

**Clinical Trial Directive 2001/20/EC – Public Consultation 2009/2010**

**Comments from EUCROF – EU CRO Federation**

**08 January 2010**

Name of Organisation	Country
<p><b>EUCROF</b> European CRO Federation <b>Secretariat</b> 60, Rue Carnot F-92100 Boulogne-Billancourt</p> <p>Tel: +33 1 46 99 94 54 Email : <a href="mailto:info@eucrof.eu">info@eucrof.eu</a></p> <p>Representative on this matter : <b>Dr. Dagmar Chase</b></p> <p>Tel: +49 89 92 92 870 Mobile: +49 172 85 36 338 Email: <a href="mailto:dagmar.chase@clinrex.com">dagmar.chase@clinrex.com</a></p>	<p><b>CRO Associations of EU Member States:</b></p> <p>Czech Republic France Germany Italy Spain The Netherlands UK</p>

## PREFACE

In this document feedback is given with respect to the “Consultation items” in the Public Consultation paper, issued by the European Commission on 09 October 2009.

Input was sought through EUCROF members representing CROs in different EU Member States. In particular, feedback was given by:

- Germany
- The Netherlands
- Spain
- UK
- Italy
- Belgium (EUCROF applicant)

EUCROF consists of seven local CRO associations at the moment:

• ACRO-CZ	Czech Republic	25 CROs
• ACRON	The Netherlands	33 CROs
• AECIC	Spain	23 CROs
• AFCROS	France	50 CROs
• AICRO	Italy	10 CROs
• BVMA	Germany	26 CROs
• CCRA	United Kingdom	35 CROs
<b>TOTAL</b>		<b>202 CROs (legal entities)</b>

## **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?**

It seems very difficult to measure the impact of the EU CT Dir on improved subject protection and safety. Although acknowledged in a large number of fora at the Commission/EMA conference in October 2007, objective data are difficult to receive.

EUCROF thinks that the suitability assessment of clinical trial sites (qualification of investigators, facilities and site staff) is an example of the EU CT Directive leading to improved protection of trial subjects. However, this might be limited to countries where the local ECs are taking an active role in the assessment and supervision of trial sites and might not be valid for countries where the site qualification is based on a statement granted by the investigator and the sponsor.

The requirement for experts in ECs for paediatric trials or for trials in adults not able to give legal informed consent probably also contributes to higher protection of trial subjects.

Regarding SUSAR reporting within fixed timelines to a centralized data base, it is felt that this would lead to improved subject protection in case of proper functioning of the system. The intention was right, however the implementation of the SUSAR reporting system in the Member States does not allow for real signal detecting because of many reasons (please Consultation Item N°6).

## **CONSULTATION ITEM N°2:**

**Issue: Multiple and divergent assessments of clinical trials:  
Is this an accurate description of the situation? What is your appraisal of the situation?**

Generally, it is felt that the description is correct. In addition to overlaps of responsibilities of the two bodies NCA and EC, there are differences in review criteria even regarding the central scope of the NCAs, the review of the IMPD. The Competent Authority in the Czech Republic, for example, is known for demanding large amounts of stability data, e.g. data for all batches over long time periods, while all other NCAs find much less data to be sufficient. Almost for every international study the list of deficiencies for the IMPD varies considerably between the different NCAs involved. In an estimated 20 % of international studies national amendments of the study protocol have to be implemented as a response to concerns raised by only one or a few NCAs. (In addition, national amendments resulting from diverging Ethics Committee opinions have to be implemented.)

There are reports of studies that were rejected by the German CA, whereas other NCAs approved the submitted study protocol. Even after extensive communication between the sponsor and the German CA (which is generally seen as very positive that this is possible), the CA did not approve the protocol and the study took place without German sites.

It is not easy to understand, why in one EU MS the study is allowed to be conducted, whereas in another EU MS it is rejected, although all EU countries are supposed to follow the same procedures.

In terms of CA versus EC assessment:

EUCROF members experienced each kind of possible outcome in the assessment of study protocols:

- similar comments / recommendations from the EC and CA
- CA raised objections, but the EC did not
- EC raised objections but the CA did not

It seems that the subjective component of the evaluation weights far too much.

In summary: Either patients in the approving country are exposed to a bad protocol or patients in the rejecting country are deprived of good research.

Input: The Netherlands

Very good experience is reported with the approach in The Netherlands, where the Ethics Committees do the actual assessment of the CTA-dossier. A limited number of highly qualified and competent Ethics Committees is under close supervision of the National Competent Authority. This circumvents the problem how to divide the scope of the assessment between EC and NCA.

