Consultation item n°1: Can you give examples for an improved protection. Are you aware of studies/data showing the benefits of Clinical Trials Directive?

EFPIA response

Improved protection

Industry sponsors have mixed views on the Commission statement that "the Clinical Trials Directive has brought about improved protection". No examples of or justification for this assertion are given in the Consultation document.

It might be considered that the introduction of a competent authority assessment of (Clinical Trial Authorisations) CTAs in some Member States (MS) where this did not previously exist might result in improved safety or ethics, but it should be borne in mind that clinical trials already, prior to the introduction of the Directive, had to comply with Good Clinical Practice (GCP) and with the Declaration of Helsinki when they supported applications for marketing authorisation (Directive 91/507/EEC). Furthermore adequate resources are necessary to enforce the requirements in all EU countries in order to guarantee the same level of protection across the Community.

However we see a few areas where the Clinical Trials Directive contributes to increase Patient Protection:

- Clinical Trials sponsored by Academic or Investigator Institutions have been brought up to the same level of requirements as Trials sponsored by 'commercial' organizations, e.g. in terms of Request for Authorization to commence the clinical trial, safety reporting or IMP handling. Conversely, the current proposal to differentiate the clinical trials sponsored by Academic/Investigator institutions and Commercial Organization in terms of requirements would therefore be considered as a step back in terms of Patient Protection.
- Healthy volunteer trials are now in scope of the legislation in all Member States.
- The requirement of one central Ethics Committee opinion per Member State has contributed to raising standards in terms of patient protection and informed trial oversight. It represents some improvement compared to the multiple opinions issued by local Ethics Committees.
- Pharmacovigilance procedures have been strengthened (for example the annual safety reports include international data and allow good updates of the product safety information)
- The implementation of the EudraVigilance database for clinical trial-related safety reports may have helped increase the safety of trial participants, as the same information should be accessible to all National Competent Authorities (NCA) at the same time. However, some of this benefit may be considered to have been undermined by differences in reporting requirements in different Member States.

- The provision for systems and responsibilities of NCAs for inspections – these reinforce the importance of GCP and the protection of the rights of subjects, e.g. new standards provide better protection of patient identity. GCP is more enforced and GCP inspections increased thus improving compliance
- The Clinical Trials Directive has also enabled an increased transparency of information on clinical trials across Europe. The European Database of Clinical Trials (EudraCT) has given competent authorities in the EU Member States crucial administrative and scientific information on clinical trials and has increased data sharing and coordination between Member States. This increased transparency has lead to competent authorities having increased awareness of planned and ongoing clinical trials in other countries in the EU. This has specifically lead to competent authorities being informed of the status of clinical trials in other Member States through data sharing and the transparency of the EudraCT database resulting in immediate awareness of, e.g., identified safety concerns and studies put on hold. This allows other competent authorities to directly be involved in discussions/actions addressing safety issues/concerns identified by other competent authorities in other Member States
- The Directive may have lead those companies which had little central regulatory oversight of clinical trial activity at a Member State level to implement systems aimed at more closely monitoring clinical trials at a country level from a central location. These systems allow quicker and more effective action to be taken following new information that impacts the risk benefit of the study to the patient.
- The protection of clinical trial subjects, and in particular that of more vulnerable populations, minors and incapacitated adults not able to give informed legal consent has been emphasised.

Studies/data showing the benefits of Clinical Trials Directive

One such reference has been found as follows:

[1] **Research ethics committees in Europe: implementing the directive, respecting diversity**

A Hedgecoe, F Carvalho, P Lobmayer, F Raka

http://jme.bmj.com/cgi/content/abstract/32/8/483

Consultation item n° 2. The Consultation Paper outlines a situation whereby "the Clinical Trials Directive sets out common rules for the authorization regime by the NCA' which are in practice applied very differently by the respective NCAs of the Member States concerned." It also notes "it has to be pointed out that there are relatively few clinical trials where the application of the regulatory framework leads ultimately to divergent decisions in different Member States." Further difficulties (in particular in relation to the assessments made by two distinct bodies, the NCA and the EC of each Member State concerned,) are outlined. The Commission raises the following two questions: **Is this an accurate description of the situation? What is your appraisal of the situation?**

EFPIA response

Although the Commission's description of the situation is reasonably accurate, many sponsors disagree with the statement that divergent decisions are rare. There are many occasions when divergent decisions are adopted in different Member States, and these situations can be extremely disruptive to the conduct of the trial (examples of difficulties faced by companies are listed below). It is suggested that the reason why it seems that "there are relatively few clinical trials where the application of the regulatory framework leads ultimately to divergent decisions in different Member States" may be that in such a situation sponsors may prefer to withdraw their application.

Moreover, the impact on the time and resources required by sponsors to manage and respond to different or duplicated requests from different Member States must not be underestimated, even when the eventual authorities' decisions are not divergent.

Examples given by companies:

- In our experience it is happening more often that clinical trials are not approved in one Member State while being approved in several other Member States due to differing views, e.g. on protocol related aspects or Investigational Medicinal Product Dossier (IMPD) requirements. Dealing with country specific protocol amendments or quality aspects (as a result of divergent decisions) might impact the conduct and analysis of a trial.

- Experience of multi-country studies is that it is very unusual not to receive divergent assessments and that these do lead to different requested changes in the protocol. This may lead either to a trial not being run in the Member State or to having to make multiple amendments to the protocol thereby delaying access to treatment for patients and increase in administrative burden and costs.
  A change to the protocol in different Member States also leads to countries conducting and controlling the trial differently, which can have an affect on the overall result of the whole study.

- Difficulties arise not only as a result of Member States imposing additional national requirements or as result divergent assessments being made. The fact that sponsors receive different requests from different Member States at different points in time is the source of additional difficulties.

- The problems do not arise only as a result of difference in the assessments made by the National Competent Authorities and Ethics Committee of a Member State. There are also differences in the assessments made by a Central Ethics Committee and local Ethics Committees (resulting in divergent questions and opinions even though their assessments were based on same documents and data). Overall, this results in delays, amendments and even the withdrawal of the CTA from some Member States.

- We experienced in many instances difficulties with the categorisation of Investigational Medicinal Product (IMP) or Non-Investigational Medicinal Product (NIMP). In a study comparing one novel entity vs. placebo with drug "Y" as a background treatment, "Y" was not accepted as background treatment in some EU countries which led the company to withdraw the CTA in these countries.

- A placebo-controlled design was approved in seven Member States, but refused in another one.

Consultation item n°3: In section 3.2 the Consultation paper outlines the weaknesses of the Clinical Trials Directive and outlines four types of weaknesses. The Commission asks the following two questions: **Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?**

EFPIA response

Overall the description is considered to be fairly accurate. However while it is true that large resources are needed to track differences in national requirements, coordinate activities, take care of the "chain reaction" resulting from a punctual assessment/decision from one body in one Member State (or to take the decision that is preferable to withdraw an application – see response to previous consultation item) these activities are not necessarily entirely managed by 'dedicated departments". Some companies may contract out at least some of these activities.

Information on manpower, costs

It is very difficult to accurately quantify the impact unless the company has been keeping specific records targeted at collecting this information over the last few years. However all functions in most companies involved with the initiation, conduct and oversight of clinical trials have been impacted. There has been increased consumption on resources in all of these functions, including regulatory affairs, clinical operations, clinical trials supplies, compliance and pharmacovigilance. The divergent approach to the regulation of clinical trials across Member States adds to the complexity, number of tasks performed and the inability to reuse documentation for different Member State National Competent Authorities (one company even states "there currently is not one NCA that requires the same set of documentation as another NCA").

It is also noted that some Member States have seen local introduction of significant administrative fees by hospitals as they pass the increased cost of complying with the administrative requirements on to the Sponsor.

Resources are required to translate local language Member State requirements and further interpret what is intended.

