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

Introduction

The European Patients' Forum (EPF) welcomes this opportunity to contribute to the Commission's second public consultation on the assessment of the functioning of the Clinical Trials Directive (Directive 2001/20/EC).

We believe the review process should have as its objective a better functioning, more proportionate, and more patient-centred approach to the design and regulation of clinical trials. To ensure this, EPF and its members believe it is necessary to meaningfully incorporate the patients' views in the review. In particular, we strongly believe that this review is an opportunity for reform towards more patients' involvement throughout the research process, greater trust and confidence in medical research and improved participation rates.

EPF and its member organisations provided extensive input into the first round of public consultation, in 2009/2010. We identified a number of issues of key concern to patients, and we are greatly concerned that those issues have not been addressed in the Commission's concept paper. These issues are addressed in the EPF Statement, submitted separately.

Methodology of the EPF response

A draft response document was developed on the basis of the key issues identified in EPF's first response, and with input from EPF's Policy Advisory Group. The paper was then sent to EPF's membership for comments and feedback. A final draft response was developed based on input from members, and incorporating input from other health NGO allies where appropriate. This was sent to EPF's membership for final approval before submitting it to the Commission.

Consultation topics

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

Three options were considered:

1.1. Single submission with separate assessment
1.2. Single submission with subsequent central assessment
1.3. Single submission with subsequent "coordinated assessment procedure" (CAP)

Consultation items no. 1 & 2: Single submission with subsequent separate assessment
EPF agrees with the Commission's appraisal that a single submission would significantly reduce the administrative work of sponsors for submission of documentation to the Member States concerned. However, we are not in favour of keeping independent national separate assessments as this would not resolve the problem of delays and difficulties caused by divergent assessments. Moreover, it is doubtful whether the Commission could be able to manage what is needed in each Member State within reasonable time limits.

Consultation item no. 3: Single submission with subsequent central assessment
EPF agrees with the Commission's appraisal that a single submission with subsequent central assessment would be difficult, as it does not take enough account of national and local circumstances, and the very large number of trials and substantial amendments each year would pose a problem. Moreover, a committee structure involving all 27 Member States would be costly and impractical to maintain, particularly as most clinical trials only involve up to 5-6 Member States.

Consultation item no. 4: Single submission with subsequent "coordinated assessment procedure" (CAP)
This is the best option in EPF's view. There are however some concerns that would need to be addressed for the CAP to work in practice. All the Member States are very different from each other, and sometimes it would be difficult to reach a reasonable compromise for all the MS involved in the process. The CAP therefore requires improved cooperation between MS and an effective procedure for resolving conflicts.

EPF would like to investigate further with two member organisations with divergent views on this issue and address this at the forthcoming meeting with the European Commission.

1.3.1. Scope of the CAP

The Commission proposes that the CAP would be used *only* for: risk-benefit assessment; compliance with requirements for manufacturing and importation and labelling requirements of the medicinal products; and the completeness and adequateness of the investigator's brochure. Ethical issues are and should remain within the remit of Member States.

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

Yes.

Consultation item no. 5: CAP. Do you agree to include the aspects listed above and only these aspects, in the scope of the CAP?
EPF believes that the issue of multiple ethics assessments should be addressed, as currently there is a lot of divergence and Member States even have multiple Ethics Committees (national, regional, local) and multiple procedures within MS. This is clearly a source of delays and fragmentation. A national coordination procedure resulting in a single national opinion may be one possible way forward.

Furthermore, EPF believes that the *procedures and principles* of ethical review should be better harmonised through *guidelines or recommendations* applied at EU level.

In this context, EPF particularly calls for the Directive to include a provision regarding patients' involvement in Ethics Committees – please see EPF statement for elaboration of this point.

In addition, EPF would strongly encourage further cooperation among national Ethics Committees in order to exchange experiences, information and good practice.

1.3.2. Disagreement with the assessment report

The Commission proposes three options for resolving disagreements among Member States about the assessment done under the CAP: (a) allowing individual Member States an "opt out" if justified on the basis of a "serious risk to public health or safety of the participant"; (b) MS would vote and take decision by simple majority; or (c) the matter could be referred to the Commission or the European Medicines Agency for a decision.

Consultation item no. 6: Which approach is preferable? Please give your reasons.
EPF believes an EU-level decision would be best to avoid any bias in decision according to disclosures in some MS; however the opt-out may be the more realistic option. In this case the reasons for divergent opinions should be analysed at EU level and published (by the EC or the Agency), which could gradually lead towards more convergence.

1.3.3. Mandatory vs. optional use (Concept paper, p. 6)

The Commission puts forward three possibilities: (a) CAP would be mandatory for all clinical trials; (b) mandatory for all multi-national clinical trials; or (c) optional.

