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## ASSESSMENT OF THE FUNCTIONING OF THE ‘CLINICAL TRIALS DIRECTIVE’ 2001/20/EC

### SUMMARY OF RESPONSES TO THE PUBLIC CONSULTATION PAPER

#### 1. INTRODUCTION

The Commission issued, on 9 October 2009, a public consultation paper ‘Assessment of the functioning of the “Clinical Trials Directive” 2001/20/EC’ (CTD).<sup>1</sup> This consultation was part of the impact assessment exercise announced by the Commission in December 2008.

The deadline for responding was 9 January 2010.

The Commission has received 106 responses following this paper. 60 responses came from hospitals, investigators and ‘non-commercial’/‘academic’ sponsors, 22 from the pharmaceutical industry and contract research organisations (CROs), 10 from national competent authorities (NCAs), i.e. ministries or agencies and the European Medicines Agency (‘the Agency’), 6 from Ethics Committees (ECs), 3 from patient organisations, and 5 from other entities and individuals.

In accordance with the applicable guidelines, the responses have been published by the Commission.<sup>2</sup>

This paper summarises the responses to the public consultation document. In doing so, it not only reflects the majority views, but aims to give a ‘snapshot’ of the range of responses. For the sake of brevity, the paper does not reproduce the consultation items. Therefore, this summary should be read in conjunction with the consultation items set out in the consultation paper.

The public consultation is part of the ongoing impact assessment exercise. The information and views gathered in this public consultation will be worked into the impact assessment report, which will be finalised and published in the course of 2010/2011.

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<sup>1</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/clinicaltrials/docs/2009\\_10\\_09\\_public-consultation-paper.pdf](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/clinicaltrials/docs/2009_10_09_public-consultation-paper.pdf)

<sup>2</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/clinical-trials/developments/responses\\_2010-02\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/clinical-trials/developments/responses_2010-02_en.htm).

## **2. GENERAL REMARKS**

The public consultation was welcomed by practically all respondents.

The references to the ICREL study were criticised in several respects: some respondents considered that ICREL did not sufficiently reflect the negative impacts of the CTD. Other respondents stressed that ICREL was based on a relatively small number of respondents and therefore questioned the robustness of the data.

One respondent criticised the focus on procedural as opposed to ethical issues. Another respondent criticised the structure of the consultation paper, which did not follow the articles of the CTD but was based on the structure of an impact assessment exercise (problem description — policy options — socioeconomic assessment of the policy options).

## **3. EXAMPLES OF BENEFITS BROUGHT ABOUT BY THE CTD (CONSULTATION ITEM NO 1)**

Many respondents doubted that the CTD had brought about improvements in terms of safety and rights of participants. It was argued that, if anything, the safety standards for phase I trials had improved, as they were more often performed in hospitals than in the past.

On the other hand, several respondents stressed that the quality of clinical trials in terms of data reliability had improved. Poor-quality studies had been avoided.

Also, respondents highlighted that the CTD had led to more communication between academia and industry and amongst academia. Training opportunities had increased since the CTD, as well as internal audit standards.

Some respondents highlighted that, following the implementation of the CTD, supervision and communication of the sponsor with the investigator was more continuous (IB update, SUSAR, substantial amendments, etc.), and that supervision of sites had improved and become more harmonised. The clearer separation of responsibilities was highlighted as a benefit.

However, many respondents stressed that, although concepts were in principle good, they did not work in practice or did not achieve their aim. A much-quoted example in this respect was the rules for SUSAR reporting.

## **4. MULTIPLE AND DIVERGENT ASSESSMENT OF THE CLINICAL TRIALS APPLICATION**

### **4.1. Description of the situation (consultation item No 2)**

Many respondents disagreed with the Commission's statement in the public consultation paper that there were relatively few clinical trials where divergent decisions were ultimately taken on the clinical trials application in different Member States (MSs). On the contrary, respondents stressed that it was 'very unusual *not* to receive divergent assessments'. Respondents stressed that, if the

ultimate decision was not always divergent, it was because sponsors withdrew applications.

It was recalled that these difficulties would increase with an increase of multinational trials, which is likely in view of low prevalence conditions.

Respondents stressed also that different requests for information from NCAs showed a different approach to the concept of clinical trials authorisation.