### **CONSULTATION ITEM N°3:**

**Weaknesses: Multiple and divergent assessments of clinical trials:**

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

As not all National CAs can have sufficient qualified staff (please see footnote 19, page 10) it is easy to understand that there might be different results / recommendations after the review by NCAs. There might also be some time pressure to meet the timelines for responding to the submitted documents.

In general, the description is correct. The time the sponsor needs for the initial application procedures is 4-6 days per "average NCA". This is exclusive preparation of study documents like protocol, IMPD, investigator's brochure, patient information / informed consent form. The time is required for the collection of information regarding the current application procedures, the preparation of documents required for the application only (EudraCT application form, national application forms, authorization

letters, preparation of smaller forms), translation issues, discussion of national peculiarities between sponsors and local CROs, evaluation of deficiency letters, preparation of replies to deficiency letters.

The time is required for every NCA and if the application procedure could be done by one reviewing authority the efforts for application procedures for multinational studies could be reduced considerably. E.g., for an international study in 4 countries the time would be reduced from 20 days to 5 days.

#### **CONSULTATION ITEM N°4:**

##### **Options to address the issue as regards the assessment by NCAs:**

**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?**

##### **Concerning 3.3.1:**

The VHP procedure is attractive for only a selection of studies. The main reason for not choosing the VHP procedure is however:

The VHP does not solve the problem that different NCAs have different requirements for the documents to be included in the application dossier. Even if general approval is obtained via VHP, the applicant will still have to prepare, e.g., the special French application forms or will have to wait for the original of the first signed agreement with a study center, which is demanded by the Polish NCA. If the VHP can not circumvent these national peculiarities, the attractiveness of the VHP is very limited. This issue is recognized even by some NCAs.

Appreciated: Submission to be done electronically, no hard copies to be distributed.

##### **Concerning 3.3.2:**

This option offers opportunities for a considerable improvement of the authorization procedure. It is absolutely appreciated to implement one or both of these procedures.

By the majority of EUCROF members giving input to the consultation paper, it is felt that option (b) is the preferable solution as soon as more than one Member State is involved. On the other hand there are votes to maintain the option of CTA-application per Member State for mono-center studies and small-scale multi-center studies. This option will be more appropriate for early phase clinical trials (Phase I and Phase IIA).

Concerning option (a) the following issues have to be considered:

1. In some EU Member States there is no real assessment of application dossiers by the Competent Authority. The major assessment is done by the central Ethics Committee. This applies to Member States Italy, the Netherlands, Belgium, partly to Austria. If these countries become reference Member States, the evaluation might not be made by the NCA but rather by the central Ethics Committee.
2. The sponsor should have the possibility to influence the choice of the reference Member State. Some NCAs are known for rather arbitrary requirements or non-substantiated demands (e.g., Poland, Spain, Czech Republic). If the respective country becomes a reference Member State the authorization of the study might get at risk.

Option (b) would result in following benefits:

- No differences in application forms and submission procedures (all in English).
- The authorization would be valid throughout the Community and the clinical trial could be rolled out in the entire EU without additional follow-up authorizations of additional Member States concerned. It will be easier to conduct clinical trials in EU Member States, the conduct of a clinical study in the EU will get more attractive for applicants as less administrative work will be required.
- Furthermore, hopefully a reduction in CA fees would be a result of a centralized procedure.

Local legislation would of course need to be adapted, NCA staff could be allocated more efficiently in a centralized procedure and duplication of work could be avoided.

**CONSULTATION ITEM N°5:**

**Assessment by Ethics Committees:**

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

The problems with Ethics Committees can be summarized as follows:

1. In many Member States Article 7 of the Directive 2001/20/EC has not or only partly been implemented. In these Member States, namely Italy, the Netherlands, Spain, there might be a central Ethics Committee which issues formally a single opinion. However, the local Ethics Committees are re-evaluating the study after the single opinion is issued. The sponsor is obliged to

modify study documents according to their opinion and to reply to their deficiency letters.