Resources are needed for presubmission discussions to clarify Member State requirements.

Resources are needed for the publishing of submissions since there are different Member State requirements for format/presentation of documents (CZ, SE, NL, DE, UK among many who have different electronic and paper requirements)

Some specific illustrative examples given by companies are provided below:

- Total cost for outsourcing of pharmacovigilance administration related to Ethics Committees submissions at one company's affiliate 484 004 Euros from 2006 to 2008.

- The administrative burden as well as scattered approval timelines has resulted in over 200% increase in the workforce (at the corporate and individual Member State level)

- The resources needed in 2008 for initiating 27 studies (average 6.7 countries/study) were 5 totally dedicated full-time equivalents (FTEs) and in total 12 FTEs because staff has to be shifted to provide the necessary support.

- The costs associated with fees have increased by approximately 60% and the manpower has increased by approximately 40%

Information on delays

Examples given by companies are provided below:

- Despite the assurance from Member State National Competent Authorities that CTA approval times meet the 60-day requirement of the Directive, we have experience of the time from submission of the dossier to approval frequently taking over 120 days in some Member States.

- Between 2003 and 2007, we noted a 5% increase in the average time between protocol finalisation and inclusion of the first patient in an EU country.
  CTA approval times, however, can vary considerably, even though a clear timeline is stipulated in the Directive. While the average NCA approval time in most MS is within the Directive's permitted 60 days, delays have been noted in CTA approval times in almost all Member States for at least one study (i.e. the assessment time has been longer than 60 days), with some assessments taking between 140 and 301 days.

(Specific information on timelines in relation to the operation of the Clinical Trial Directive in Spain is attached)

- One company indicated that variations in standard approval timelines, the questions asked by each NCA and the time required to respond could provide huge variations in clinical trial approval times and gave a recent example of a phase III clinical trial in 19 EU Member States where the time for the CTA to be approved by the different NCAs ranged from 28 days (Member State where no questions were asked) to 139 days where an NCA had concerns about the protocol and several rounds of questions and a meeting with the agency were required.

- Another company gave the example of one multi-centre multinational phase III study whose clinical trial application was submitted in June 2008 and which got a final approval in mid October 2009.

- Timelines ranged from 2 months to 8 months for obtaining the necessary NCA and EC clearance for including a first patient in a recent phase IV trial in 7 EU countries respectively

- It is also reported that in some Member States there is no defined time between submission and clock start, which allows the NCA 'pre-submission time' of indeterminate length.

- Current delays in approval times 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 EC contribute to the complexity. Some countries do not in fact observe the principle of one central ethic committee review, with only local feasibility assessed (typically by the local EC) in other sites.

- As a general rule, the more countries are involved, the more complicated the submission is, the more final approvals are delayed

Other examples for consequences given by companies

Companies often report that US IND applications for a particular trial are cleared in 30 days and that ethics approval are also obtained faster which result in the first patient included in global trials often being a US patient.

More worrying is the fact that companies also report that they often experience situations where the approvals in the EU countries (or some of these) are delayed due to the issues described in the Consultation Paper and this leads to patient screening in EU Member states only able to start when overall global enrolment of the trial population is about to close. The EU Member States therefore end up with no subjects or very few subjects in the trial.

Consultation item n°4: In section 3.3, The Commission Consultation Paper outlines options to address the issue of multiple and divergent assessment of clinical trials as regards the assessment by NCAs. The European Commission then asks the following questions:
- 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?

EFPIA response

ü ***Reliance on voluntary cooperation between NCAs:***

The 'Voluntary Harmonisation Procedure' (VHP) was launched by the Clinical Trials Facilitation Group (CTFG) as a pilot in early 2009. The VHP initiative allows for regular exchanges between NCA assessors which should logically lead to a convergence of review practices, data- and format expectations. Assessment sharing may be of particular relevance where expertise may not be universally available For commercial sponsors, the main advantage of the VHP is to be able to process a single list of questions at one point in time.

It is still too early to properly assess the merit of the VHP. It is important however, to consider its limitations which are:

- The VHP is not set up as a 'mutual recognition' or 'worksharing' procedure with the aim of making more efficient use of European resources. National assessments are in fact performed in parallel and subsequently shared between the participating NCAs.

- Since participation is voluntary, NCAs are free to opt out at any time and choose not to participate. This uncertainty reduces the predictability for the sponsors.

- After a successful VHP, the sponsor still has to prepare and submit national CTAs in all concerned member states and has to meet all the so called 'national requirements'.

- The VHP does not address the fundamental problems linked to a divergent interpretation of the Clinical Trials Directive. As long as these problems remain (ex. different remits of NCAs vs ECs, definition of IMP, substantial amendments, GMP requirements) no voluntary concept will be able to fully succeed.

ü ***Community-wide streamlining of the NCA-authorisation process for clinical trials:***

(a) Assessment made by a reference Member State, authorisations either issued nationally or by the Community for the Member States concerned. Disagreements would be referred to a sort of "arbitrage procedure".

For Marketing Authorisation Applications (MAAs), the mutual recognition procedure (MRP) was supplemented in 2005 with the so called decentralised procedure (DCP). The change was made because the MRP (initial assessment by a single Member State, with further subsequent review by other MS) was not working satisfactorily for initial applications. In particular, the overall timelines for the procedure could be very lengthy and true mutual recognition of the initial assessment was rarely achieved. We are not aware of any convincing argument why an MRP-like process could be more efficiently applied to Clinical Trial Applications.

The DCP on the other hand offers some potential for greater efficiency, as it is based on simultaneous and identical submissions in all concerned member states. It should be noted, however, that the DCP has primarily been used for the assessment and approval of generic medicinal products, for which it might be argued that there is less potential for divergent Member State opinions as the supporting data packages is much smaller and simpler than for products containing new active substances, and benefit/risk has, to a large extent, previously been determined based on the reference product. It is difficult, therefore, based on existing experience, to be confident that a DCP-like process could be effectively extrapolated to the assessment of CTA.

Any MRP or DCP concept assumes and requires a high degree of harmonisation between all the Member States. Unless this is the case, numerous complications would follow. For example, it is well known that there are today important differences between CTAs in different member states. These differences include core information, such as certain elements in the IMPD. Unless a revised EU clinical trial legislation was to become more detailed and prescriptive, simultaneous submissions of identical CTAs within the context of a decentralised CTA procedure would not be feasible. Furthermore, the definition of IMP and substantial amendments might vary according to procedure and to the choice of Reference Member State (RMP). The respective remit of the CA and the EC also varies from one Member State (and potential RMP) to another.

It is also important to point out a difference between clinical trials and marketing authorisations which is the need for flexibility and quick actions with regard to clinical trials. In clinical trials, the country selection is often secondary to the choice of clinical investigators and availability of patients corresponding to study entry criteria. New investigator sites and countries will have to be added quickly if patient recruitment is unexpectedly slow. On the other hand, slowly recruiting investigators sites (and countries where they are located) may have to be rapidly closed. The need for such flexibility for the sponsor does not fit well with a decentralised concept.

(b) A single assessment drawing on the scientific expertise from the EMEA and an authorisation valid throughout the Community.

EFPIA strongly supports the creation of a Community CTA review of trials to be conducted within the EEA as a *complement* to the present regulatory framework. **The key principle being a single CTA dossier submitted centrally, reviewed once and resulting in the granting of a Community clinical trial authorisation - valid throughout the countries of the EEA**. Moreover, an electronic-CTA format and structure, which should be based on the e-CTD specification, should be defined and implemented within this new pathway**. It is of the utmost importance that the Community CTA is set up by a European Regulation in order to allow a direct application in all Member States of the European Union.**

A Community approval system would by necessity need to be coordinated and managed centrally. The proposed procedure should be managed by an existing structure, i.e., the European Medicines Agency, rather than through establishing some new European body or institution. There are strong arguments for assigning the task to the EMEA. The EMEA already manages the EudraCT and EudraVigilance CT databases, coordinates GMP and GCP inspectors groups, issues guidelines relating to product development and clinical trials. The different EMEA scientific committees (e.g., SAWG/CHMP, PDCO) increasingly provide detailed feedback on clinical trial design issues. A direct involvement of the EMEA in the evaluation of clinical trial protocols, would also establish a link between EMEA scientific advice and Community marketing authorisation applications (which is currently missing).