A large number of examples were given where Member States diverged in their assessment. These examples related, *inter alia*, to stability data, 'borderline products', yearly revisions of the authorisation granted, additional 'validation times'.

On the other hand, some respondents pointed out that multinational clinical trials remained, in terms of number of protocols, the exception. It was also mentioned that, even within one Member State/Agency, assessors might come to different conclusions. It was also stressed that differences in assessment could stem from differences in culture, clinical practice, health systems, and — generally — 'local acceptability'. It was suggested that the issue be discussed in terms of the 'multiplicity' or 'divergency' of clinical trial assessments.

Respondents also took this consultation item as an opportunity to discuss divergent assessments of Ethics Committees. While this was not raised in the public consultation paper, respondents argued that this was the main challenge today when rolling out a clinical trial. It was stated that additional follow-up questions were very common.

## **4.2. Consequences**

Respondents stressed as a main consequence of this situation the lack of coherence of the protocol in a multinational clinical trial. In this context it was stressed that Member States were not even aware of changes introduced to different 'national versions' of the same protocol, which was highly unsatisfactory.

Many respondents, however, stated that the multiple assessments as such did not create safety issues.

Many respondents highlighted the costs created by the present system. Concrete examples were given (man-days per Member State involved). It was highlighted that this was particularly a problem for publicly funded research, and research on paediatric populations as well as rare diseases. The particularly negative impact on SMEs and academic sponsors without much in-house regulatory expertise was stressed.

As regards delay of the 'first patient in', many respondents stressed that timing issues were not necessarily linked to the CTD, but also other factors (logistics, recruitment, etc). The point was made that a 'staggered start' in different MSs could even be aimed for by the sponsor.

Other consequences highlighted were reduced competitiveness on a global scale, and the increased need for academic institutions to work with the

pharmaceutical industry to profit from the latter's in-house regulatory expertise.

It was also stressed that, increasingly, clinical trial sites were chosen on the basis of regulatory experience with the national competent authorities, rather than suitability of patients, sites and investigators. Also, there was a risk of 'NCA shopping'/'authority hopping' and 'Ethics Committee hopping'.

## **5. STREAMLINED AUTHORISATION (CONSULTATION ITEM NO 4)**

### **5.1. Recognition of one NCA's assessment by another NCA**

Many respondents welcomed such a possibility as an option for streamlining the authorisation procedure in multinational clinical trials.

Respondents highlighted the need to remain flexible and to keep deadlines short. In particular, possible 'arbitration' between Member States was seen as creating the risk of approvals being delayed, thereby extending the process.

The experience in the areas of medicines authorisation was highlighted, where similar procedures had been in place since 1975, and still posed difficulties in terms of delays. In this respect, it was stressed that the 'decentralised procedure', in the area of medicines, in practice largely applied to generic products, where scientific disagreement was typically not so large. Issues of language were raised.

It was also asked how a 'lead'/'reporting'/'reference' Member State would be chosen.

Other risks inherent in such a procedure were also highlighted: a Member State with less rigorous review might become too influential in Europe. On the other hand, collaboration might lead to a system where the issues of all national competent authorities taken together were put forward for a multinational clinical trial.

### **5.2. Central authorisation**

Again, respondents made many comments concerning similar 'models' that exist in the area of pharmaceuticals authorisation in the EU.

Many respondents welcomed such an option to address the divergent assessment of clinical trial applications in MSs.

It was highlighted that a centralised authorisation would lead to a 'continuum' in terms of marketing authorisations for centrally authorised products (including surveillance and scientific advice). The possibility of a 'rolling review' was raised.

It was suggested that a 'central system' should be limited to the investigational medicinal product (IMP) dossier, which would be centrally stored.

It was underlined that such a system would need to be run efficiently, which had a major impact on resources and staffing of national competent authorities. The idea of a rolling review was raised.

There were several critical voices, highlighting that this would create a new central bureaucratic structure, which might be slow and expensive, in particular for SMEs and academic researchers. Training and education was more important. Also, existing cooperation between national competent authorities and Ethics Committees would be lost. As regards existing models, the experience with the issuing of decisions for paediatric investigation plans was cited as a negative example.

Several remarks made regarding section 5.1. (above) were also valid for this part.

