



**IPHA response to the  
European Commission  
Concept paper on  
*The Revision of the 'Clinical  
trials Directive' 2001/20/EC*  
May 2011**

## **BACKGROUND**

The Irish **Pharmaceutical Healthcare** Association (IPHA) represents the international research-based companies who are responsible for developing, manufacturing and bringing innovative medicines to the Irish market.

We welcome the opportunity to comment on the Concept paper on the revision of the Clinical Trial Directive and believe that the removal of barriers to the conduct of clinical research in Europe is essential to the development of new medicines and the improvement of the health of EU citizens.

## **IPHA POSITION ON CONSULTATION QUESTIONS**

### **1. Consultation item no. 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.

**Yes**, IPHA agrees with this appraisal. We believe that a single electronic submission of Clinical Trial Applications for initial authorisation and any subsequent amendments through an EU portal, administered by the European Medicines Agency, would greatly reduce the administrative work of sponsors. An essential pre-condition would be that the procedure must not add administrative burdens or delays. The supporting documentation required for such a submission should be streamlined, minimised and ideally sent out for public consultation.

### **2. Consultation item no. 2 – Independent assessment by each Member State**

Preliminary appraisal: A separate assessment would insufficiently address the issue set out above: The difficulties created by independent assessments would remain.

Yes, IPHA agrees that an *independent assessment* of the information by *each Member State* would insufficiently address the issues set out in the consultation document.

### **3. Consultation item no. 3 – 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.
- 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.
- The involvement of all Member State is not needed, as very few clinical trials are rolled out in more than five or six Member States.

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.

Yes, IPHA agrees that a central assessment is not appropriate for clinical trials and would not be workable in practice as it would not take ethical, national and local perspectives into account.

### **4. Consultation item no. 4 – Single submission with a subsequent “coordinated assessment procedure” (CAP) – completeness of catalogue**

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.

Yes, IPHA agrees with the concept of a single trial submission with a subsequent Coordinated Assessment Procedure (CAP) along the lines of the decentralised procedure for marketing authorisations. Additionally, IPHA agrees that the catalogue (*referred to in the concept paper*) is complete.

### **5. Consultation item no. 5 – Scope of the CAP**

Scope: Only the risk-benefit assessment, as well as aspects related to quality of the medicines and their labelling would be suitable for the CAP. In particular, ethical aspects related to informed consent, recruitment and reward as well local aspects related to suitability of sites, the investigator, and national rules are not suitable for the CAP as they relate to ethical issues or to local expertise.

**Yes**, IPHA agrees that the risk-benefit assessment as well as aspects related to quality of the medicines and their labelling (*i.e. section 'a' in the concept paper*) would be suitable for the CAP. However, some aspects outlined in section b of the concept paper could be included in terms of calculation of fair market value reimbursement as a percentage of the average salary of healthcare professionals in the country where the study is to be performed.

With regard to the functioning of the CAP, the overall approval timeline should be 60 days for both competent authorities and ethic committees in all EU Member States. In the event of queries, responses can be provided within 90 days, but no stop clock should be foreseen (contrary to what currently exists). Harmonized timelines for the review by competent authorities and ethic committees of substantial amendments (review timelines as well as response timelines) should also be defined.

## **6. Consultation item no. 6 – Disagreement with the assessment report**

**Options 2 (majority vote) and 1 (opt out)** could be used to address disagreements amongst Member State about assessments performed under the CAP. Options 2 and 1 are complementary – a vote could be taken by all member states and if the outcome was deemed unacceptable to a member state, they could opt out. Where there was a stalemate after a vote, this could be referred to the Clinical Trial Facilitation Group for arbitration - however, timelines would need to be defined.

## **7. Consultation item no. 7 – Mandatory vs. optional use of the CAP**

**IPHA agrees** with proposal 2 that CAP should be mandatory for all multinational clinical trials (*i.e. provisions on authorisation in the Clinical Trials Directive maintained only for single-country clinical trials*).

## **8. Consultation item no. 8 – Low-risk trials and shorter timelines**

IPHA agrees that review timelines could be shortened where the risk to trial subjects is low and where the assessment in the CAP is largely limited to issues of data reliability. To this end, these types of trials (termed 'type-A trials') could be identified in a pre-assessment. However, IPHA believes that the term 'minimal risk' should be more clearly defined to avoid multiple interpretations.