EFPIA believes that the concept of a Community CTA review procedure offers many advantages to any type of sponsor (be this academic, industry or non-governmental organisations). It further provides "the missing link" referred to above between EMEA development issues (i.e., CHMP Scientific Advice, PDCO Paediatric Investigation Plans) and MAAs. It also allows for the preparation and submission of a unique, standardised CTA dossier and avoids multiple CTA assessments. For the Community CTA, there would be a single set of requirements for the CTA across all Member States. The Member States would not be entitled to request additional documents 'for national use'. An outline of what a Community CTA procedure might look like is provided below (smaller fonts)

Submission of the electronic-CTA would be made to a central EMEA electronic submission repository to support the assessment of the CTA. The EudraCT system would be used to support the same functions (e.g. completion of the CTA application form and provision of details to NCAs on proposed and ongoing clinical trials) as in the existing, national CTA system.

A clinical trials secretariat of the EMEA (the 'Secretariat') would validate incoming CTAs according to a single, pre-specified, content list. Once validated, the application would be evaluated by a 'designated assessment team' acting on behalf of the entire EEA.

The clinical trials 'assessment coordinator' would be responsible for selecting a multinational team of assessors, the assessment team, based on their proven expertise and availability (e.g. biotech CMC expertise, biostatistics, advanced therapies, paediatrics) and drawn from across all Member States. The Member States would provide the EMEA with a list of their clinical trial assessors (quality, safety and efficacy) but also where applicable, external agency experts and their respective field of expertise (e.g., biotech CMC, biostatistics, pharmacogenomics, advanced therapies, paediatric medicines).

The clinical trials assessment coordinator would lead the assessment team and would be responsible for ensuring that questions raised by the assessment team are based on sound scientific principles and are not influenced by national preferences. The assessment team would not be allowed to request additional (i.e. 'country-specific') documents when they receive a validated Community CTA. The questions would be issued to the sponsor in English.

Any concerns from Ethics Committees regarding scientific issues (e.g. inclusion/exclusion criteria) that could not get resolved together with the applicant would be addressed directly to the assessment coordinator (rather than to the national Competent Authority). Any request for a change to the protocol following an objection by an EC would be followed up by and through the assessment team. Community Authorisations and EC opinions will be immediately published in EudraCT and the concerned national Competent Authorities automatically notified. A clinical trial could commence once (a) Community Authorisation (within a time limit of 60 days for major categories of products) has been granted and (b) when/where positive EC opinions have been issued."

The Secretariat would be responsible for the administrative support necessary for coordination of the CTA review process. It would be of the utmost importance that sufficient resources be allocated to the Community CTA process to enable approvals within the legal timeframe.

Once a Community Clinical Trial Authorisation has been granted, the sponsor should have the possibility to add new investigator sites in other EEA countries after having obtained a positive EC opinion in those countries (the request sent to the EC(s) should include a copy of the Community Authorisation) without involvement of the EMEA secretariat or the designated assessment team, except for an update of the EudraCT database. Any new Community Authorisations and EC opinions (in their respective countries) uploaded on EudraCT should automatically be notified to all national Competent Authorities by the EudraCT system. Within the Community process, the EMEA must guarantee the application of a consistent policy for what types of changes should be submitted (or not submitted) as substantial amendments based on European guidelines. It should not depend on the preferences of individual assessment team members.

The new process would by necessity follow exactly the same rules (e.g. for amendments, safety reporting) as provided within Directives 2001/20/EC as amended and 2005/28/EC. As under the existing framework, the Community CTA review would be performed in parallel with the generation of Ethics Committee (EC) opinions.

ü ***Scope for streamlining***

§ ***All clinical trials conducted in the Community?***
§ ***Only some of the trials conducted in the Community (e.g., multinational, products falling within the mandatory scope of the centralised procedure)?***

The new procedure should be optional in nature and operate in parallel within the existing national CTA approval system. The optional character should cover the right for the sponsor to switch from one approval system to the other at different stages of development. **We believe the new procedure *should not be limited to any particular category of product, therapeutic area or development phase.***

The principles of a wide scope and flexibility are important for commercial sponsors. The advantages of the Community procedure would be greatest for *multinational trials* but appear less obvious for single country trials. It seems improbable that sponsors to any significant extent would choose submit early single country protocols (e.g. 'first-in-man' etc) within the framework of the Community procedure. As a safeguard, if this happened, we propose the health authority of the country concerned by a first-in-man study be automatically designated to the assessment team. On the other hand, it should be recognised that certain small trials may also be conducted late

in development (e.g. drug-drug interaction) and may therefore occasionally fit better with the Community concept.

Consultation item n°5: in **"**Section 3.4 Options to address the issue as regards the assessment by Ethics Committees" the European Commission has outlined various possible options for improving the ethics review of a clinical trial in particular in promoting cooperation and exchange amongst Ethics Committees as well as procedural best practices.
The options are follows:
Option 1 *One-stop shop for submission of assessment dossier*
Option 2 *Strengthening networks of national Ethics Committees involved in multinational clinical trials*
Option 3 *Clarifying the respective scope of assessment of NCA and Ethics Committees*

The questions raised in relation to this section are as follows: **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?**

EFPIA Response

The first option proposed by the European Commission is a "One-stop shop for submission of assessment dossier". The proposal outlined in section 3.4.1 has been interpreted very differently by different readers; interpretations included the following:

- One focal point in each MS where the sponsor can send the documentation for NCA and Ethics Committee separate and independent reviews
- One focal point in the EU where the sponsor can send the documentation for NCA and Ethics Committee separate and independent national (or even regional/institutional reviews)
- One focal point in each MS where the sponsor can send the documentation for a coordinated or even a global NCA and Ethics Committee
- One focal point in the EU where the sponsor can send the documentation for a coordinated pan European NCA (or a central regulatory review) and a coordinated pan European Ethics Committee review
- Other differences of interpretation (within the above mentioned interpretations) included submission of a single dossier vs submission of different dossiers to support regulatory and ethics committee reviews respectively.
- One Central Ethics Committee[1]

Overall, Option 1 was considered attractive whatever the interpretation of the proposal outlined by the Commission with the exception of one of the possible

[1] If this interpretation of the proposal was correct this option would provide an ideal solution in terms of Ethics Committee assessment for multicentre trials. One argument opposed to such a proposal raises cultural issues in individual Member States as a block to this working. We consider this to be no longer an insurmountable barrier given the multi-cultural nature of many EU Member States.

scenarios, namely, a process whereby the role of the 'one stop shop' would be fulfilled by an Ethics Committee (the reason was that Ethics Committees have no or few permanent staff members, work almost exclusively in the context of formal meetings, and do not meet frequently).

The second proposed option (Strengthening networks of national Ethics Committees involved in multinational clinical trials) was the least preferred option. Both the second and the third (Clarifying the respective scope of assessment of NCA and Ethics Committees) proposed options were considered interesting, but unlikely to have a meaningful impact on harmonisation, coordination or timelines.

However the three options taken together do highlight potential improvements to the clinical trial review process (to ensure thorough and rapid review of initial and amended applications).