### **5.3. Voluntary harmonised procedure ('VHP')**

The VHP, an initiative of Member States without involvement of the Commission and without a legal basis in Union law, was discussed by some respondents.

Respondents highlighted that the VHP was insufficient, as it covered only processes, but not requirements. The need to submit documentation in 'two waves' was criticised, as well as practical problems (additional Member States joining late, substantial amendments, etc.). The fact that the VHP was voluntary, and that one Member State did not participate, was criticised.

### **5.4. Scope, other general remarks**

Practically all respondents considered it important that any kind of streamlined procedure had a flexible, voluntary scope.

Respondents raised several critical comments, for example as regards the role of ECs (who, in some MSs, assessed several aspects that were assessed by NCAs in other MSs).

The difficulty of working towards joint assessments was stressed; this was due to different perceptions of what is adequate health care, different standard health therapies, and differing standards of nursing care in the EU.

Also, it was highlighted that any kind of new, streamlined, procedure did not necessarily reduce paperwork.

Some respondents discussed whether an opt-out should be foreseen.

Finally, respondents raised a variety of other issues, such as the need for an electronic 'submission gateway', MSs' sites joining later during the trial, the use of resources in Member States, and the role of Iceland and Norway in any kind of streamlined procedure.

## **6. ETHICS COMMITTEES (CONSULTATION ITEM NO 5)**

### **6.1. Strengthening networks**

The idea of stronger networks and links between ECs in the different MSs was welcomed by many respondents. A European Forum was suggested.

However, some respondents urged that this should not lead to inter-MS decision making and that networking should not lead to harmonisation of ethical issues.

Also, some respondents feared that these networks might lead to an accumulation of all MS requirements and that negative assessments in one MS might impact on the work of the EC in another MS.

It was also stressed that the concept of ‘networking’ was vague and that strong leadership, with an umbrella body, was needed to make networks operational. Practical problems were raised, such as funding, language, and the fact that most EC members were not remunerated for their work in an EC.

### **6.2. ‘Demarcation’ of scope of assessment between EC and NCA**

Many respondents considered a clear demarcation as crucial.

It was also stressed that more interaction was needed on this point between NCAs and ECs.

It was pointed out that ECs assessed issues not looked at by NCAs, such as whether clinical resources were sufficient to ensure that non-participants were not disadvantaged, as well as contractual and insurance matters.

Many respondents to outline the potential areas of ‘overlap’ in the assessment. Some respondents stressed that ECs assessed ‘study feasibility’, as well as the risk-benefit in relation to a concrete clinical situation (i.e. not just in the abstract, in view of the products administered). It was stressed that ECs *had* to take safety and scientific merit into account in their assessment, which inevitably led to a double assessment.

It was recalled that the documents assessed by the EC and the NCA were partly the same but that the assessment was done from different viewpoints. This was not necessarily a disadvantage, as ECs could have more clinical expertise than NCAs.

The idea of a ‘composite regulatory authority’, merging NCAs and ECs, was raised.

### **6.3. ‘One-stop shop’**

Many respondents considered a ‘one-stop-shop’ as *the* most important short-term measure to improve the functioning of the CTD. A single contact point was suggested to this end.

However, some respondents also raised doubts. They highlighted that this approach could run counter to a concept of a clear demarcation of the scope of assessment between NCAs and ECs (see above).

Practical issues were raised, such as the impact of a ‘one-stop-shop’ on timelines, and the confidentiality of some documents.

The need for a one-stop-shop for single-centre trials was put in doubt.

Many respondents pointed out that some MS already had national one-stop-shops in place, such as UK (IRAS), IT, and ES.

#### **6.4. ‘Single EC opinion’**

The public consultation document did not raise the issue of a single, ‘European’ EC opinion. Rather, the document had made clear that *‘ethical issues clearly fall within the ambit of Member States and should remain there’*.

Nevertheless, some respondents expressed views on this matter. They stressed that local and cultural input was needed and that the local research environment had to be taken into account. Many examples were given for national and cultural attitudes, such as different standards of medical treatment, different professional obligations, different approaches to the embryo, different ethical perceptions of duration of life, quality of life, as well as the possible ‘conflict’ between the two.

