



# ABPI response to the European Commission Public Consultation Paper on the Assessment of the Functioning of the "Clinical Trials Directive" 2001//20/EC

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The Association of the British Pharmaceutical Industry represents more than 70 companies in the United Kingdom producing prescription medicines. Its member companies are involved in all aspects of research, development and manufacture, supplying more than 80 per cent of the medicines prescribed through the National Health Service. The ABPI also represents companies engaged solely in the research and/or development of medicines for human use. In addition, there is general affiliate membership for all other organisations with an interest in the pharmaceutical industry in the United Kingdom.

We welcome the opportunity to comment on this European Commission Consultation on the assessment and functioning of the Clinical Trials Directive (CTD) 2001/20/EC and encourage a process which will reduce administrative burden and continue to ensure the safety of patients.

### Key Issue N°1: Multiple and Divergent Assessments of Clinical Trials

#### **Consultation item n°1: Achievements and shortcomings**

Can you give examples for an improved protection? Are you aware of studies/data showing the benefits of the Clinical Trials Directive?

Generally, we believe that due to the harmonisation of minimum requirements at EU level, the protection of patients across all EU Member States has increased because the same degree of Regulatory scrutiny is applied to all study applications. All information is now reviewed in much more depth and the full scope and context of the study is overseen by the regulators, which is of benefit to patients. In addition, the stringency of GCP Inspection by Agencies like the MHRA is reassuring for patients. Nevertheless, adequate National resources to enforce the requirements in all EU countries need to be available to guarantee the same level of protection across the Community.

#### **Consultation item n°2: Multiple and divergent assessments of clinical trials**

Is this an accurate description of the situation? What is your appraisal of the situation?

We believe this is a reasonably accurate description of the situation.

Differing requirements remain for submission components and there is a need for EU harmonisation of content. We also need harmonisation of definitions and interpretation. Variations in definitions and interpretations of some issues, such as substantial amendments, non-Investigational Medicinal Products (non-IMP) or SUSAR reporting requirements, cause difficulties for applicants trying to implement a Global study protocol. Specific national legal requirements create even more hurdles. For example:

- In the UK, the MHRA provide a guidance document in the clinical trials section of their website detailing what they consider to be acceptable wording and requirements for contraception, this does not always match what is in global protocols.
- In France, detailed data related to biotechnology compounds are required due to local law.
- In Sweden, the non-acceptance of a QP Declaration and the requirement for GMP certificates create hurdles.
- In Poland, genetic testing is not allowed which results in national tailoring of the protocol due to the need to omit certain text on genetic testing.

Other requirements due to divergent national guidance, such as the requirement in the Czech Republic for at least 6 months of real-time stability data, make a harmonised approach for multi-country trials very difficult.

We have also been made aware of an example of significant divergent assessment by an NCA where said NCA acted under the guidance of a separate medical assessment body, which refused to accept an assessment during a follow-up phase of a protocol despite the assessment being accepted by all other participating NCAs.

The scope of the assessments by National Competent Authorities (NCAs) and Ethics Committees should clearly be defined to be synergistic instead of overlapping.

### **Consultation item n°3: Weaknesses of the CTD**

**Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?**

In agreement with the findings of the ICREL survey, we believe that the administrative workload has undoubtedly increased and with it, the cost of conducting clinical research in Europe. Resources at Sponsor level have to be increased to comply with all documentation requirements, safety reporting, detailed record keeping and tracking, expected by the GCP Inspectorates.

In addition, some NCAs have also committed significant resources for the assessment of CTAs. Larger NCAs with more dedicated resources are in general genuinely committed to try and get Approvals processed within the required timelines and to resolve issues with Sponsors that give rise to initial refusals.

In some Member's experience, current delays in approval times for CTAs are mainly due to resourcing and sometimes complex procedural set up of Ethics Committee reviews per country or region or site. Additional requirements for documents to be submitted for Ethics Committee reviews which are developed by each individual Ethics Committee also contribute to the complexity.