2. The evaluation criteria vary between the Ethics Committees. There are no common criteria to evaluate a patient information sheet or a study protocol. E.g., a German Ethics Committee questioned the principles of a protocol which followed the EMEA guideline for migraine studies; some Ethics Committees follow the Declaration of Helsinki of 1996 while others prefer the current version.
3. The requirements differ between Ethics Committees. Most Ethics Committees in the EU find a CV to be sufficient to evaluate the qualification of an investigator. In Germany, the Ethics Committees want to see a 5 paged, detailed description of the study center, a financial disclosure form, a certificate of a 1-2 days GCP course, a detailed list of experiences with former studies (listing the indication, phase, time), a statement that the investigator is familiar with the investigator's brochure. In many EU Member States only the leader of the team at a study center is evaluated (principal investigator, for whom extensive qualification documentation is acceptable). In Germany, however, every medically responsible member of the team (sub-investigator) at a center has to be evaluated, based on a set of multiple documents, whilst the evaluation of appropriate qualification of medical staff follows rules that differ considerably between the individual local Ethics Committees and that partly oppose to the declared intention of the national legislative body.
4. It is disadvantageous to leave decisions about clinical studies to committees which have historically been and which still currently see themselves not as a part of the public system but as organs of the medical associations. Therefore they see themselves subject to their own rules and do not sufficiently care about attractiveness of clinical research in the Member State. The participation of these Ethics Committee results in a large diversity of requirements for consideration of a clinical trials, for safety reporting, etc, not only between Member States but also within Member States.
5. The 60 days timeframe should be adhered to. At the moment, the 60 days are very often not met by the implemented EC procedures.

Future regulations should therefore:

1. Establish Ethics Committees, independent from professional organizations and academic institutions, which are responsible for the single opinion within the NCA. This would generate Ethics Committees which are part of the public order and which could be controlled by the legal system of a Member State. This has been realized for the central Ethics Committee in Hungary and Portugal.
2. Strengthening the single opinion by making explicitly clear that local Ethics Committees (if any) are not allowed to question or modify the single opinion and that the sponsor does not have to follow the additional advice of local

committees. A one stop shop at the central Ethics Committee would reduce administrative efforts of the sponsor considerably. Depending on the country each additional Ethics Committee means additional effort of 1 to 3 days. If the central Ethics Committee was the single contact point for Ethics Committee decisions the effort would be reduced by 0,5 to 3 days per additional center in a multicenter trial.

3. Provide clear, inclusive lists of the relevant documents which should be considered by the Ethics Committees. Example: Study protocol, patient information sheet and informed consent form, investigator's brochure, agreement with the investigator and or center, CV of the principal investigator (requiring GCP knowledge), insurance certificate and conditions, all documents used for recruitment of subjects, every document handed out to the subjects. It must be made clear that no additional documents can be requested by an Ethics Committee.
4. Determine in detail evaluation procedures, taking a risk based approach. The evaluation might cover more issues for studies in life threatening indications or in first in man studies. It is appropriate if the Ethics Committee asks - for example - for the access to an emergency unit for a stroke study, but not for a migraine study.

Option 3.4.1: This option bears the danger of slowing down the application procedure to the velocity of the slowest reviewer. In Hungary, where this option is already implemented, the opinion of local Ethics Committees has to be obtained in addition to the central committee, therefore this concept does not really work properly. On the other hand, this option could offer great benefits in case **no** local ECs would need to be involved and the submission could be done electronically (one electronic submission only).

Option 3.4.2: This option is of no immediate help for the sponsor. The administrative burden would not be reduced by strengthening networks of Ethics Committees. In Germany, which has a national network of Ethics Committees, the interaction of the Ethics Committees does not result in implementation of the best practice but in enforcing the procedures proposed by the more powerful committees (i.e. committees of the medical associations as compared to the committees of the universities).

Option 3.4.3: Implementation of this option would be helpful. See also summary above for more details.

It needs to be ensured that ECs are really making an ethical review. At the moment the process is often more on the bureaucratic side. It is too expensive and complex to be efficient. The feeling is that some of the documents included in the submission are not thoroughly reviewed, some seem to be requested just with the purpose of being filed.

EC approval should be granted in parallel to CA.



## **CONSULTATION ITEM N°6:**

### **Issue: Inconsistent implementation of the Clinical Trials Directive: Is this an accurate description of the situation? Can you give other examples**

Concerning 4.1.1:

As long as the sponsor is at risk of being non-compliant with GCP for implementing non-substantial amendments which authorities might consider as substantial, ANY amendment will be submitted to authorities and Ethics Committees for review. Furthermore it is easier for CROs to declare an amendment as substantial rather than being at risk to do things wrong or to take the time for long discussions with the sponsor. Sponsors need more guidance in decision making and need to be encouraged by legislation to actually take the decision. The opposite is the case at the moment.