## **9. Consultation item no. 9 – Scope of the Clinical Trial Directive**

**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.

**Yes**, IPHA agrees that rather than limiting the scope of the 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.

Observational studies do not require the same intensity of administrative work for the applicant or reviewer since, due to the non-interventional nature of the trials, the safety-

related aspects may be reduced or even inexistent. Non-interventional clinical trials should therefore either be subject to reduced timelines (30 days). However, the inclusion of non-interventional trials in the new Clinical Trial Directive should, in application of better regulation practices, recognise the low risk aspect of this category of trials and hence requirements, processes and timelines should be proportionate and pragmatic.

#### **10. Consultation item no. 10 – Nature of sponsor (academic versus commercial)**

**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').

**Yes**, IPHA agrees that it would be better to draw up harmonised and proportionate requirements for clinical trials rather than limiting the scope of the Clinical Trials Directive by excluding clinical trials by 'academic/non-commercial sponsors'. These proportionate requirements would then apply independently of the nature of the sponsor.

#### **11. Consultation item no. 11 – A more precise and risk-adapted rules for the content of the application dossier and 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.

**IPHA agrees** that having more precise and risk-adapted rules for the content of the application dossier and for safety reporting would help to simplify, clarify, and streamline the requirements for conducting clinical trials in the EU. This would introduce consistency and standardisation thus ultimately improving access to studies.

#### **12. Consultation item no. 12 – Other key aspects missing**

There are no other key aspects on which more detailed rules are currently needed.

#### **13. Consultation item no. 13 – Clarification of 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.

**IPHA agrees** with clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products' as it would help to simplify, clarify, and streamline the rules for medicinal products used in a clinical trial.

#### 14. Consultation item no. 14 – Insurance and indemnity

In order to address this situation, several policy options could be considered, such as:

- Removing insurance/indemnisation requirements for low-risk trials: This policy option would remove the insurance requirement for clinical trials which typically pose a low risk for trial subjects or;
- Optional indemnisation by Member State: This policy option would put Member States under an obligation to provide for an indemnisation for damages incurred during clinical trials performed in their territory, taking account the national legal system for liability. In view of the damages arising today, the burden on national budgets would be minimal.

Preliminary appraisal: Both policy options could be a viable solution.

**IPHA proposes** that to address the disparity in insurance costs in different member states the EC should develop a single set of standards for indemnity across the EU.

IPHA does not favour removing the requirement for indemnity, since the extent of risk does not necessarily correlate with the extent of damage to a rare study participant who is injured in the course of a study. It would be a disincentive to remove the offer of indemnity.

#### 15. Consultation item no. 15 – Single sponsor

The Clinical Trials Directive is based on the concept of a 'single sponsor' per trial. The single sponsor is 'responsible' for the trial vis-à-vis the national competent authority and the Ethics Committee.

It is a recurrent criticism that the concept of a 'single sponsor' renders multinational clinical trials more onerous.

Two options could be considered:

- Option 1: maintaining the concept of a single sponsor;
- Option 2: allowing for a concept of 'multiple sponsorship'/'joint sponsorship'/'shared sponsorship'/'co-sponsorship', where each sponsor is 'responsible' for a specific task or for the conduct of the trial in a Member State.

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 harmonized.

**IPHA agrees** with the concept of a single sponsor (option 1) rather than 'multiple sponsorship'/'joint sponsorship'.

## **16. Consultation item no. 16 – Emergency clinical trials**

**IPHA agrees** that to address the issue of *Emergency Clinical Trials* the Directive should take into account internationally agreed texts (*Declaration of Helsinki of the World Medical Association, the Convention on Human rights and Biomedicine of the Council of Europe, and the Guidelines on Good Clinical Practice of the International Conference on Harmonisation, 'ICH'*) thus bringing the regulatory framework in line with internationally-agreed texts.

## **17. Consultation item no. 17 – Clinical Trials performed in third countries**

Both provisions, as well as implementation work could be further supported and supplemented through the following:

- Codifying, in the revised legislative framework, the provision in point 2.7.2.4. of the detailed guidance CT-1; and
- Further supporting capacity building in third countries where the regulatory framework for clinical trials, including its enforcement is weak.

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.

**IPHA agrees**, that to increase transparency of clinical trials performed in third countries the legislation should 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 published via the public EU-database *EudraPharm*.

## **18. Consultation item no. 18 – Figures and data**

No additional comments.