children and hence would suggest deleting the phrase "in the case of adults".

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

Consultation Item No. 17: In view of the jurisdictional limits, particular consideration should be paid to clinical trials in third countries where the data is submitted in the EU in the framework of the authorisation process of 1) clinical trials; and 2) medicinal products ….. (further text provided in document)

Agreement with this appraisal. Capacity building has been identified as a priority within Enpr-EMA and a legal requirement in the clinical trials directive supports such activity as it identifies the standards required for the conduct of safe and credible trials. For data to be used for regulatory submission in EU the minimum criteria to be fulfilled should be the same as for EU, if the country where the study is performed has some additional and/or more stringent local criteria, these would also have to be fulfilled.

However "ensuring compliance with GCP" and "in accordance with ICH ethics principles" understate the profound ethical considerations for the conduct of clinical trials in low resource nations, particularly: characterization of "standard of care" when there is none outside of a Trial; "compensation for Trial participation" and "reimbursement of expenses" where a First country equivalent could be an annual income in the Third world; understanding of "voluntary" participation, given the above and considerable cultural and language differences, particularly with respect to children. There is certainly a need for increasing transparency, and regulation of conduct, and supporting capacity building for Trials in third countries.

4. Figures and data

Consultation Item No. 18: Do you have any comments or additional quantifiable information apart from that set out in the annex to the consultation document? If so, you are invited to submit them as part of this consultation exercise

No additional comments other than the fact that it might have been helpful to have identified data on clinical trials on children.