Concerning 4.1.2:

Pharmacovigilance is the least harmonized issue of clinical trials in the Community. For multinational studies it is very time-consuming for sponsors to collect reliable information about the current requirements for safety reporting. It is also quite a task to set up procedures to comply with all the differing requirements in the Member States.

Examples for lack of harmonization are:

1. In some Member States CIOMS forms are not accepted: National forms have to be used in Spain, France, and Austria.
2. Most of the differences concern reporting the Ethics Committees. E.g. in Spain the destination and language of a SUSAR report depends on the place of origin. If SUSARs occur outside of Spain they should be sent to the central Spanish Ethics Committees in English. If they occur in Spain they also have to be sent to the local Ethics Committee responsible for the center where they occurred and the language of the report should be Spanish.

Future regulations about pharmacovigilance should be detailed, strict and exclusive. It should be regulated that reporting to NCAs and Ethics Committees is done exclusively with CIOMS forms completed in English language. It should be regulated that only the central Ethics Committee which issued the single opinion is informed, and none of the other committees involved.

Ethics committees may be informed about SUSARs only by periodic line listings. It should be enforced in all Member States that line listings are to be sent to ECs rather than individual SUSAR reports. Many Ethics Committees do not have the capacity to evaluate these reports anyway. They just file them. The central institution for the evaluation of SUSAR reports should be the NCA (or EMEA), which has the expertise and personnel to accomplish this task. Ethics committees should however be informed about issues altering the benefit risk balance.

The demand to inform the investigators should also be limited to line listings. Most investigators do in fact not review individual SUSAR reports anyway. In large trials the information of all the investigators becomes a time-consuming issue without improving patient safety. If a SUSAR report does not provide any new information about the safety profile of the study medication it is of no value for the investigator. Since investigators have to be kept blinded, they can never be sure about the relevance of a SUSAR report. If the study involves administration of an authorized drug, the investigators might become flooded by reports originating from the marketing experience. This is particularly true for oncology studies. Due to all these reasons it should no longer be required to inform all investigators about individual SUSARs. Investigators should only be informed about issues which alter the benefit risk balance in an expedited way and should receive line listings otherwise in periods which are determined risk based.

Reporting to EudraVigilance is not easy. In most cases the setup of the connection to EudraVigilance is much more time-consuming than faxing SUSARs. Therefore, if countries accept SUSAR reporting by fax, electronic reporting is not the best option for a sponsor.

It is not acceptable to allow access to EudraVigilance only to people who have passed the official EudraVigilance course or who work in a company where a colleague has passed the course. In the many instances where it was tried to get a connection to EudraVigilance there were technical problems on the site of EudraVigilance (in 50% of the cases). Many times the "Send" button was not activated, ICSRs could therefore not be sent and the EudraVigilance helpdesk people were of little to no help. EudraVigilance helpdesk people often blame the sponsor if something does not work, trying to make the individual feel as he/she is the only one who has this specific problem (while information is available that it is a common issue). Solutions to problems are not made public for other users. The FAQ-list turns out to be not very helpful (were the listed questions asked in reality or are they theoretical questions?). While some NCAs still allow reporting by fax this fact is denied by the EudraVigilance website. All these issues are indicators for room for improvement.

Concerning 4.1.3:

There should be a simple, concise procedure which enables the sponsor to get clear advice by a Competent Authority whether a study is regarded as interventional or observational. This assessment should be valid for the whole Community, otherwise nothing is gained. At the moment there is no formal consultation procedure whose results are legally binding. Since the authorities' assessment of a study as non-observational has considerable legal impact for the sponsor, there should be a reliable assessment procedure. This procedure should involve the submission of the observational plan (and no more additional document except for a cover letter) to a Competent Authority (e.g. model of reference Member State or centralized procedure), the evaluation within an acceptable time period (e.g. 14 days) and the issue of a legally binding assessment, which lists detailed reasons in case the study is regarded as non-observational.

Additional comment:

Very few rules for clinical studies with medicinal products have been harmonized with the help of the Clinical Trials Directive 2001/20/EC. In many Member States the implementation of the Directive has been taken as an opportunity to change legislation according to national motivations. In many Member States the requirements of the Directive 2001/20/EC were sort of added to the national procedures.

Please find examples in the comments to consultation item n°8.

#### **CONSULTATION ITEM N°7:**

**Weaknesses: Inconsistent implementation of the Clinical Trials Directive:**

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

##### Insufficient patient protection

No comment.

##### Increase of administrative costs:

The description is correct. Before the implementation of the Clinical Trials Directive the application at the NCA was not necessary in many Member States. By implementation of the Directive these administrative costs have been added to the basic costs required to start a clinical study.