A clearer definition of substantial amendments based on the impact of the change on patient safety under the responsibility of sponsors is needed and would reduce the high number of amendment procedures and with this, some resources and administrative burden.

#### **Consultation item n°4: Assessment by Ethics Committees - Streamlining**

Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?

The ABPI supports Option b), which is aligned with EFPIAs preferred option, additional ABPI Member Company comments are presented below:

##### **Option a) Common agreement between Member States**

This option relies on a rapid assessment then rapid consultation and agreement between the various NCA in order to achieve an approval within a given time period. The fastest NCAs are able to arrive at a national decision within 60 days at present. This does not include consultation and consensus building with other Member States. Divergent national requirements and submission of an application in all participating countries is not likely to reduce administrative burden.

The Voluntary Harmonisation Procedure is a procedure that currently pilots this option. Due to the excellent commitment of some NCAs the few procedures which were assessed in such a consultative way went well. However, given the number of the CTA applications and the participation of many Agencies in this process, stringent legal mechanisms and procedures would need to be implemented for scheduling work, consulting etc.

In addition, the current mutual recognition system for marketing applications also demonstrates some of the weaknesses of the system, in that some agencies are overloaded with applications and slots are fully booked for 2 years in advance.

This is an unacceptable situation if mirrored for a thriving research Community where development times impact even more on patient access to new safe and effective compounds.

However, this option may have a benefit for some clinical trials involving a very small number of countries, such as 'first-in man' trials.

##### **Option b) Single authorisation for the entire Community**

This option is preferable for multi-national clinical trials. However, adjustments to respective national legislations would be required to ensure that the 'common agreement' is acceptable to all NCAs. In order to reduce the workload on the NCAs, this process would need to be coordinated by the EMEA together with each NCA. It would need to be completely clear that submission to the Reference Member State (RMS) is the only submission and would not then require a further local NCA review, otherwise (as occurred with central and local Ethics Committees), this will create an additional step and a longer approval process.

The co-ordination of the assessment would be lead by a dedicated Central function using EU or national assessor resources based upon availability or expertise. Adequate expert resources for the assessment of a large number of applications need to be ensured. A single application, submitted centrally that results in a Community wide approval would save both time and money.

There is a risk in having single RMS review because they may reject a protocol outright. The study could not then be conducted in any EU country. Currently a study may be rejected by one or two countries but still be run in the others.

There is a risk that the NCAs involved in review may not agree and have frequent arbitrage procedures which would add time to the review process.

If the option remains to submit to the local NCAs individually, it may be difficult for NCAs to predict workload. If resources of the NCA reviewers are reduced because of a reduction in duplication of reviews across countries; when companies do submit locally will it be possible to meet the review timelines?

If a Centralised procedure was brought in we would not want to lose the current benefits of (fairly) fast approvals in the UK.

#### **Consultation item n°5: Assessment by Ethics Committees**

Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?

All Ethics Committees use internationally agreed standards such as the Declaration of Helsinki as basis for their assessments. Although, there will be issues of medical practices varying across member states and to a lesser extent this within Member State regions. Nevertheless, we believe that an opinion from a Central Ethics Committee on the methodology of a clinical trial could be acceptable for the Community. We note that the Commission already uses only one European Ethics Committee to give opinions on research proposals under their FP7 framework program. Using local Ethics Committees to judge the suitability of the Investigator, site capacity and capabilities would provide added value.

#### **One stop shop**

The 'one-stop shop' option would require strengthening of the existing national networks for respective Ethics Committees. In addition, it would require a coordinating centre (similar to the EMEA role proposed for NCAs in consultation item number 4) to reduce workloads for respective member states. We currently have a similar situation in the UK. A key point for the ABPI Member Companies is that different people within a Company enter different information, so the system needs to be flexible enough to allow this and not have just one entry person per study.

We believe that this option could work for multinational trials, as the central co-ordination body will also plan the Ethics Committee consultation in a similar way to the NCA approval. It would mirror the NCA approval mechanism and may have the best chances to align within the current timelines. A stronger link and co-ordination of assessments between the two distinct functions would optimise efficiency and probably outcomes.