Detailed comments on the various options

With regard to option 1 and after having eliminated two possible interpretations of the proposal outlined by the Commission (Single Pan European Ethics Committee which was clearly not an option proposed by the Commission, and possibility for an ethics Committee to fulfil the role of 'one stop shop') the main comments are as follows:

A "one stop shop" for submission of the CTA to both the NCA and Ethics Committee (EC) would significantly simplify sponsors' processes for preparation and submission of CTAs, especially if this can be done electronically. Duplication of effort (e.g. within sponsors' regulatory affairs and medical functions) could be reduced, and the risk of different information being inadvertently submitted to NCAs and ECs would be removed

Ideally CTAs would be submitted to a single coordinator, ensuring simultaneous review and provision of combined CA and EC questions. A coordinated provision of CA and EC questions would avoid the need for multiple protocol amendments and submissions by the applicant (including changes requested by other NCAs and ECs during review) and multiple reviews by CA and EC) at individual review points. Regulators and ECs would also share expertise and learnings, highlighting to each other key areas of CA/EC review and agreeing review responsibilities to avoid duplication of questions/ presentation of divergent opinions.

However, the respective assessment scopes would need to be clear (i.e. it is essential that option 1 is combined with option 3), and there should be some recognition of the challenges of divergent requirements, and guidance on how to build a common submission.

In particular, some restrictions on access to specific parts of the CTA would need to be imposed for the EC(s). For example, production and quality control information is commercially confidential and therefore must not be made public; therefore complete quality/CMC information in the IMPD is not normally provided to ECs to preserve confidentiality.

All NCAs and ECs must be willing to waive any current requirements for paper copies for this approach to be truly beneficial. Appropriate security to ensure protection of the submitted information would need to be implemented.

It would be critically important to avoid the increase of administrative amendments to the CTA application form, and have defined criteria of what is not required to be submitted.

We believe that this option could be particularly valuable for multinational trials if there was central a co-ordination body which would plan the EC consultation in coordination with a central regulatory review point.

With regard to Option 2 - Strengthening networks of national Ethics Committees involved in multinational clinical trials (collaboration)-

This option is the least preferred because it is too vague in practical next steps. Furthermore, there have not been any steps towards a stronger co-operation of Ethics Committee over the last 5 years, and there is much skepticism as to the chance that this approach may result in a better use of the ECs resources, eliminate differences in requirements or assessments, or improve timelines.

Genuine cooperation of Ethics Committees within the EU is desirable, and in theory strengthening networks of ECs may help to improve the consistency of assessments in different Member States. This could also provide a useful mechanism for resolving conflicting positions on points such as need for DSMB, submission of interim data, etc. However a strong leadership would be required for the co-ordination of a Network of EC working together, and based on the experience gained from the MA approval process, this may take a long time to set up and build trust in order to come to an acceptable output. This may also require an "umbrella" body representing members of ECs in the different Member States. This organisation should provide training and hold meetings to share best practices with regard to review of CTAs. Perhaps they could share comments on the same CTA and set up a coordinated review process in the longer term. It would also require having one central EC established per country.

Other concerns in relation to this option include the following:

- this option may just end up a talking shop with no influence; language difficulties between countries (if multi-national); smaller EC's will lack the necessary resource to conduct this activity. One would have to avoid any situation where there is a competition amongst ECs, or there may be discrimination between less experienced ECs compare with more expert ones;

- there is the possibility that negative EC assessments in some MS may also be adopted in MS that might otherwise have accepted a CTA, which could severely limit sponsors' ability to conduct trials in Europe. Sharing of information between ECs during the assessment process may cause delays to approval of CTAs as some ECs await the outcome of others' assessments. Efficient procedures and systems for the sharing of information will be needed;

- this option does not address the issue of administrative burden, nor does it provide clarity on the respective roles and document requirements of Ethics Committees and Competent Authorities;

- the timing of submission to Ethics Committees is often different; it is not clear how this could be addressed.

With regard to option 3 - Clarifying the respective scope of assessment of NCA and Ethics Committees

In theory, clear delineation of the respective NCA and EC assessment roles should help streamline the review processes, with both a reduction in assessment time (at least in those NCAs and ECs where the assessments overlap), and a reduction in the time and effort required by sponsors to respond to unnecessary questions.

The principal difficulty with this option will be defining the respective roles clearly enough, so that they are consistently applied across the EU. We are concerned that in practice each Member State will still have its own requirements, and therefore there will probably not be harmonization of the documents, or review timelines.

Legal clarity in responsibilities and scope of assessment will almost certainly be achieved by defining a minimum set of responsibilities, and defining particular accountabilities. This does not mean that NCAs and ECs cannot, and will not often, step beyond these in the interest of 'full review.' This could lead to an outcome of little change from the present.

This option would work best if built into a Regulation, as it would stop individual Member States implementing their own adaptation (of a Directive for example), and thus moving away from a consistent approach.

We believe that Ethics Committees should focus their attention primarily on study feasibility, ethical considerations and patients' rights, while competent authorities should perform the scientific assessment and ensure patients safety. It would be desirable to have a certification scheme and adequate training for the ECs to clarify the scope of assessment. In addition, the communication between the NCAs and the ECs should be strengthened.

Consultation item 6: The Consultation Paper outlines three "prominent examples" of inconsistent implementation i.e. substantial amendments, reporting of serious adverse reactions (SUSARs), scope of the Clinical Trial Directive (in particular for trials at the borderline between interventional trials and non-interventional trials) and raises the following two questions: **Is this an accurate description of the situation? Can you give other examples?**

EFPIA response

Amendments

Intelligence suggests there is inconsistency not only in the classification of amendments as substantial and non-substantial but also in the ability to submit overlapping amendments to a clinical trial (e.g. a CMC change and a protocol amendment). For example it would seem that although allowed in the majority of countries, this is not possible in France, is discouraged in the Netherlands and may vary depending on the ethics committee in Italy.

Pharmacovigilance

- For IMPs that are also registered (marketed), there is inconsistency between different HAs as to whether they require serious, related, expected AEs to be reported as MAH. The IMB and some other HAs say no need to report, while others e.g. MHRA appear to require such cases. A clear statement in the CTD (and Volume 9a) is needed to define if serious, expected, related AEs from clinical trials should be reported, where the sponsor also holds an MAH for the suspect IMP. Such cases currently fall into a gap between the CTD and Volume 9a.

- With regard to semiannual SUSAR reports, the IMB have stated that they only want them on request, while most other HAs require them to be submitted. It would help sponsors if a consistent approach could be adopted by all HAs.

- The IMB require country specific information to be included with the Annual Safety report (ASR), which is not mandated in the detailed guidance to the CTD e.g. recruitment figures per Irish site, number of patients withdrawn per Irish site and number of patients completed per Irish site. In the spirit of the CTD, all HAs should require in the ASR only the information mentioned in the detailed guidance to the CTD, since having to provide specific additional information adds complexity for the Sponsor.

- There is confusion around the reporting of SUSARs with Non Investigational products (NIMPs), especially where the NIMP is provided by the sponsor as background therapy for all patients. This matter was raised by the IMB, who felt that such SUSARs should be reported. The requirements (if any) for reporting SUSARs with NIMPs should be clarified in the CTD.

- In addition to disparities in the requirements among NCAs, there are other potential root causes of over- or duplicated reporting and inconsistencies of reported cases. These include a lack of common understanding or interpretation by NCAs and sponsors regarding: seriousness; expectedness and the nature and content of the reference document relevant for the expectedness assessment; causality; understanding of definition of IMP and NIMP; definition and understanding of the condition under research and reportability of cases related to the condition.

Inconsistent process for reporting deviations of GCP in an expedited way to the HA.

This should be limited to serious breaches (refer to UK legislation) and harmonized across Europe".