The time the sponsor needs for the initial application procedures averages at 4-6 days per NCA. This is exclusive the preparation of study documents like protocol, IMPD, investigator's brochure, patient information / informed consent form. The time is required for the collection of information about the current application procedures, the preparation of documents required for the application only (EudraCT application form, national application forms, authorization letters, preparation of smaller documents), translation issues, discussion of national peculiarities between sponsors and local CROs, evaluation of deficiency letters preparation of replies to deficiency letters.

In addition to the administrative costs caused by the application procedure at the NCA, the administrative efforts for the assessment procedures by the Ethics Committees have also been increased by the implementation of the Clinical Trials Directive. The overall procedure was somewhat simplified by the implementation of the single opinion in some Member States. In quite a few Member States this one opinion has not been fully realized (e.g., in the Netherlands, in Italy, in Spain). However, the implementation of the Clinical Trials Directive has been taken as an opportunity to increase the demands of the Ethics Committees concerning the initial consideration procedures and the amendment approval procedures and notification requirements during the study. This might be partly explained by the increased responsibility of the committees.

In Germany the administrative costs concerning Ethics Committee approval have more than doubled after implementation of the Clinical Trials Directive. This is due to the increase of documents required to prove qualification of centers and investigators. Before 2004 the CV was sufficient to illustrate qualification. In 2009, each principal investigator **and** each sub-investigator (as they are all investigators in Germany) has to provide a list of studies in which he/she has participated (with title,

duration, phase), a certificate of a GCP course (with unclear criteria which courses are accepted), a commercial disclosure form, a confirmation that the investigator's brochure has been read.

In addition, if a sponsor prefers to conduct the study under the same protocol in all Member States concerned, all comments / recommendations of all participating ECs / CAs have to be collected and summarized in one amendment. This does not only mean that the administrative costs have gone up, this also means a delay in study start which ultimately results in loss of revenues (for commercial sponsors).

#### **CONSULTATION ITEM N°8:**

##### **Options to address the issue: Inconsistent implementation of the Clinical Trials Directive:**

**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?**

##### **Option 4.3.1:**

Regarding SUSAR reporting, please see also Consultation Item N°6.

The major problem with Pharmacovigilance in clinical trials is – from the sponsor's point of view, the diversity of requirements, mainly of the Ethics Committees. This problem could be solved by implementing a rule that there will be no more expedited reporting to Ethics Committees. Safety reporting can be done by line listings, which should be uniformly defined (e.g. by defining that only serious adverse reactions should be reported).

The follow up and assessment of ASRs is not a major problem from the sponsor's site.

The procedure for notifying substantial amendments should be made more clear and enforced to be followed by everybody in the same way. As mentioned under Consultation Item N°6, more detailed guidance should be provided as to what is regarded and – also important – what is not regarded as a substantial amendment. A very exhaustive list of examples is necessary to provide sponsors with a sound basis for decision making.

In addition, in case of doubt, an implicit advice procedure as to what is regarded as substantial or non-substantial might be a solution. The outcome should be binding in the whole Community in order to overcome the problem of diversity.

##### **Option 4.3.2:**

It would be highly appreciated by EUCROF to transform the Clinical Trials Directive into a Regulation, since the Clinical Trials Directive 2001/20/EC did not succeed in uniform procedures for clinical trials in the EU. Divergent applications are actually a consequence of transposing the Directive into national laws.

Some examples of failed harmonisation are:

1. Article 2 of 2001/20/EC: In Germany the clinical trial Directive's definition of the investigator is not correctly implemented into national law. In Germany any medical doctor involved in a clinical trial at a study center is regarded as an investigator (and not as sub-investigator). This forces the sponsor to document the qualification of a lot of persons to the Ethics Committees in great detail. Any change of a "sub-investigator" is a substantial amendment, as it is considered as a change of an investigator. The administrative burden for large hospital trial centers is enormous.
  