#### **Strengthening networks of national Ethics Committees**

Ethics Committee review should remain within the individual country to allow local practice, local patient population and cultural issues to be addressed. Strengthening networks of Ethics Committees involved in multinational trials sounds good in principle, but it would be prudent to

strengthen the links within a country first as there is still a lot of discrepancy between what Ethics Committees in e.g. the UK will approve. An alternative idea could be to have therapeutic area aligned central Ethics Committees that are made up of professional members who are experienced in the therapeutic area.

Strong leadership is required for the co-ordination of a Network of Ethics Committees and based on experience gained from the Marketing Authorisation approval process; it may take a long time to set up and build trust in order to come to an acceptable output. In general, Member States should only be allowed to "opt" out exceptionally and in well justified cases. A similar clause as in the Advanced Therapy Regulation may be a solution. In case a member State "opts" out, the clinical trial cannot be performed in that country.

#### **Clarifying respective scope of assessment of NCA and Ethics Committees**

Clearer identification of what is required for Ethics Committees to review and what is required by the NCA would be very helpful and reduce duplication of review. Good communication between the two functions and a clear distinction of roles and responsibilities is required to allow an efficient and value added parallel review. We believe that a clear identification of roles and responsibilities of NCAs and Ethics Committees during the assessment of a CTA is paramount for streamlining the system.

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## **Key Issue N°2: Inconsistent Implementation of the CTD**

### **Consultation item n°6:**

**Is this an accurate description of the situation? Can you give other examples?**

Feedback from our member Companies indicates that each of the examples provides an accurate description of inconsistencies in the implementation of the CTD. Additional comments below:

#### **Section 4.1.1 Substantial amendments**

We agree that there are more notifications made than necessary and this should be rectified. For example adding a new investigator or site to an approved study should be a local consideration and not required to be approved by the NCA. Clarification is needed in the implementation guidelines regarding which changes require a substantial amendment and which perhaps only need to be brought to the attention of the NCA, but need no procedural review.

#### **Section 4.1.2 Reporting of SUSARs**

In relation to the comments on harmonised SUSAR reporting on Page 8 of the Consultation, it should be fed back that this has not been realised and that common guidance should be implemented across Member States. We would like to feed back that the European Commission are correct in their statement that the multitude of different reporting regimens has not aided safety assessments by either the NCA or Ethics Committees. For the regulatory aspect, we would favour reporting to Eudravigilance only and for Ethics Committees, the reporting should be streamlined and simplified to make the data easier to understand. We believe this point also ties into Section 4.2 as it relates to insufficient patient protection (i.e. is the volume of information going to Ethics Committees impairing their ability to know what they should be looking at and what the data means?) and increased

administrative costs of duplicate reporting to multiple Authorities. Clarification in the implementing Guidelines regarding reporting of SUSARs to EudraVigilance and alignment of Safety reporting requirements to international standards (ICH) is needed.

There are amendments to the implementing guidelines necessary to address further inconsistencies relating to:

- Interpretations of what constitutes IMP
- how to interpret drug labeling / re-labeling requirements (in for example Annex 13)

### **Consultation item n°7: Weaknesses**

Is this an accurate description? Can you quantify the impacts? Are there other examples of consequences?

We generally agree with the Commission's assessment. Nevertheless we would like to point out that the increase in administrative cost should not be looked at in isolation because the increased costs of more stringent GMP and GCP requirements in all countries are certainly a benefit for patient protection.

Some aspects may need to be reconsidered in this respect to balance the increased cost with the actual patient benefits considering various existing practice in Member States, e.g. using GMP facilities to re-label clinical supplies in some countries (but not in others) may need to be reconsidered based on actual data..

We agree that the divergence in SUSAR reporting requirements has created a complex system. In order to immediately lower the administrative burden within the current system while maintaining the patient protection, we would propose that local SUSARs need to be notified only to the respective NCA. Further, all SUSARs should be made available to all Agencies via EudraVigilance and the provision of the Annual Safety Report.