On the other hand, some respondents stated that the standards applied by ECs were universal. It was also pointed out that the Commission, in the framework of its assessment of research proposals for funding, operated a ‘European’ review of the ethics of research proposals.

Ideas were raised, such as the possibility of an ‘opt-out’, for critical issues (e.g. research with medicinal products based on stem cells).

#### **6.5. Other issues**

Respondents addressed many other issues in this consultation item:

Some respondents complained that the concept in the CTD of a ‘single EC opinion per MS’ had still not been fully implemented, as some MSs worked with a ‘satellite system’. Also, MSs failed to coordinate the work of ‘their’ ECs.

In procedural terms, much criticism was levelled at the fact that assessments of ECs and NCAs did not always happen in parallel and that there was a lack of discussion and communication between the sponsor and the EC.

Many respondents addressed issues of training, qualification and expertise of ECs. It was argued that pan-European training was needed, as well as quality standards and an accreditation/certification system for ECs complying with minimum standards in the EU.

Some respondents addressed practical issues, for example doing away with the need to submit paper copies, and using more widely the single application

format for ECs in EudraCT. More clarity was asked for concerning the translation needs for documentation.

## **7. INCONSISTENT IMPLEMENTATION OF THE CTD (CONSULTATION ITEMS NOS 6 AND 7)**

Respondents pointed at numerous difficulties linked to the inconsistent implementation and application of the CTD in the different MSs. The public consultation was also taken by respondents as an opportunity to highlight possible infringements of the CTD by Member States.

The following issues were discussed in particular detail:

### **7.1. Substantial amendments (SAs)**

Respondents highlighted that the differing classifications in MSs of amendments as ‘substantial’ posed major difficulties in multinational trials. As it was not possible to ‘tailor’ a set of SAs for each specific country, a sponsor of a multinational trial submitted them to all NCAs, which was perceived in some MSs as over-reporting. Moreover, sponsors tended to err on the side of caution.

It was stressed that national, ‘unilateral’ steps to clarify the notion of ‘substantial’ (e.g. national guidelines) were counterproductive as they increased inconsistencies in the Union.

In terms of substance, the main difficulties stemmed from the administrative workload created by the addition of trial sites and changes of investigators. Other difficulties were posed by changes in the label of the IMP, which were considered as SAs in some MSs.

It was suggested that the EU could move to a ‘do and tell’ approach. ‘Grouping’ of SAs should be possible. Also, the definition of ‘substantial’ should be much tighter. In this respect, it was asked how SAs were dealt with in the regulatory system of the US.

The CTD was criticised for not laying down a deadline for acceptance of SAs by the NCA.

### **7.2. Reporting of suspected unexpected serious adverse reactions (SUSARs)**

Practically all respondents criticised the existing rules heavily. It was argued that this aspect was the least harmonised in the area of clinical trials legislation in the Union. The present system created a false sense of security, and was counterproductive. It was based on ‘quantity instead of quality’. However, there were also voices arguing that an increase in SUSAR reporting in recent last years might not necessarily be over-reporting, but rather the result of increased awareness, training, and education.

At the outset some respondents questioned whether SUSAR reporting made sense at all if the IMP was authorised or well-known.



Moreover, the very different rules in the MSs were highlighted, with MSs asking for different information, in different formats, and to be submitted to different entities. It was pointed out that some MSs allowed for line-listing of the reports to the ECs.

As regards electronic reporting, many respondents highlighted difficulties. It was argued that the database ‘Eudravigilance Clinical Trials Module’ (‘EVCTM’) was not functional, that registering was very burdensome (3-day training course with the Agency), that the connection failed frequently during reporting, and that training and keeping staff up to date was difficult.

On the other hand, it was acknowledged that EVCTM could be a useful tool if double reporting could be avoided and data was of sufficient quality. In this respect, it was stated that double reporting could only be avoided by using a single reporting code.

It was argued that the annual safety report was of more relevance than SUSAR reporting.

Many respondents argued that the present practice of reporting SUSARs to ECs was inefficient and useless. It ignored the role of ECs in the process. Alternative possibilities were discussed, such as giving access to EVCTM, providing a line listing, or doing away with the practice of reporting SUSARs altogether.