2. Article 6 of 2001/20/EC: The assessment procedure at the Ethics Committees is as divergent as ever. Many Member States have their own application forms (usually a big one and several smaller ones for different purposes), sometimes these forms vary even between intra-national Ethics Committees. The EudraCT application form is not used very often. The Ethics Committee maintain different requirements for documents to prove the qualification of a center. The only uniform issue in the EU is that you have to submit a protocol, a patient information sheet / informed consent form, a protocol synopsis, insurance documents, an investigator's brochure, the investigator agreement. These items have been part of Ethics Committee dossiers long before the implementation of the Clinical Trials Directive, which has done nothing for harmonization in this field. (cf. thesis of Ralf Rickert (2009): A Review of the Availability of Information on Ethics Committee Requirements for Clinical Trials in the EU: "The findings of the examinations described in this master thesis clearly confirm that one of the main objectives of the Clinical Trials Directive, namely to harmonise the procedures for ethical review of clinical trials and to reduce the administrative burden, has still not been achieved. Furthermore, it has become obvious that even though a considerable amount of information on the EC application requirements are available in English in a number of European countries, it is currently not possible for foreign applicants to fully undertake the EC applications in most of them. In fact, nowadays the only way to complete the ethical review process successfully is to go back to consultancies/CROs with specific knowledge about the conditions in the desired countries.").
  
3. Article 7 of 2001/20/EC: There is no actual single vote in Italy, the Netherlands, Spain, and probably other Member States.
  
4. Article 8 of 2001/20/EC: The guidelines are not respected by many Member States. National legislation and opinions of authorities and Ethics Committees are not overruled by these guidelines. The guidelines reflect a degree of harmonization which is just not existent (cf. thesis of Ralf Rickert (2009): A Review of the Availability of Information on Ethics Committee Requirements for Clinical Trials in the EU: "Furthermore, a country-by-country comparison

of the application requirements obtained from the website survey [of Ethics Committee websites] against those specified in the corresponding country tabulation of the European detailed guidance on EC procedures (ENTR/CT2) was carried out. This yielded a number of deviations and therefore the validity and reliability of the country tabulation in the detailed guidance is called into question.”).

5. Article 9 of 2001/20/EC: The major parts of the application dossier to be sent to the NCAs are structurally harmonized, but it is the additional items which make the life of the applicant difficult. In Germany, in addition to items like the EudraCT application form, the IMPD, the protocol etc., additional documents like a declaration about data protection, a declaration of the sponsor's representative, a statement about gender distribution, a statement about the identity of electronic and paper documents have to be submitted. Only little things, but harmonization was meant to be something different. On the other side of the river Rhine, in France, the counterpart of the German additional small things are some more extensive forms like the “Courrier de demande d'autorisation d'essai clinique”, a form called “Répertoire public des essais cliniques autorisés – Informations sur l'essai” which asks for pieces of information to be published in the French clinical trial data base, a form about the collection of tissue samples. In Portugal, application dossiers are regarded as invalid if files are not called with exactly the names specified in the NCAs guideline document. In Hungary, the application dossier has to be accompanied by a sample of the study medication. In Italy, the NCA is degraded to an online study data base, where the protocol outline has to be entered. The entries are then printed and used as application form. The problem is, that access to the database is only granted after shipment of some paperwork and often there are “technical problems” which cause much delay for the following application process, for which the database printout is a prerequisite. The Polish NCA expects at least one signed investigator agreement and a proof of establishment of the CRO in the EU. The Romanian NCA is requiring to receive a set of contractual documents as originals (something which is also known from Poland). The United Kingdom and the Czech Republic are two of the few Member States whose NCAs ask only for the core study documents.

In addition to Ethics Committees and authorities other institutions are involved in clinical trial conduct in many Member States. The sponsor might not have to get approvals from these institutions, in most cases they have only to be notified, but this notification involves considerable administrative costs, both by collecting information about notification duties and by conducting the notification. It has to be mentioned that in Germany the “Bundesamt für Strahlenschutz” has to give approval as soon as radiation is involved for trial reasons – this can take up to 9 months and is totally unacceptable. Furthermore, in Germany, all organisations involved in a study and all investigators have to be notified to the local federal state authorities; the local authorities have even to be notified about the date of approvals of amendments; any new investigator (in Germany this is every new medical doctor involved in a study) has to be notified to the local authority; for multi-

center studies the administrative costs for these notifications equal or exceed those of the application procedures! In France the CNOM has to be notified about contracts with investigators and the CNIL about data transfers. In Spain some reviewing boards of the autonomous regions have to be notified.