See also our response to Item 6 relating to the streamlining and simplification of reporting to Ethics Committees.

### **Consultation item n°8: Options to address weaknesses**

Can you give indications/ quantifications/ examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail? In particular, are the divergent applications really a consequence of transposing national laws, or rather their concrete application on a case by-case basis?

The ABPI will endeavour to support the EFPIA position on this issue; comments from ABPI Member Companies did not clearly favour one option over another.

## Key Issue N°3: Regulatory Framework not always adapted to Practical Requirements

### Consultation item n°9:

Can you give examples for an insufficient risk-differentiation? How should this be addressed?

We are generally against a system that introduces standards based on sponsor classification. However, we support the principle that the requirements for the regulatory oversight should be proportional to the actual risk of a clinical study for the participants. The level of the risk may vary according to the phase of clinical development, the mechanism of action of the new compound, existing clinical experience, the characteristics of the patient population exposed and the involvement of an external Data Safety Monitoring Board (DSMB). The legal framework could define certain criteria which would provide for a lower level of regulatory oversight for lower risk proposed research. Sponsors should be able to make this risk assessment for their proposed study and include a justification in the clinical protocol.

The current rigid regulatory system provides hurdles for conduct of low risk studies, which make it impossible to conduct clinical trials in some countries. The requirements for a biological product used for the first time in humans are the same as for a clinical trial involving a licensed product.

We have been informed, for example, of a recent experience, where the labelling requirements for the use of a licensed ophthalmic product in a very small container could not be met in some countries due to lack of space. This does not present risk to a patient who will get information through the mandatory patient information sheet. As a consequence the trial could not be conducted in those countries and patients could not participate in the clinical research.

However, while there are different insurance requirements across respective member states, this type of identified issue will not be resolved. Therefore, changes in national legislation to standardise insurance requirements for clinical trials may be the only option to resolve this specific issue.

### Consultation item n°10: Requirements not always adapted to practical circumstances

Do you agree with this description? Can you give other examples?

The Pharmaceutical Industry has been able to work under the current rules despite the hurdle of increased burden. However, we acknowledge the bottleneck this creates for academic centres when conducting multinational studies. We would support the adaptation of this requirement to better reflect the practice of academic research in order to maintain the current high level of scientific expertise, Industry-Academia collaboration opportunities and make research in Europe more efficient and dynamic in the future.



### **Consultation item n°11: Review of existing implementing guidelines**

Can a revision of guidelines address this problem in a satisfactory way? Which guidelines would need revision, and in what sense, in order to address this problem?

We agree that in the short-term, revision of the existing implementing guidelines is needed to achieve a greater harmonisation in parallel to more long-term legislative changes. It would be important to involve all stakeholders in the guideline revision process to ensure that the revised requirements can be implemented in practice. The revision of the guidelines should be driven by the overall objective of reducing administrative burden, risk proportion, harmonisation and seamless integration of clinical research into drug development. A strong leadership commitment from the European Commission to move the process forward in a timely manner would be very welcome.

It is worth noting that a change in the guidelines could address the problem of increased costs of conducting clinical research in the EU but only if incorporated into respective national legislation and therefore agreed by all Member States. We require agreement to unify/standardise respective rules for reporting, labelling etc.

### **Consultation item n°12: Review of existing Directive and adaptation of requirements**

In what areas would an amendment of the CTD be required in order to address the issue? If this was addressed, can the impacts be described and quantified?

EFPIA's position has consistently been that the nature/stringency of the requirements and obligations should not be driven by the status/identity of the sponsor. There is no plan to change this policy. ABPI supports this position.

We believe that several areas of the CTD text would need to be amended and the existing Q&A documents would need to be included into the legal texts to provide further clarification. It would be important for national transposition to not result in divergent national requirements.

### **Consultation item n°13: Review of existing Directive, excluding academic sponsored CT**

Would you agree to this option and if so what would be the impact?