It was stressed that the definition of ‘serious’ was not in line with guidance of the International Conference for Harmonisation’ (ICH). Existing Commission guidelines were criticised for lack of coherence and clarity.

As regards the scope of reporting, numerous examples were presented where the rules for SUSAR reporting were unclear.

Finally, it was stressed that global harmonisation was insufficient, as third countries did not accept the format of SUSAR reports used in the Union.

### **7.3. Annual safety reports (ASR)**

Some respondents questioned whether annual safety reporting made sense for authorised medicines used in the authorised indication. Generally, it was asked who actually read this information and acted on it, in view of the limited feedback from NCAs and ECs.

### **7.4. Definition of ‘clinical trial’ and ‘non-interventional study’**

As regards the definition of ‘clinical trial’, respondents gave numerous examples where questions arose in practice. It was stressed that this ‘borderline’ was crucial for issues of insurance and approval.

Many of the examples related to situations where a medicinal product was administered in order to obtain a physiological response, i.e. without the product being the object of the investigation. It was pointed out that these studies did not fall within the definition of ‘clinical trial’.

The definition of ‘non-interventional’ was repeatedly discussed. Criticism was levelled at the fact that a study could become a clinical trial just by adding an observation or diagnostic measure. It was also stressed that many cancer products were used off-label, in particular for children medication.

It was stressed that clinical practice in MSs differed, for example as regards visits or laboratory exams, as well as standards of care. This made a harmonised approach particularly challenging.

Respondents asked for guidance as to what kind of additional interventions would be acceptable to consider a study as non-interventional. The notion of ‘low-risk intervention’/‘minimal-risk intervention’ was put forward. Other respondents argued that risk was not a good criterion. It was highlighted that non-interventional studies could have a major impact on future treatments.

It was argued that non-interventional studies should be regulated, but separately from the CTD.

#### **7.5. Investigational medicinal products (IMP)**

Respondents criticised the fact that the IMP/non-IMP borderline was not always clear, and gave numerous examples. It was stressed that a trial could involve many IMPs, and that these could be authorised in one MS but not in another. During a trial, an IMP might be removed which rendered another, non-IMP, an IMP.

Many respondents argued that rules for labelling, tracing, and destruction were disproportionate and stated that MSs had taken steps to adapt requirements set out in the CTD and in implementing guidance.

#### **7.6. Other issues**

Numerous other issues were addressed in this section, including insurance, the end of the trial, the application form to the NCA, monitoring, declaration of the qualified person, shelf life and stability data, and follow-up safety studies.

Also, numerous examples were given on the impact of these differences in terms of staff needs, and costs for running trials, including publicly-funded trials.

### **8. MAKING THE CTD INTO AN EU REGULATION (CONSULTATION ITEM NO 8)**

The views of respondents diverged widely.

Many respondents stressed the advantage of a Regulation, such as the absence of transposition into national laws, which would avoid any ‘add-on’ to the CTD of existing national requirements. Also, respondents highlighted the advantage of quicker implementation of a Regulation as compared to a Directive. It was pointed out that transition measures in Member States rendered the regulatory framework in the Union ‘similar, but different’, thus removing the benefit of harmonisation.

Other respondents raised doubts. They stressed that the legal form of a Directive gave flexibility to NCAs, in particular as regards non-commercial trials. These respondents also stated that the difficulties lay more in application than in implementation. Many issues required a case-by-case decision.

It was also argued that a Regulation might lead to lower protection of subjects in some MSs, while other respondents feared the contrary, i.e. that a Regulation would be a ‘collection’ of all existing national additional requirements.

In the context of this consultation item, many other issues were raised. It was stressed that some rules were *per se* national (e.g. the rules on civil liability). The fact was criticised that there were no official translations of national transposing laws. It was suggested that the CTD should clearly prohibit any ‘add-ons’ in terms of requirements in order to conduct a clinical trial.

## **9. INSUFFICIENT RISK DIFFERENTIATION (CONSULTATION ITEM NO 9)**

There was very large agreement amongst respondents that the CTD did not sufficiently differentiate between the risks posed by clinical trials.

