

Association of Clinical Research Organizations Comments in Response to the European Commission Public Consultation on the Assessment of the Functioning of the “Clinical Trials Directive” 2001/20/EC January 8, 2010

I. Introduction

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-man studies through postapproval and pharmacovigilance research. Last year, ACRO member companies conducted more than 9,000 clinical trials involving nearly 2 million participants in 115 countries. With more than 66,000 employees engaged in research activities around the world, of which over 23,000 are located in the European Union/European Economic Area (EEA), ACRO advances clinical outsourcing to improve the quality, safety, and efficiency of biomedical research.

The European Commission's 09/10/2009 Public Consultation on the Assessment of the Functioning of the “Clinical Trials Directive” provides a welcome opportunity to assess the effectiveness of the Clinical Trials Directive (2001/20/EC) and to propose options with the goal of improving the functioning of the Directive while minimizing unintended negative consequences that may hinder the advancement of medical science. ACRO's member companies have greatly invested in the clinical development infrastructure in the EU and are committed to assisting the Commission with the development of improvements that support the vital continuance of research in the region. With this in mind, we are pleased to submit comments on the above-referenced topic during the public consultation.

II. General Comments

It is recognised that the implementation of the EU CT Directive has resulted in benefits in some areas; however, there are other aspects which work less well given the different interpretation and implementation in national legislation within Member States. Given that it is indeed a Directive, it has been transposed differently between Member States which creates insufficient harmonisation in many areas, e.g.:

- document requirements needed for an application to the regulatory authority and the ethics committee
- validation and review timelines
- classification of studies including non interventional studies
- differentiation of ‘standard’ documents between countries e.g. insurance, delegation letters, Informed consents
- classification and management of substantial and non substantial amendments

This means that very detailed regulatory intelligence, together with practical experience of the implementation in each respective country is required for definitive national authority information which is not readily available. This is very labour intensive and necessitates the need for Companies ideally having dedicated regulatory groups focussing on the management of clinical trials within the EU.

III. Boxed “Consultation Item” Comments

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?

ACRO is not aware of any studies/data showing the benefits of the Directive.

Consultation item n°2: Is this an accurate description of the situation? What is your appraisal of the situation?

The text in section 3.1 summarises the situation accurately. ACRO agrees that the different application of the regulatory framework by Member States does not, in the majority of cases, lead to divergent decisions on clinical trial applications. However, prior to reaching a final decision, the questions raised by the national competent authorities on an identical scientific dossier are frequently very different in both number and nature and indicate a significantly divergent approach to dossier assessment. For example, some countries like France, Germany and the Netherlands request much more detailed viral safety information for biologics than other countries and focus the review of CMC data on these aspects. In Hungary you need hospital budgets agreed before you submit, while the UK and Belgium require very little. Some countries like Germany have additional national requirements (gender distribution statement etc.), which appear to relate primarily to advancing broader governmental policies than to the actual application review.

Some NCAs request to review Informed Consent Forms, which may lead to comments in addition to those usually received from the ECs. Furthermore, there is no alignment on what constitutes a substantial amendment (e.g. with regard to shelf-life extensions). There is also considerable diversity whether any changes may be submitted during the initial CTA review process. This national diversity makes the approval process of a multi-national trial logistically challenging and can have a high impact on timelines.

We understand that this view is supported by initial experience in the pilot phase of the Voluntary Harmonisation Procedure, which has led to a recent revision of the procedure in an attempt to reduce the number of questions raised following the individual evaluations of the different competent authorities involved. We agree that the process is further complicated by the lack of definition of the scopes of the respective assessments of competent authorities and ethics committees. This is especially the case in relation to the assessment of first in human clinical trials and other healthy volunteer studies. Prior to the implementation of the Clinical Trial Directive (when regulatory agencies in several countries did not assess applications for these trials), ethics committees assessing these types of trials frequently included specialist toxicological or other pre-clinical expertise in order to provide the committee with assurance that the sponsor's proposals would pose an acceptable level of risk for the participating human subjects. This practice has continued and, in many cases, duplicates the scientific evaluation and assessment of risk posed by the trial that is now carried out by the competent authority.