The ABPI supports the EFPIA position outlined in Item 12. The legislation was adopted to harmonise patient protection and safety and having differing standards would undermine this objective. Therefore, we are against the creation of a two tiered system based on sponsor classification, but support a system based on a proportionate approach of the risk to the participants.

## Key Issue N°4: Adaptation to Peculiarities in Trial Participants and Trial Design

### Consultation item n°14:

In terms of clinical trials regulation, what options could be considered in order to promote clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants?

We do not believe that the clinical trial legislation would need to be altered to promote paediatric trials. The legislation as such does not create a hurdle for conducting paediatric clinical trials and the requirements for all clinical studies should follow the same principles. In some Member Companies experience, patient recruitment and complex trial designs create bottlenecks for paediatric research today.

Political support at the EU and national level to promote research in children and educate parents about the realities of clinical development is needed. The conduct of Global paediatric study programs with simplified designs as agreed with EMEA and FDA may solve some of the issues.

To support a speedy paediatric drug development, we would suggest considering incentives to provide, for example, priority evaluation of paediatric studies designed to address an unmet medical need within a shorter timeline.

### Consultation item n°15:

Should this issue be addressed? What ways have been found in order to reconcile patient's rights and the peculiarities of emergency clinical trials? Which approach is favourable in view of past experiences?

We believe some uniform practical legal provisions to handle informed consent in emergency situations would be helpful to avoid legal uncertainty for treating physicians. The ethical considerations should be carefully balanced against the urgency of the situation in which time is usually very critical.

A simplified process to obtain consent from legal representatives or an independent second doctor may be considered after general approval of the protocol by an Ethics Committee.

## Key Issue N°5: Ensuring Compliance with Good Clinical Practices (GCP) in Clinical Trials performed in Third Countries

### Consultation item n°16:

Please comment? Do you have additional information, including quantitative information and data?

ABPI will endeavour to support the EFPIA position on this issue; however, comments received from our Member Companies are included below.

All clinical research conducted by Global pharmaceutical companies is according to internationally agreed principles. Sponsors usually have internal quality control and assurance functions to ensure robust data generation, data integrity and GCP compliance. Statements to certify GCP and GMP compliance are included in the regulatory submission documentation.

Today, GxP inspections are carried out by a NCA under the co-ordination of the EMEA and further initiatives for closer transatlantic and international collaboration to maximise inspection capacity are underway. EU support programs to facilitate capacity building in third countries for supervision and enforcement of international principles could be an option.

### Consultation item n°17:

What other options could be considered, taking into account the legal and practical limitations?

ABPI will endeavour to support the EFPIA position on this issue; however, comments received from our Member Companies are included below.

We would support the Member States to work toward a harmonised Inspection standard that would further promote consistency in the conduct of Inspections and which would focus on the highest risk compliance attributes based on regulation. Such harmonisation may further serve to reduce the number of inspection observations by the various inspectorates that are not necessarily based on codified "regulation" but which are rather cited based on a particular inspectorates view point of how sponsor processes would optimally be executed.

### Consultation item n°18:

What other aspect would you like to highlight in view of ensuring the better regulation principles? Do you have additional comments? Are SME aspects already fully taken into account?

No comments received from member Companies

## Additional Comments

We would like to request the harmonisation and simplification of GMP requirements for clinical trials. The interpretation in UK law of what constitutes manufacturing is different to

other EU states and can cause problems for sites e.g. they are not allowed to make a sticker label for an infusion bag of IMP as this constitutes labelling which requires a GMP certificate; this results in unlabelled bags being sent to wards which are more likely to result in mis-dosing.

We welcome the MHRAs excellent example of reduction of administrative burden regarding non-IMPs; these do not require a CTA in the UK and we hope this will remain the case in future.

The ABPI would like to thank the European Commission for the opportunity to input into the review of the functioning of the Clinical Trials Directive and hopes that this process of review will remedy the current shortcomings and unintended negative consequences of the Directive, while taking the Global dimension of clinical trials into account and reducing administrative burden.

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