However, there were also some sceptical voices. These outlined that a more risk-based approach decreased the predictability of the assessment, and increased the risk of divergent application of the CTD. It was also stressed that there was often a lack of confidence on the side of the sponsor as well as the NCA. It was argued that the main ‘barrier’ for a risk-based approach was the inspectors (as opposed to the NCAs assessing the trial). It was also argued that a risk-based approach increased ‘corner-cutting’ in a sector driven by the desire for fast approval.

Regarding risk criteria, many factors were brought forward. It was asked critically what risk was meant — that to safety, rights, or data robustness.

Regarding the marketing authorisation criteria, some respondents stressed that the criteria applied ignored issues of compassionate use and well-known off-label use, which was in particular relevant for paediatric research.

Many examples were given where the CTD did not sufficiently factor in risk. These included the non-IMP dossier, use of radiotracers, and collection of biological material with a simple additional intervention, monitoring, and IMP labelling, including issues of IMP destruction. Some respondents stressed that the rules did not sufficiently take into consideration the administration of IMPs in a pure hospital setting.

It was argued that a ‘broad brush’ with generic risk categories was difficult to implement. The risk had to be established for each individual trial. In this context, many respondents highlighted the need for good guidelines, as the problem was only partly rooted in the Directive itself. A Commission guidance document ‘on acceptable risks’ was suggested.

## **10. ADAPTATION TO PRACTICAL REQUIREMENTS (CONSULTATION ITEM NO 10)**

Under this consultation item respondents discussed a range of different issues related to the CTD and its implementation.

### **10.1. Requirements of Good Manufacturing Practice**

Some respondents argued that the existing GMP requirements were not suited to certain IMPs, such as cell and gene therapy products.

Also, applying GMP rules for early-phase products was criticised.

### **10.2. Single sponsor**

Responses varied widely. Some respondents stressed that it was difficult for a sponsor to take responsibility for a clinical trial in so far as it was performed in another MS. They argued that there should be a concept of co-sponsorship/shared sponsorship/joint sponsorship. By way of criteria, processes or territories of Member States were discussed.

Other respondents remarked that the main issue in this discussion was one of funding and insurance, and that some sponsors were not used to international cooperation in terms of regulatory compliance.

Also, some respondents stressed that the present system worked well, and that the concept of a single sponsor was the most valid and transparent approach. It was stressed that, in the case of multiple sponsors, it would become difficult to uphold the integrity of a protocol and that, generally, the establishing of responsibilities would be weakened. In this connection, it was underlined that divergences in protocols were often not 'picked up' by the sponsor after the trial had finished.

Several respondents highlighted that the main problem in this issue was confusion of the concept of 'liability' (in terms of compensation of damages vis-à-vis injured parties) with the concept of 'responsibility' (in terms of accountability towards the administration authorising and supervising the trial).

Generally, it was highlighted that the issue of a 'single sponsor' was particularly critical for some sponsors in view of the divergent rules for clinical trials and compensation claims in the EU, which made it difficult for some sponsors to accept responsibility.

### **10.3. Insurance**

Insurance was cited as a major challenge for sponsors in today's regulatory framework in the EU. The lack of flat-rate insurers and EU-wide insurance policies was lamented. It was stressed that policies did not sufficiently take into account the risks, and that the amount and duration of cover differed widely in the EU. An EU-wide insurance was suggested and advocated as a 'silver bullet' for academic research.

**11. REVISION OF GUIDELINES (CONSULTATION ITEM NO 11)**

Practically all respondents agreed that existing guidelines needed improvement, while stressing that this would be only an interim step to address the most urgent shortcomings and uncertainties of the CTD, in particular as regards safety reporting. Parallel work on implementation of the CTD as well as its revision was needed as well as strong leadership by the Commission in this process.

It was suggested that more stable guidelines be included in future legislation.

**12. EXCLUSION OF ACADEMIC RESEARCH FROM THE SCOPE OF THE CTD (CONSULTATION ITEM NO 13)**

There was practically unanimous agreement that the CTD should not discriminate *per se* between types of sponsors. The following arguments were put forward:

- The aims of the CTD (safety and rights of patients, data reliability) were independent of the type of sponsor;
- The difference between academic and non-academic was difficult to draw in practice (the different and changing terminologies — ‘investigator-driven’/‘investigator-sponsored’/‘investigator-initiated’ showed this);
- Discrimination would put existing cooperation between ‘academic’ and ‘non-academic’ sponsors at risk;
- Acceptability of non-commercial research would suffer and such research might lose credit;
- Publication of study results might become more difficult;
- Existing competition between small companies and large academic entities would be distorted;
- Clinical trials would have to be re-conducted for use in marketing authorisations, which was inefficient and unethical.