Consultation item n°3: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

The paper highlights many of the weaknesses of the CT Directive, such as the administrative costs, the absence of the best review being provided in each MS due to lack of expertise, and the need to await approval in all CAs before finalising a common protocol and inefficient use of MS resources, yet this is not an entirely accurate reflection of the

situation. The costs of submitting substantial amendments compared to amendments and/or notifications that were required prior to the current legislation varies amongst MS. Overall, the costs have increased, but this is primarily for patient safety reasons. Prior to the implementation of the CT Directive a number of NCAs didn't review the applications thoroughly.

The use of a harmonised system for substantial amendments should streamline the core submission preparation. However, as there is not a harmonised agreement of what constitutes a substantial amendment and since some MS also require certain non-substantial amendments to be submitted, such a streamline process has not been fully optimised.

In general, companies do not await approval in all CAs. Any request to change a protocol that cannot be addressed on a MS-specific basis (such as change in primary end point) is likely to result in a MS being dropped from a programme. In this way it is possible to commence a study as soon as it is approved in a given MS. Failure to do so would have had a significant impact on start up times and therefore time to market, which has not been seen in practice.

The examples of possible MS outcomes are not comprehensive. Any possible combination of the following variable is possible:

- Initial request valid/not valid
- Clock stopped/clock not stopped (MS-specific)
- Grounds for non-acceptance provided/no issues
- Clock stopped/clock not stopped (MS-specific)
- Responses required/ not required
- Responses include/do not include protocol amendment
- Approval/rejection

In general, ACRO does not have concerns about the quality of the review in any specific MS.

Consultation item n°4: 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 paper proposes several options:

Voluntary harmonisation: The current approach is only available for selected study types and to be more useful should be extended to all study types. While in theory it should offer advantages of a harmonised review, however it is limited in the following ways:

- Review time is up to 60 days (for a core review) plus a further 20 days (for national approval): For many MS this extends the review period: In addition, to an additional 20 days beyond the statutory 60 days, many MS aim to (and achieve) approval within 30 days (if no questions are asked), like Austria, Belgium, UK. This does not make the VHP particularly appealing. At this time, this seems to be more an educational effort in order to achieve harmonisation across EU NCAs than a genuine benefit for sponsors.
- The procedure does not allow for additional MS to be added after the review has been completed: This is impractical since many studies, particularly in certain indications, often require the inclusion of further MS to facilitate timely recruitment.

- Many of the issues of concern in CTAs are those that are outside the scope of the core review (such as local consent forms) moreover the time available for their resolution is compressed into 20 days. These are the types of issues that are often addressed by both MS and ECs and, as such, can lead to contradictory requests e.g. changes to ICFs
- It has some pitfalls (national applications with diverging documentation requirements still required after VHP step; overall process longer than national assessment in some countries like Austria, Belgium, the UK) which do not make it particularly appealing. At this time, this seems to be more an educational effort in order to achieve harmonisation across EU NCAs than a genuine benefit for sponsors.
- If protocol design changes too radically for Germany they may not accept as a substantial amendment but require a new CTA with a different EudraCT number.
- The “reference member state” model (option 2) might be more appealing than option 1 if timelines were competitive as compared to national approval timelines. However, a lot of work would need to be invested upfront into the harmonisation of the understanding of the EU Clinical Trials Directive and national documentation requirements. It also needs to be explored if all agencies truly have the capacity to function as “reference member state”, given the fact that the smaller countries have only a very limited staff number working on CTA review.