Consultation item no. 7: Which option is preferable? Why?
EPF considers that the CAP should in principle be applied to all multi-national trials, as the problems with multiple assessment usually occur in multi-national trials. The CAP would be an opportunity to minimise the bureaucracy and resulting costs/ delays for patients.

However, the CAP could be optional at least to start with, if it appears that making it mandatory for all multi-national trials would result in further delays and problems. Allowing the CAP as an option would mean that if the system works well, it will be increasingly used. It would, however, be important to assess carefully how the CAP would work in practice, and how well it takes into account the needs of patients with different chronic diseases.

1.3.4. Tacit approval and time lines

Under the CAP, tacit approval would no longer be possible. The Commission proposes that while the time lines of the CAP should not be longer than those currently provided in the Directive (generally 60 days), they could be shortened in case of "trials posing only a minimal risk" to the safety of the participating patients compared to normal clinical practice. Such trials would be called "Type-A trials".

Consultation item no. 8: Do you think such a pre-assessment [into "low risk" and other trials] is workable in practice? Why? Why not?
EPF considers that the safety and wellbeing of patients involved in clinical trials are the most important considerations, and should always prevail over the interests of science and society. We have some reservations about the possibility to pre-define any trials according to low or high level of risk. It is probably easier to ascertain that the risk would be very high by definition for certain compounds, but at the end, all products are potentially dangerous.

Patients ultimately bear the personal risks of participating in clinical trials. Therefore, the patients' perspective is necessary for accurate risk assessment. If such a pre-assessment system is even considered, EPF is of the view that the definition of any criteria for designation of trials as "high" or "low risk" necessitates meaningful involvement of patients/patient representatives. Similarly, patient involvement would be absolutely crucial for any case-by-case assessment of specific trials into different risk categories. For more details regarding patient involvement in risk assessment, see EPF Statement.

2. Better adaptation to practical requirements and a more harmonised, risk-adapted approach to the procedural aspects of clinical trials

In order to arrive at better harmonisation of procedural aspects, the Commission is putting forward the following options.

2.1. Limiting the scope of the Directive

- Either through enlarging the definition of "non-interventional trials" thus excluding more trials from its scope; or through excluding trials by "academic/non-commercial sponsors" from the scope of the Directive. The Commission believes this option is not preferable.

Consultation items no. 9&10: Do you agree with this appraisal? Please comment.
EPF agrees with the Commission that it would be better to come up with a set of harmonised and proportionate requirements for all trials.

Academic research is crucial for the development of new knowledge especially in fields that do not attract commercial interest, for instance because the number of patients is too small or industry has a conflict of interest. Bringing established compounds in new applications, or

developing off-patent products for new groups of patients, are areas of activity that are often initiated by academics and then picked up by niche SMEs.

While it is important to have a workable framework for regulating non-commercial trials, that does not hamper but encourages independent research, nevertheless *all clinical trials should be subject to the same safety and quality standards*, and excluding non-commercial trials from the Directive is not a solution. Furthermore, the definition of what is commercial and non-commercial is not always straightforward.

If the current Directive can be modified to facilitate all research, including non-commercial trials, then there will be no need for a separate framework.

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

The Commission supports a risk-adapted approach to accommodate varying levels of risk in different clinical trials: the Directive should include provisions adapted for lower and higher risk situations particularly as regards the content of the dossier and safety reporting. To achieve this, the Commission proposes to add Annexes to the Directive that would include a single, EU-wide, risk-adapted, set of rules for the above two topics.

Consultation item no. 11: Do you agree with this appraisal? Please comment.
EPF: Patients, due to their individual experience and specific situation, perceive the risks involved in participating in a clinical trial differently from investigators, regulators, sponsors, or lay persons on Ethics Committees.

Because of individual reactions, and the need to take into account different possible side-effects of the treatments, this points to the need for a broad involvement of patients in the assessment of safety issues in general and risk-benefit assessment in particular. Patients' involvement in any risk assessment is crucial to ensure that the assessment neither over- or understates the risks and potential benefits. We refer to our answer to question 8 above and to the EPF Statement in this respect.

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

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

In order to address the legal uncertainties around the definition of IMP, and other medicinal products no specifically regulated in the Directive, when conducting multi-national trials, the Commission proposes a combined approach to simplify, clarify and streamline the rules for medicinal products used in the context of clinical trials:

- The definition of IMP would be clarified by narrowing it to ensure that only medicines that are the object of the study are covered by the definition;

- Introduction of the notion of 'auxiliary medicinal products' which could be subject to a proportionate regulatory regime separate from IMPs;
- The rules for the dossier requirements, reporting and labelling for both categories could be set out in an annex to the Directive.

Consultation item no. 13: Do you agree with this appraisal? Please comment.
EPF agrees with the Commission's preliminary appraisal.