Interpretation of the definition of an Investigational Medicinal Product (IMP):

Interpretations of the definition of an IMP vs a "non-investigational medicinal product" (NIMP) still differ despite the publication of the EU "Guidance on Investigational Medicinal Products (IMPs) and other Medicinal Product Used in Clinical Trials". For example in the case of the common scenario of a 2-arm study of NCE + baseline therapy versus placebo + baseline therapy, the baseline therapy is regarded as an IMP in some Member States.

This results in inconsistent regulatory expectations in different Member States in relation to the same protocol. This causes confusion and has an impact on the content of the Investigational Medicinal Product Dossier (IMPD), supply/logistics, labelling, and pharmacovigilance.

Management of expanded access/continued access programs

The approval of Expanded Access/continued Access programs (EAP) is not consistently managed with some countries requesting a clinical trial protocol for the EAP while the clinical trials Directive is not really adapted for this kind of protocol (examples of issues: drug provision as only objective not accepted; or provision until commercially available is not always accepted as an end date).

Chemical and Pharmaceutical Quality Documentation

Despite the publication of a "Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials" and Q&As in this area, the Member States expectations are still not aligned.
There are different requirements for QP declaration, stability updates are handled differently, etc.

Forms, certificates, statements, etc.

Many countries have specific additional requirements and/or require that specific local forms (including application forms) be completed, various certificates or statements be submitted; in Poland original notarised copies of some documents are required.

Data Privacy

There are diverging requirements pertaining to **data privacy** (in some cases constraints) (Norway, Portugal, Denmark, France, Germany – approval for CT scans);

In some Member States the national rules actually preclude certain data to cross their borders, however, other Member States allow free transit. This leads to a much more complex design of clinical trial databases, and the output of such can be affected by the lack of consistency between MS regulations.

Miscellaneous

- Different requirement in relation to labelling requirements, possibilities of re-labelling, possibilities of direct to site shipments, import requirements, destruction of samples requirements.

- Local EC review still exists in parallel to central EC and the scope of the local EC role is unclear.

- Local insurance requirement (global Sponsor's policy not being accepted) means doubling up insurance cover. At the same time no clear guidelines or methodology for assessing the appropriate insurance levels in some countries, which has lead to several conditional approvals.

Consultation item n°7: The Consultation Paper highlight two weaknesses in relation to the inconsistent implementation of the Clinical Trial Directive issue (Insufficient patient protection and Increase of administrative costs for sponsors) and raises the following questions: **Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?**

EFPIA response

Accuracy of the description

Overall the description is considered to be fairly accurate. However the assessment of the possible impact on patient protection of an incoherent regime of transmitting and processing information on SUSARs needs to be somewhat moderated.

We would agree that inconsistent reporting of SUSARs is a weakness resulting from inconsistent implementation of the Clinical Trials Directive, but not entirely that this would directly result in insufficient patient protection. The routine and proactive safety monitoring/surveillance activities conducted by study sponsors are designed to ensure the protection of patients participating in clinical studies.

Divergent views as to whether a trial is interventional or non-interventional (sponsor, NCAs) in themselves carry a risk of not reporting appropriately.

Quantifying the impact of the weaknesses

One company has assessed that the costs associated with the conduct of clinical trials in Europe had increased by 200% with the implementation of the Clinical Trial Directive but other companies indicate that it is impossible/very difficult to precisely quantify costs associated with inconsistent implementation of the Clinical Trial Directive, or to differentiate these costs from those arising as a consequence of divergent assessments.

However it can be surmised that due to the implementation of the Directive the documentation and submission requirements have increased and therefore more resources in different functional areas have been required to fulfil these new obligations. Additional local requirements can easily lead to a massive increase in the administrative burden in the affected countries (e.g. multiple notifications due to the federal structure of some countries). Furthermore, due to inconsistencies in the implementation it is often necessary that decisions that have been made centrally must be rechecked on a local level to make sure they apply for a specific country (one example is the substantial amendment).

Taken together, this leads to the situation that one and the same topic must be evaluated multiple times on multiple levels without adding real value or increasing patient safety.

As a specific example for a global company, if all SUSAR reporting could be centralised with just EMEA reporting and not requiring reporting to each CA it would release resources on more value added activities like signal detection and interpretation

Another example for trying to quantify the impacts of these weaknesses is to look at the different version of the IMPD (IB, Quality section and/or Risk/Benefit assessment) for the different countries participating in a given clinical trial. We can potentially end up with one different version per country due to:

- One country cross-referring to a previous study, including all subsequent substantial amendments.
- One country cross-referring to the initial IMPD approved for a previous study, excluding subsequent substantial amendments.
- One country submitting a previous version and subsequent substantial amendment
- One country submitting a previous version and only part of the amendments considered as substantial as per National Regulations

- One country submitting the 'brand' new IMPD
- One country asking additional GMP certificates

The tracking and maintenance of those dossiers represents a significant part of the FTEs involved in the dossier preparation (entry and update of the tracking system and publishing of different versions)

Other examples for consequences

- In order to simplify their safety reporting process, avoid potential under-reporting due to interpretation biases and reduce administrative burden and associated costs, some sponsors (especially in multinational trials) are reporting Suspected Adverse Reactions – SARs (or Suspected Adverse Events -SAEs) and all cases that are suspected to be related to the research condition, whatever the influence on patient safety could be. Such over reporting may introduce false positive signals.

- In terms of patient protection, local insurance is intended to be for the patients' benefit (allowing them not to travel to make a claim). However, when there is a lack of experience of local insurance companies and/or local agents of global Sponsors in the area of clinical research, this may compromise the coverage of patients, both in terms of wording the insurance, the timelines for processing a claim and by not managing to prevent fraudulent claims. Also local agents may not have a validated methodology to ember assess the risk and to recommend levels of coverage appropriate in the specific Member State, which could lead to insufficient or inappropriately high levels of coverage.

- We would like to point out that the increase in administrative cost should be stratified against the increase of cost related to the application of GMP requirements to all investigational medicinal products and GCP requirements to all interventional clinical trials. .
  While compliance with the standards of good practices is certainly beneficial to patient protection some requirements may need to be reviewed in considering whether the burden they impose is proportionate to their expected benefit for the patient. For example 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.

- In general, the non-harmonization of requirements and assessment of the original CTA and later amendments and the different assessment timelines have an impact on the start-up and end of studies

Consultation item n° 8: 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.

EFPIA response

Requests for Authorisation:

Clearly differences in the legislation for clinical trials exist between Member States as a direct result of differences in the interpretation of the requirements of the Directive and of additional requirements above those of the Directive being added to the Member State legislation. Many of these are listed in the Commission guideline CT 1 Attachment 1, but there are also several other Member State-specific requirements not listed.

However even within the core components of a CTA (protocol, IB and IMPD) there are:

- different formatting requirements for technical documents;
- different expectations on the level of supporting data;
- different expectations on aspects of the protocol.

The result is that in many cases Member State-specific IMPDs are required and, following the review of the CTA for the same protocol in multiple Member States, different questions / grounds for non-acceptance are received from the reviewing bodies. Thus there is further complexity added through case-by-case application.

Substantial Amendments:

We are not aware of any instances where the Member States have adopted laws that are inconsistent with or contrary to the Directive 2001/20/EC or the guidance provided in ENTR/CT 1 with regard to the notification of substantial amendments to CTAs. A modicum of subjectivity in the definition of a substantial amendment given in these texts allows for different interpretations. These different interpretations are driven by organisation' or individuals' differing tolerance to risk. Thus it is likely that in the case of substantial amendments, the different implementation is driven by case-by-case application of different interpretation of the Directive and Commission guidance document.

The desire to improve consistency led to some useful additional guidance on substantial amendment that was added to the Commission guidance in CT1 Revision 2 in October 2005. However there has also been generation of additional local guidance by some organisations (e.g. national agencies, GCP inspectorates, Ethics Committees) that is more inclusive of the kinds of changes regarded as substantial amendments. There have also been communications (public or otherwise) from some

NCAs or ECs indicating specific categories of changes that are regarded as substantial amendments (e.g., any change to the IB). This approach does not allow for a proper consideration of the impact of a change and therefore deviates from the correct definition of a substantial amendment.