Rather, respondents highlighted that the key lay in recognising differing standards of risks and adapting regulation accordingly.

**13. PAEDIATRIC CLINICAL TRIALS (CONSULTATION ITEM NO 14)**

Many respondents highlighted that the challenge in this area was not so much legislation, but risk perception in Ethics Committees and insurance providers, as well as personal and financial resources.

Many respondents stressed their concerns that clinical trials with children were automatically considered as high-risk and that not enough account was taken of the actual risk of the standard treatment.

It was argued that, in particular in these trials, long-term measurement was more important than short-term reporting, such as SUSARs.

It was also highlighted that cooperation between the Paediatric Committee (PDCO) at the Agency and the NCAs in the subsequent authorisation of clinical trials at national level was insufficient.

Many practical problems were raised, such as the transfer of children from specialist hospitals to other, non-specialised, hospitals, the need to adapt pill sizes to children, and training in GCP for nurses.

The need for networks was highlighted while acknowledging that this was not enough to ensure that approaches were consistent.

## **14. EMERGENCY TRIALS**

Most respondents agreed that the situation as established by the CTD was unsatisfactory. Many examples and ideas for improvement were put forward by making reference to laws in the MSs, in third countries (US, CH), or other EU initiatives (e.g. organ donation). Other ideas concerned accreditation of clinical trial centres, as well as ‘adapted’ (i.e. shorter) informed consent forms.

The relevance of this issue from the point of view of data protection rules was highlighted.

## **15. CLINICAL TRIALS IN THIRD COUNTRIES**

### **15.1. Problem description**

While practically all respondents agreed that this was an important policy issue, many respondents criticised the problem description as being founded on prejudice and not fact- and evidence-based.

In particular, many respondents stressed that European companies did not apply double standards and were committed to high-quality research independently of the location of the trial site.

Also, some respondents questioned the argument that clinical trials in non-OECD countries were actually cheaper, in particular when factoring in costs for logistics. It was stressed that non-OECD country trials could be of a quality that was equal to or even higher than in the EU. It was also mentioned that some important non-OECD third countries did not authorise clinical trials in their territory before they were authorised in the EU.

Finally, it was underlined that non-OECD countries were very heterogeneous. It was also argued that clinical research in ‘third-world countries’ remained the exception today.

## **15.2. Policy options**

The options put forward in the public consultation paper were largely welcomed. Many examples were given of existing capacity-building programmes.

The importance of transparency of trials in third countries through public registers was stressed by many respondents.

Other ideas included strengthening the assessment of data submitted to the Agency in view of ethical concerns, as well as a list of GCP-compliant third countries.

It was suggested that public assessment reports in the framework of the marketing authorisations should address the ethical considerations of clinical trials data.

As a possible ‘linkage’ to the EU jurisdiction (thereby requiring GMP compliance), it was suggested that consideration be given to whether an IMP in an EU trial was used by the same sponsor in a clinical trial in a third country.

Some respondents opposed the idea of a ‘clock-stop’ when assessing clinical trials data in the framework of the authorisation of a clinical trial in the EU.

## **16. OTHER ISSUES**

The consultation was used by practically all respondents as an opportunity to highlight numerous additional issues. These concerned many different areas that were not specifically addressed in the public consultation paper. Examples include the following:

- The peculiarities of clinical trials involving imaging and diagnostic radiopharmaceuticals;
- Extending the scope of the CTD to other health-related products and services;
- The legal status of guidelines referred to in the CTD, in particular international guidelines;
- Minimum exclusion period for voluntary healthy participants (database);
- Scope of inspections, including GCP training;
- Sanctions for GCP non-compliance;
- Costs for IMPs in clinical trials;
- Involvement of patients when designing a clinical trial;
- Composition of ECs;

- The role of ‘informed consent’ and the practice of ‘re-consenting’;
- Differences among and appropriateness of the level of fees in the MSs;
- Interface between the CTD and legislation on authorisation of genetically modified organisms.

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