2.4. Insurance / indemnisation

Investigators or sponsors of clinical trials must have insurance in place for possible injury or death of patients. The rules are the same for all trials, regardless of the different levels of risk. This has led to additional costs related to insurance, making trials more costly. The Commission proposes that a solution could be either to:

- remove insurance requirements for low-risk trials; or
- oblige Member States to provide for an indemnisation for any damages incurred in clinical trials performed in their territory, taking account of the national legal system for liability. (It is not considered that this would lead to much additional burden on national budgets.)

Consultation item no. 14: Which option is favourable, in view of legal and practical obstacles? What other options could be considered?
EPF's preliminary view is that removing insurance requirements is not an acceptable solution from the point of view of protecting the participating patient, even for trials deemed low risk for researchers and sponsors also. . The question of who defines the risk level, and what would happen if a clinical trial changes from a low-risk category to a high-risk one in the course of the trial, would need to be addressed. The second option (indemnisation by Member State) may be preferable. This issue will need to investigated further very carefully to ensure patients are protected.

2.5. Single sponsor

In order to facilitate multi-national trials, the Commission considers two options: (a) maintaining the concept of single sponsor, or (b) allowing multiple/joint/co-sponsorship, where each sponsor would be responsible for a specific task, or a specific MS in the case of multi-national trials. The Commission concludes that the first option is better as long as it is clarified that the concept of 'responsibility' does not equal legal liability in case of damages, and the regulatory framework is truly harmonised (since the main problem seems to stem from the divergent requirements of MS for conducting trials, rather than the single sponsor concept itself).

Consultation item no. 15: Do you agree with the Commission's appraisal? Please comment.
EPF can agree with the Commission's appraisal that it is better to have a properly harmonised framework. However it may be possible to allow multiple sponsorship as an option, as it is possible that the benefits in some cases can outweigh the difficulties of coordination.

2.6. Emergency clinical trials

The Commission proposes that the Directive could be amended, taking into account various internationally agreed texts including the Helsinki declaration, the Convention on Human rights and biomedicine, the ICH guidelines on good clinical practice – so that under certain conditions, informed consent and the information from the investigator may take place during or after the clinical trial, if the patient is unable to do so, the situation is urgent, it is not possible to seek consent from parents or a legal representative, and no previous objections are known. In such cases the informed consent would need to be obtained as soon as possible from the patient or their parent/legal representative. All other rules for clinical trials would still apply.

Consultation item no. 16: Do you agree with the Commission's appraisal? Please comment.
EPF prefers not to answer this question. We suggest that it needs to be considered further in detail, with input from patient organisations. Some questions have been raised as to whether the internationally agreed texts themselves have been prepared without any patient input.

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

The issue of good clinical practices (GCP) has been extensively discussed in the 2009-2010 consultation responses, as well as in the working group of the European Medicines Agency where EPF is a participant. That group has been working on a draft guidance document whose purpose is to clarify the practical application of ethical standards for clinical trials conducted in third countries. The paper will determine the practical steps to be taken during the provision of guidance and advice in the drug development phase, and during the marketing authorisation phase.

The Commission proposes that the provisions currently existing in the detailed guidance document "CT-1" and drawing on the implementation work at EMA, could be codified in the Directive as follows: "*All studies* [submitted in the authorisation process of a clinical trial] *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*."

The Commission also proposes that capacity-building in third countries where the regulatory framework for clinical trials (including enforcement) is weak, should be further supported.

Consultation item no. 17: Do you agree? Please comment.
Clinical trials in third countries should apply the same standards of safety and protection of patients as in the EU, including that the safety and wellbeing of participants must always prevail over the interests of science and society.

EPF is a member of the Working Group on Third Country Clinical Trials at the European Medicines Agency and contributed to the reflection paper drafted by the group. The discussions are still ongoing. In this context, EPF has emphasised the importance of the following aspects:

- Free, informed consent, particularly regarding patients in potentially vulnerable situations, and children. It is crucial to ensure that the informed consent procedure is indeed meaningful, and not only a "ritual" step in the process.
- Information provided to patients must be adequate, comprehensive and understandable, and communicated in a manner that takes into account the local social and cultural context.
- Free or affordable (in the local context) access to treatment post-trial should be ensured, for trial participants and for the wider community as appropriate.
- Appropriate and effective sanctions to address cases where non-compliance does occur.
- The EMA guidance on clinical trials in third countries should also make at least a recommendation that patients' representatives should be involved whenever possible in clinical trials processes.

Please see EPF Statement, and our feedback to the EMA working group, which elaborates on these points.

EPF is also strongly supportive of capacity-building efforts to support countries where the regulatory framework is weak. This should include sharing examples of good practices (and examples of bad practices) on patient involvement, including the benefits of patients' involvement, for example in Ethics Committees; protection of patient groups that may be in situations of vulnerability; and how to ensure access to treatment following the end of the trial. Whenever possible national, regional or local patient organisations should be involved in these capacity-building processes.

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? If so you are invited to submit them as part of this consultation exercise.
No.