From a pan European perspective, national attempts at improving consistency are self-defeating as they are only implemented locally and perpetuate a disharmonised approach between Member States.

EudraVigilance Reporting (SUSARs):

Minor variations in requirements as regards notification of SUSARs to NCAs are generally of minimal practical impact. However, variation in the requirements as regards notification of SUSARs to ECs and investigators does have significant practical implications.

While the Clinical Trial Directive requires sponsors to notify ECs at the same time as notifying the competent authorities, ENTR/CT3 indicates that sponsors may utilise periodic line listings instead. However, some competent authorities (Austria, Cyprus, Germany, Hungary and Slovenia) have not allowed this practical alternative, and insist that local ECs are informed on a case-by-case basis.

A similar issue exists as regards notification of SUSARs to investigators. While ENTR/CT3 allows for the use of periodic line listings for this purpose, the Clinical Trials Directive is not specific and the NCAs in Austria, Czech Republic and Germany insist that investigators are informed on a case-by-case basis.

Hence, sponsors have to choose whether to implement a single system for notification of SUSARs on a case-by-case basis (i.e. adopt the 'lowest common denominator' approach) or operate two systems, the second to accommodate countries where periodic line listings are allowed for this purpose.

It is evident that many ethics committees and investigators have complained to sponsors about the volume of SUSAR reports that they are now receiving, especially in those countries where case-by-case notification is required. In addition to having to manage the paper load, many find it difficult to determine what the value is of all of these reports. One pharmaceutical company estimated that it issued 26,000 periodic line listings plus a further 138,000 individual SUSAR case reports to investigators and ECs across Europe during the 12 months to 30 June 2006. It estimated that it issued >900 SUSARs each month to local ethics committees and investigators in Germany – the local investigators complained that the sponsor *"delivers a haystack and fails to identify the hidden needle*" as a result of the volume of SUSAR reports generated. Likewise, the company's UK affiliate observed ""*Ethics Committees have wanted to suspend a trial because they misunderstood the significance of a single SUSAR report; current processes may not always help our customers understand the true safety profile of an investigational product and can actually hinder research."*

It is widely acknowledged that the impact of SUSARs on the ongoing safety profile of an IMP is more evident when data are collated in a periodic report, especially when accompanied by a short summary of the developing safety profile. Therefore, given

the above, it is suggested that the Clinical Trials Directive is amended to clearly indicate that SUSARs should be communicated to ECs and investigators as periodic line listings, and not directly linked with expedited notification to national competent authorities.

Annual Safety Reports:

NCAs are more consistent in their interpretation of the requirement for Annual Safety Reports (ASRs). However, the provisions are ambiguous with respect to the scope of an ASR and the content of line listings and summary tabulations.

ENTR/CT3 should clarify whether line listings and summary tabulations should be periodic or cumulative in nature, preferably in accordance with the draft ICH E2F (DSUR) guideline which will soon reach step 4

Which option is preferable for improving the situation?

To be effective in improving the situation the legislation should

- include a provision that effectively prevents the Member States from issuing conflicting national guidance on clinical trials other than on national procedural advice. (It is an obligation of the Commission to provide the detailed guidance on the request for authorisation of a clinical trial and no other local guidance should be necessary)
- include a provision that effectively prevents the Member States from adding to the CTA requirements described exhaustively in ENTR/CT 1
- include a provision that effectively prevents the Member States from applying different reporting standards from those described in ENTR/CT3. It should be clarified that there should be no need for individual SUSAR reports to investigators and ECs unless in exceptional cases there is an immediate impact upon benefit-risk, trial conduct or public health.

Without these provisions in the Community legislation, no amount of clarification in a revised Directive or associated guidance removes the possibility that individual member states could implement divergent legislation. In this situation, a Regulation with one associated detailed guideline to address the issues discussed would be preferred. However, a Regulation that accommodated every Member State's national interests and requirements would be disastrous. For a Regulation to improve the situation, it must be written with the principle of risk adaptation foremost in mind.

Nevertheless, revisions to legal texts in whatever form are unlikely to completely prevent different approaches being taken to aspects like the questions raised at the review of CTAs and on substantial amendments, because of their case-by-case application. Therefore, the ENTR/CT 1 guideline could usefully be revised to describe an exhaustive and unambiguous set of requirements for CTAs. In addition, for substantial amendments, some additional guidance on best practice and process may assist some Sponsors, particularly on how to proceed with non-substantial amendments. It may also be useful to consider examples of changes that would categorically be considered as non-substantial amendments, as long as it was stressed that the examples were not an exhaustive list.

Section 5.2.1 Requirements not always risk commensurate and **Consultation item no° 9: can you give examples for an insufficient risk-differentiation? How should this be addressed?**

EFPIA response

EFPIA believe that the development of a risk based approach to the regulatory oversight of clinical trials may be appropriate while strictly requiring compliance with principles of Good Clinical Practices.

The development of a medicinal product is a stepwise process involving the evaluation of both animal and human efficacy and safety information, while ensuring that the quality of the investigational medicinal product is appropriate for the intended use. When planning clinical trials, risk factors are identified progressively throughout the development process, and post-authorisation.

The risk for a clinical trial participant varies depending on the type of trial and a number of factors, for example:

- nature of the substance,
- mechanism of action
- extent of knowledge/research and development stage,
- patient exposure,
- population having received the IMP or the authorised medicine,
- dosage regimen,
- indication, etc), .

The nature of the sponsor (commercial vs non commercial) itself is irrelevant in relation to a possible risk for research participants because the protection of patient rights and safety must be ensured in all settings/cases. Even though non-commercial trials may not be conducted to generate data aimed at supporting application for marketing authorisations (for new products, new indications, new dosage forms, new routes of administration, as post-authorisation commitment studies, etc), they are expected to be used to guide medical practice and therefore their scientific integrity is critically important. For example, trials using a new dosing regimen may pose a risk due to potential lack of efficacy, while trials comparing authorised products used strictly within the terms of the marketing authorisations are low risk.

Finally, a new indication may be identified by a non commercial sponsor during the course of a trial. Such results should not generally be required to be repeated in the framework of an application for a marketing authorisation in the EU. This would be ethically questionable, especially if the study involved the paediatric population or was an emergency clinical trial.

EFPIA agrees that there currently is insufficient risk differentiation regarding the requirements in relation to the regulatory oversight of interventional clinical trials using medicinal products. In reality, there is virtually no risk differentiation at all.

Some real life examples of insufficient risk differentiation are given below:

- Labelling requirements:
  Due to a lack of space, the labelling requirements for using an authorised Ophthalmic product contained in a very small container could not be met in some countries. The patients were not at risk since they had access to the relevant information via the mandatory patient information sheet. Since the requirements were inapplicable, the trial could not be conducted in those countries where they could not be waived.

- Use of dietary supplements in clinical trials and an inappropriate reliance on pharmaceutical GMP standards for substances consumed by the ton worldwide. A company set up a global Phase IV study that included vitamin D in one of the treatment arms. Commercial vitamin D supplements contain calcium which was unacceptable for this study. The company had to source vitamin D from a food supplement manufacturer, but was obliged in the EU countries to wait more than 6 months until the manufacturer gained GMP authorisation from their national authority that had a memorandum of understanding with the EU.

- Request for a full IMPD for an (EU)-approved comparator

However, a risk-based approach may not be easy to develop, and depending on the scope may raise extremely complex issues, for example:

- Different approaches could be considered across a spectrum of clinical trial scenarios which present different degrees of risk. At one end of the spectrum, for example, might be first time in human type clinical trials, and at the other extreme, the use of an authorised medicinal product in a manner that is consistent with the particulars of the SmPC. A risk-based approach has already been considered in the EMEA guideline entitled "GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS" which was "intended to assist sponsors in the transition from non-clinical to early clinical development by outlining factors influencing risk to be considered in the non-clinical testing strategy and designs of first-in human clinical trials".