6. Article 11 of 2001/20/EC: The EudraCT data base is not used by some Member States. Italy and the Netherlands have set up national databases which the sponsor has to consider in spite of or in addition to the EudraCT data base. It is not clear if the information sent to the Spanish and Romanian NCAs ever gets to EudraCT.
7. Article 13 of 2001/20/EC: Movement of IMPs in the EU is relatively free, but it is not always without obstacles. In Finland the IMPs can not be shipped from other EU Member States directly to the sites, but only via a warehouse. In Austria, the import of medication from EU Member States has to be notified to the NCA with a two page form to be sent every 6 months. In France, the medication to be shipped into the country from other EU Member States has to be accompanied by a notification form stamped by the NCA.
8. Article 14 of 2001/20/EC: Labelling requirements are perhaps the most harmonized issue of the whole Directive, due to the beneficial Annex 13, but even here many details differ between Member States. In Germany, the EudraCT number has to be printed on the label and the sponsor has to be named together with the CRO (Annex 13 allows either sponsor or the CRO to be named). Belgium, France, Finland demand the name of the investigator to be printed on the label, which is optional in other Member States. Italy sometimes asks even for the investigator's address (cf. thesis of Astrid Weyermann (2006): Labelling requirements for investigational medicinal products in multinational studies: bureaucratic cost driver or added value?" It is concluded that especially the divergent national implementation of the EU-requirements may be regarded as a bureaucratic burden. This may result in increased costs especially in multinational clinical trials without providing additional benefit for subjects and safe conduct of the CT [clinical trial].").
9. Article 15 of 2001/20/EC: One major problem with inspections is not the difference between EU Member States but between inspectors and NCAs/ECs in the same Member State. There should be a rule that inspectors must not rate something as a finding of the sponsor which has been reviewed and approved by either the NCA or Ethics Committee. E.g. in Austria it was an inspection finding that the study site was divided in two parts, while this had been made known to and had been approved by the Ethics Committee. In Germany protocols, patient information sheets / informed consent forms, IMP labels were reviewed and criticised by an inspector, although these texts have already undergone intensive review during the application procedure. It is extremely confusing for sponsors that different departments (assessing department and inspectorates) within the same authority or different

authorities in the same country (local federal state authority versus state authority) evaluate things differently and the sponsor is confronted with GCP non-compliance although has done everything according to applicable rules and regulations.

10. Articles 16 and 17 of 2001/20/EC: While in many Member States the central Ethics Committee is informed about any SUSAR which occurred in studies with the same IMP, in some states the Ethics Committees are only informed about local SUSARs. An extreme example is Spain, where the destination and language of a SUSAR reports depends on the place of origin. If SUSARs occur outside of Spain they should be sent to the central Spanish Ethics Committees in English. If they occur in Spain they also have to be sent to the local Ethics Committee responsible for the center where they occurred and the language of the report should be Spanish.

11. Article 19 of 2001/20/EC: Requirements for the legal representative vary between Member States. While in Germany the authorities expect that the sponsor's representative has oversight of all of the operations of the real sponsor, in the United Kingdom the sponsor's representative acts rather like the sponsor's agent, and authorities demand little insight in the sponsor activities of the legal representative.

The transformation of the Directive into a Regulation would only be successful if the following is considered:

- Any national add-ons must be prohibited. The Regulation should clearly define in detail, for example, the kind of documents and information to be provided to get an approval for a clinical trial and the Regulation should state that additional documents and information must not be required in any Member State by neither an NCA nor any Ethics Committee nor any other organisation, institution, reviewing board, authority.

- In many EU Member States there are other organisations, institutions, reviewing boards or authorities involved in the conduct of clinical trials. The Regulation should state that the only entities involved in the approval, evaluation or notification requirements for clinical studies are the Competent Authority and the Ethics Committee(s). If a Member State wants to maintain functions of other institutions, these institutions should be addressed by the Competent Authority and the Ethics Committee(s), but not by the applicant. Otherwise the ultimate goal to making the EU more attractive for clinical research will remain at risk.

Finally, it has to be mentioned that one CRO from the Netherlands strongly voted for a revision of the Directive and not changing the system to a Regulation, however, the majority of CROs providing input voted for a Regulation.

## **CONSULTATION ITEM N°9:**



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

A risk based approach mainly with respect to adaptation of administrative burdens would be very welcome. The European Science Foundation Report on Investigator Driven Clinical Trials (IDCT) has come up with a proposal of risk categories of clinical trials which could be followed. It is, however, of utmost importance that a risk base solution is not limited to non-commercial trial but applies to all clinical trials.

**CONSULTATION ITEM N°10:**

**Single sponsor: Do you agree with this description? Can you give other examples?**

The description is correct. The issue is relevant for non-commercial trials mainly. However, it should be possible to agree on one principal sponsor by contract. In addition, this contract between "sponsors" should list the responsibilities of each individual sponsor. This contract could be reviewed by EC/CA if needed. The Q&A document version 4 (July 2009) issued by the European Commission addresses this issue quite well.