  This global risk based approach would make a lot of sense from a scientific and regulatory perspective. However, such an approach would require further elaboration by experts in risk identification and mitigation, and depending on the degree of differentiation of trials into separate risk-based categories that was considered possible and appropriate, it might require the development of a complex decision tree.

- Another type of risk-based approach could define certain criteria which would call for a less stringent regulatory oversight, or the submission of less detailed

background documentation. For example, involvement of an external Data Safety Monitoring Board (DSMB), administration of an authorised medicinal product, administration of an authorised medicinal product which is also used in the condition, use of commercially available substances that do not meet the definition of a medicinal products.

- It could also be decided that graded levels of requirements would be applicable depending on certain factors. For example, the level of requirements in relation to labelling, IMPD or non IMPD, monitoring, etc.

The principle would have to be mentioned in the legislation. It could be further elaborated in a Commission Regulation, with additional details being provided in guidance documents.

Article 1.2 of Directive 2001/83/EC outlines the purpose of compliance with Good Clinical Practice as follows "Compliance with this good practice provides assurance that the rights, safety and well being of trial subjects are protected, and that the results of the clinical trials are credible."

We believe that the rights, safety and well being of trial subjects must always be protected, and that conducting trials without taking the necessary measures to provide assurance that the data and reported results are credible and accurate would be unethical. The requirement of scientific and social value could not be fulfilled either.

Therefore we believe that all clinical trials and in particular all interventional clinical trials should be performed in compliance with GCPs whoever is the sponsor and whatever the clinical trial phase.

<u>In conclusion,</u>

- EFPIA agrees that there is insufficient risk differentiation with regard to the requirements to meet in relation to the regulatory oversight of interventional clinical trials using medicinal products.
- The development of a risk based approach to the regulatory oversight of clinical trials may be appropriate while strictly requiring compliance with principles of Good Clinical Practices.
- However a risk-based approach is not easy to develop.
- Such an approach would require further elaboration by experts in risk identification and mitigation, and the differentiation of trials into separate risk-based categories.
- The principle would have to be included in the legislation (and could be further elaborated in a Commission Regulation), with additional details being provided in guidance documents.
- The nature of the sponsor (commercial vs noncommercial) itself is **irrelevant in relation to a possible risk based approach**
- All clinical trials and in particular all interventional clinical trials should be performed in compliance with GCP.

Section 5.2.2 Requirements not always adapted to the practical circumstances and **Consultation item n°10: Do you agree with this description? Can you give other examples?**

EFPIA response

It is acknowledged that the single sponsor requirement may create a bottleneck for academic centres, however joint/co-/multiple sponsorship schemes may create confusion. We believe that most difficulties may stem from issues regarding insurance policies (for example, difficulty for any sponsor to find insurers prepared to meet Member States specific legislation concerning the damage to be covered /ceiling of coverage; huge insurance premium), and the funding of these trials.

Consultation item n°11: 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?

Consultation item n° 12: Is this an accurate description of the situation? What is your appraisal of the situation?

EFPIA response

We consider that introduction of new/revised implementing guidance documents can at best achieve incremental improvements. It will realistically never achieve a satisfactory level of harmonisation between the Member States. The adoption of appropriate legislation that prevents national interpretation or 'gold plating' of the rules is the preferred option. This legislation should also provide more detail on the rules applicable throughout the EEA.

Still, short- and medium term, improved guidelines are important elements. Improved EU guidance will only help if the Member States agree to be fully committed to harmonisation and that national differences are simply not tolerated in relation to data requirements, labelling, ASRs, SUSAR reporting, timelines and requirements for substantial amendments. This would be a critical first step towards harmonisation of requirements across the EU.

Example areas that may (short- and medium term) require further detailed guidance, or greater implementation detail within appropriate EU legislation to provide appropriate detail for harmonised Member State implementation, are given below:

- IMP scope and NIMP criteria to be sufficiently detailed to eliminate ambiguity
- Clinical supply labelling - precise details to be outlined to prevent national rules and additional requirements
- Format and content of ASRs - Annual Safety Reports to contain periodic line listings of all serious ADRs notified to the sponsor during the year under

review, and cumulative summary tabulations of all serious adverse events notified to the sponsor, in accordance with the ICH E2F guideline[2]

§ SUSAR reporting practices - SUSARs to be communicated to ethics committees and investigators via periodic line listings, each accompanied by brief summary of the evolving safety profile of the IMP.

Some issues such as insurance needs should still remain in the local remit as this cannot be harmonised but certain minimum criteria/requirements could be included in the guidance as prerequisite for approval.

Consultation item N°13 (Adaptation of the Directive to "practical necessities", make a distinction between non-commercial and commercial sponsors; EFPIA is opposed to a distinction based on sponsorship)

EFPIA response

To achieve the objectives of the Regulatory Framework and guarantee best protection to all research subjects, we maintain our belief that the nature/stringency of the requirements and obligations should not be driven by the status/identity of the sponsor, but rather by the nature of the investigation to be carried out. We therefore do not agree with the Commission proposals for an outright exclusion of 'academic' sponsors from the rules of the CT Directive. However, we do recognise that some sponsors find difficulty in complying with the legislative requirements. We also recognise that this can have an impact on the ability for those sponsors to conduct clinical research in the EU.

We believe that there should be a review of the legislation to identify those provisions of the legislation that cause difficulty for 'academic' and other sponsors. These provisions should then be considered within the context of impact on the safety of participants in the trial and the integrity of the data generated. If, by excluding these provisions, there is no impact on the safety of clinical trial participants or quality of the data, the reasons for including those provisions in the CT legislation and applying them to all sponsors needs to be reviewed (see comments on consultation items n°9 and n°10).

This approach would then remove those elements of the legislation that are problematic for 'academic' sponsors while maintaining the high standards of patient safety and data integrity, and ensuring consistency in application of the EU legislation across all clinical trials' sponsors.

It is important to ensure that all clinical research conducted is undergoing the same scrutiny to assure the same level of patient protection and robustness of data.

[2] This ICH guideline will reach step 4 very shortly. At step 4 the ICH guidelines are endorsed by the CHMP and a timeframe for implementation is established. The guidelines are subsequently published by the European Commission in the Rules Governing Medicinal Products in the European Union.

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?

EFPIA response

The Clinical Trial Directive provides an appropriate legal framework for the protection of the paediatric population participating in clinical trials and we have no evidence that this legislation creates a hurdle for conducting paediatric research.

Notwithstanding situations where some Member States seem to be extremely reluctant to authorise clinical research for paediatric medicines, the development of medicinal products for the paediatric population is mostly hampered by the following constraints:

- difficulties in recruiting patients
- complex trial designs, heavy schedules
- the fact that in some instances the Paediatric Committee, or other regulatory committees, ask for trials that National Competent Authorities, and more frequently Ethics Committees consider unethical or inappropriate.

It is suggested that various measures could be considered that may contribute to addressing these issues. A few examples are listed below:

- political support at EU and Member States level to promote paediatric research (in particular in communicating to parents the importance and need for such research, and of the protection of their/the children's rights)
- encourage a dialogue between the various parties involved in the assessment of paediatric development programs or protocols (relevant EMEA committees, CHMP working parties, CTFG, ECs, etc.); it is to be noted that an optional community CTA would greatly facilitate this dialogue
- facilitate the development and acceptance of global paediatric development programs (e.g. agreed by both the appropriate EMEA committee and the FDA) including studies with simple designs and careful consideration of the size of the population to be included, the need for invasive tests, a poor acceptance of placebo, etc.
- in the context of the development of paediatric development plans, improve recognition of the challenges of participation in trials for parents/families of paediatric subjects (including the fact that some treatment schedules may be burdensome and time consuming for working parents).

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?

EFPIA response

Some clinical trials may have to be conducted in emergency situations, and such trials raise complex ethical issues because the patients concerned are frequently unable to give informed consent, or their consent capacity is impaired/they have inadequate time to understand all relevant information, and it may be difficult to reach their relatives and/or legal representative within tight timelines (narrow therapeutic window) prior to initiating the procedure/treatment.

While the emergency/critical care community may consider that provision for emergency research situations is necessary, society overall is probably not familiar with the constraints faced by the researchers conducting studies in patients with acute medical conditions.

Therefore it is advisable to promote communication and public discussion of the issues surrounding such research in order to raise public awareness and understanding.

Clearly, individuals, prospective research participants and their relatives should retain the right to refuse to participate in such research (similar to the right to refuse to donate organs), with the possibility to notify their will in registries, or their medical records, for example.

Consideration should be given to the development of a range of measures aimed at maximising patients' rights, and enhancing their protection in emergency situations (these could be cumulative). Examples include:

- consulting/involving the patient/subject community concerned in the proposed research (e.g. prior to initiation of the research, communication of plans for the research, and its risks and expected benefits, to the relevant community)
- opening registries specific to a given research area where individuals could mention whether they would accept or object to participating in the research
- provisions be made so that the patient's consent should be sought as soon as his/her condition is restored
- establishment of an independent data monitoring committee to exercise oversight of the research.

Protocols, informed consent forms, and information in relation to the mechanisms used to maximise patients rights and enhance the protection of the patients involved in the proposed research in emergency situations, should be reviewed systematically by an Ethics Committee which has relevant expertise in the field.

To ensure high quality research and protect research participants' best interests, preference should be given to those centres with proven expertise in emergency research, or accredited to conduct such research by the relevant regulatory bodies.

Consultation item n° 16. Section 7 of the Consultation Paper pertains to compliance with GCPs in clinical trials performed in third countries. The author notes that the percentage of clinical data supporting application for marketing authorisation generated in third countries is increasing, indicates what are the reasons for this trend and outlines the specific challenges this situation raises.
The following questions are raised: **Please comment? Do you have additional information, including quantitative information and data?**

EFPIA response

First, a definition for "third countries" should be offered. If this refers to countries that have a less regulated clinical trial approval and oversight process it would be helpful to specify which missing elements in the Health Authorities oversight requirements would qualify a country to be considered a "third country".

The reasons for conducting clinical trials in third countries are well presented. Although in the public opinion the reasons given for placing clinical trials in third countries are often assumed to be financial (lower costs) companies represented in EFPIA refer to faster access to patients and support of filings for marketing applications in these countries as the primary reason for involving these countries in a clinical program. In fact, many of these countries (e.g. China) require data from local patients as a prerequisite for the filing of a marketing application. Companies have started to involve these countries in their global clinical trial development programs rather than conducting additional local trials. This has allowed to speed up the approval process in these countries and also to save costs.

It is correct that costs for staff personnel involved in a trial are lower than in OECD countries but these savings are often counterbalanced by higher costs for the logistics (e.g. cold chain transportation for investigational medicinal product and bio / laboratory samples). In addition, experience from the expansion of clinical trial programs into countries of the former Eastern block that was observed in the light eighties and early nineties, showed that within a relatively short time period costs per patient grew to finally more or less match cost per patient in OECD countries. We expect the same phenomenon to occur also in the non-OECD countries.

From a quality perspective there is consensus that at least companies represented in EFPIA apply a global quality management system with one set of SOPs. ICH GCP, Declaration of Helsinki and other established internationally established norms (e.g. rules about the reporting of safety data and specifically requirements and timelines for the reporting of SUSARs) are applied and enforced globally. On a study level also a global quality plan is designed and implemented, e.g. same standards for monitoring, QA and auditing.

When third countries are involved in a global trial the risk of poor IEC / IRB control is of lesser concern as properly equipped and constituted IECs / IRBs located in an OECD country are also involved in the trial.

There is awareness that local constraints or peculiarities in the practice of medicine need to be addressed and resolved to ensure not only compliance with the letter of established guidelines and regulations such as ICH GCP E6 but also with their spirit. In this context the following considerations may be of significance:

- access of the population at large to medical treatment,
- literacy of patients,
- cultural peculiarities impacting on the informed consent process (e.g. involvement of the family or community in the decision making of the patient),
- cultural behaviours impacting on the awareness or even willingness of patients to report adverse events to the investigator,
- type and quality of background treatment or
- technical or logistic limitations (e.g. adequacy of laboratory equipment, storage of investigational medicinal product)

When facing such challenges very careful consideration needs to be given to ethical consideration balancing respect of local culture and habits with risks of coercion through the exploitation of patients in need.

EFPIA is not aware of the existence of other reference documents pertaining to ethical matters in relation to the conduct of clinical trials in general and clinical trials in developing countries in particular.

Consultation item N°17: What other options could be considered, taking into account the legal and practical limitations? taking into account the legal and practical limitations?

EFPIA response

Whilst the consultation paper section 7.2 refers to "a continuing risk", it is unclear what the level of this risk is and what assessment and information this is based on. For example, there are third countries in which ICH GCP has become law and/or in which investigators have to achieve local GCP accreditation before they can participate in clinical trials. In addition there are active local inspectorates in place that have an inspection program, oversight or a well-established compliance network.

It should be noted that an article by Johan Kerlberg “US FDA site Inspection Finding, 1997-2008, Fail to Justify Globalization Concerns” provides a detailed analysis of worldwide FDA inspections and comes to the conclusion that Eastern European and Rest of the World countries actually have fewer inspection findings on average than other regions. A copy of this paper is attached.

One of the options for strengthening scrutiny of clinical trial results performed in third countries outlined in the consultation paper section 7.3.6 raises very serious concerns. It proposes to consider the possibility of a clock stop for a GCP inspection during assessment of a CTA when the results of clinical trials performed in third countries are submitted in the dossier of a request for authorisation of a clinical trial. Such a

clock stop would significantly delay the conduct of clinical trials in the EU, introducing a further disincentive to conduct trials in the region. There will be numerous occasions when a company will submit a CTA in the EU that is supported by clinical data, some of which will have been obtained from study centres outside the EU. The huge administrative burden of collating and including in clinical trial applications documentary evidence of GCP compliance of all sites in all applicable countries should not be underestimated. Moreover, it is unacceptable, in the reasonable time scale for obtaining clinical trial authorisation, to allow additional time for the conduct of inspections at 3rd country sites. Therefore, it must be sufficient in a CTA for the Sponsor to confirm compliance with GCP for all studies which by inference covers all sites in all countries.

A paternalistic approach to clinical trials in third countries should be avoided and additional bureaucratic hurdles should not be implemented. Sponsors should describe in the clinical study report what measures were applied to identify ethical and process challenges in conducting the trial in these territories, how patients' rights and well-being have been ensured and, where applicable, what mitigating actions have been implemented when challenges arose and what metrics were used to assess the impact of corrective and preventive actions.

If a trial only involves countries with a lesser regulatory standard and especially when in the countries involved there may be doubts about the competency of the IECs / IRBs involved then sponsors should either always involve a certified IEC / IRB (e.g. belonging to one of the WHO certification schemes such as FERCAP, SIDCER) or an IEC / IRB located in the region of origin which is tasked with the scientific and medical review of the clinical protocol.

To promote the sharing of best practices in resolving ethical and practical challenges encountered when conducting clinical trials in third countries a knowledge sharing platform could be considered.

In addition, partnering with other entities conducting trial in these territories (e.g. WHO TDR) should be promoted.