**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?**

Modification of guidelines is of little use as it does not provide a means of enforcement of their contents. If not in accordance with their own opinion or interests, authorities and Ethics Committees in the Member States do not care about guidelines. A lot of what is written in current detailed guidance documents is simply ignored by NCAs and/or ECs in Member States (examples: handling of substantial amendments, SUSAR reporting).

**CONSULTATION ITEM N°12:**

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

As mentioned before, most EUCROF representatives vote for a Regulation. The Regulation has the chance (as long as national add-ons are prohibited) that all

Member States need to adhere and could not add their own, often contradictory, addenda.

Consultation no. 8 list a number of fields where urgent action is required.

### **CONSULTATION ITEM N°13:**

#### **Exclusion of academic trials from the scope of the Clinical Trials Directive: Would you agree to this option and if so what would be the impact?**

EUCROF votes for academic sponsors following the same rules as industry sponsors. If it is indicated that lighter rules can be applied to academic trials and heavier rules to industry trials, just because “industry can afford them”, it means that rules are an artifact to maintain a system.

Removing academic studies from the scope of the Directive or future Regulation could lead to a “back door” approach as seen previously, with inefficient monitoring, etc., thus bearing potential risk for trial subjects.

Also, it is not acceptable - because unethical – to exclude academic trials totally from being included in marketing authorization applications. This would necessitate repetition of clinical trials, which is per se controversy to ICH-GCP.

### **CONSULTATION ITEM N°14:**

#### **Adaptation to peculiarities in trial participants and trial design: 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?**

The current legislation on clinical research for paediatric medicines imposes a high burden on companies. The requirement to compile a paediatric investigational plan after the end of phase I studies,

- which describes the planned clinical studies and formulations for all age groups of the paediatric population,
- which has to be approved in time-consuming procedures and
- for which any changes have to be approved in a time-consuming procedures,

makes it very unattractive to develop medicinal products in the European Union which could be useful for children. For a pharmaceutical company it will economically better to invest in drugs with no use for children. For the small and innovate companies the development of a drug that might be useful for a paediatric population might not be possible, especially if the population of children with this indication is small. It might be more profitable for a venture capital company to invest in a pharmaceutical company which develops a drug with a class waiver, since for this drug no formulations have to be developed for children before it even has been shown that the drug is effective and safe. No approval procedures have to be undergone for the probably often changing PIP covering all future studies, in parallel

to the approval procedures for the clinical studies themselves. In the light of the costs of these procedures, the incentives might not be so attractive.

While EUCROF explicitly welcomes the ultimate goal of having better medicines for children, doubts have to be raised whether the current legislation will succeed in reaching it.

#### **CONSULTATION ITEM N°15:**

##### **Adaptation to peculiarities in trial participants and trial design:**

**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?**

Emergency trials should be addressed in the Clinical Trials Directive (or future Regulation) following the standards of the Declaration of Helsinki of 2008 and the Bioethics Convention of the Council of Europe.

#### **CONSULTATION ITEM N°16:**

##### **Ensuring compliance in third countries:**

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

Specific diseases (e.g. HIV, bilharziosis, malaria) need to be investigated in those countries, in which they mainly occur – to facilitate the patient recruitment and to bring benefit especially to those patients. A precondition must be that these patients will have access to the study medication, finally registered (e.g. medication not too expensive, will be registered in the respective countries ...).

#### **CONSULTATION ITEM N°17:**

##### **Ensuring compliance in third countries:**

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

All study results should be published, a summary of report within a specific fixed time frame (e.g. within 1 year, as required in Europe) should be mandatory.

A public list of non-compliant sponsors/sites/individuals should be made possible (like the FDA debarment list for sponsors who do not follow the GCP standards).

Populations in third countries should be considered as special populations and specialists should be involved in the ethical review to ensure the ethical soundness and pertinence of the trial.

Strengthened scrutiny should only be acceptable if it does not lead to prolonged scrutiny. We are already in the EU behind other countries in the speed to implement trials: further bureaucracy would only worsen this position.

**CONSULTATION ITEM N°18:**

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

Clarity of regulation is the key. Currently the individual Member States are inconsistent with almost every aspect of what the Clinical Trials Directive originally was intended for.

Generally, it is felt that the number of inspection should be increased, especially in third countries.

SME – like academic sponsors - should follow same procedures as large companies: Procedures should be created to protect patient rights in clinical research, to provide safe and efficient drugs to the market, not considering who is paying the research (SME, big pharma, academic, investigators).