A procedure similar to that of the mutual recognition/decentralised approach for MAAs, with a RMS and decision making procedure:

- This could be acceptable if all of the issues described for the voluntary procedure are satisfactorily addressed, in particular the decision making procedure would need to extend to decisions made by new MS introduced to the study after the initial approval. Timelines need to be competitive with national approval timelines.
- The process for the “arbitrage” needs to be outlined, in particular the impact that this will have on overall timelines and whether or not there will be a standard basis for rejecting applications, across MS.
- It should be clarified if a role similar to that of the Reference Member State would be established and, if so, whether this MS would continue to act in this capacity if the product is ultimately the subject of a centralised marketing authorisation.
- The role of Norwegian and Icelandic regulatory authorities should be clarified. It is recommended that they also participate in the process.
- A lot of work would need to be invested upfront into the harmonisation of the understanding of the EU Clinical Trials Directive and national documentation requirements. It also needs to be explored if all agencies truly have the capacity to function as “reference member state”, given the fact that the smaller countries have only a very limited staff number working on CTA review.

A procedure similar to that of the centralised procedure for MAAs, managed by the EMEA and with Commission decision making:

- As above, this could be acceptable if all of the issues described for the voluntary procedure are satisfactorily addressed, in particular the Commission decision making procedure would need to be relatively quick, compared to that applicable for MAAs.

- It should be clarified how the resources of many agencies would be adversely impacted by the need to contribute to a CTA review for which is not being conducted in a given MS. The paper states that about 20,000 out of 30,000 trials are conducted in one or more sites in one MS (see Table 2). Although this does not equate to the same percentage of total CTAs (given that multinational studies account for 60% of all CTAs), it does imply that 2 out of 3 studies only impact one MS. An alternative centralised approach could be considered, that involves only those MS where the study is to be conducted. A mutual recognition process for additional MS added to the study after the initial approval would be required.
- While a process for “arbitrage” is proposed for the procedure above, it should be clarified whether a similar process would be available in this centralised approach.
- It should be clarified if a role similar to that of the (co-) rapporteur would be established and, if so, whether this MS would continue to act in this capacity if the product is ultimately the subject of a centralised marketing authorisation.
- The role of Norwegian and Icelandic regulatory authorities should be clarified. It is recommended that they also participate in the process.
- It is stated that this procedure would result in a continuum between the clinical trial process and the marketing authorisation process. It should be noted that currently this type of continuity does not always occur within individual MS between the stages of scientific advice and CTA submission. As such, it should be clarified how this can occur between the stages of CTA submission and MAA submission. Thus, there is no guarantee that agreement on trial related issues obtained during national scientific advice, will continue to be valid at the time of submission of the CTA. This can occur where MS assessors for scientific advice and for CTAs are not the same.

The paper suggests different options for the scope for streamlining the CTA review process:

- All CTAs: This would be appropriate for a mutual recognition type of procedure.
- Only for CTAs that are the subject of a multinational trial: For a mutual recognition type of procedure, limiting this type of procedure to only multinational trials will have no impact on the number of applications reviewed by a given MS. By definition, the procedure only involves MS if the study is being conducted in their own country. Table 2 of the report indicates that multinational trials account for about 60% of all CTAs. For centralised procedure involving all MS, reducing the scope to multinational studies only would only cut the amount of reviews by about half. A multinational study with only 2 countries would still be subject to evaluation by all MS.
- Only for IMPs with certain characteristics: The experience of sponsors is that MS divergences in outcome may be more common for products with novel characteristics, however less novel products can also be the subject of divergent decisions.

It is also important that the development of a medicinal product in the EU must not be hindered due to a centralized review process. The review needs to be flexible, so that the primary objective, that patients get access to effective and safe medicines is still met. The intent of the Paediatric Legislation to promote the development of Paediatric Medicines was positive. However due to the strict assessment a significant number of companies have stopped their development due to the high development costs associated with the PIP.

ACRO's preferred option would be, for trials involving more than one Member State, a process whereby a single dossier (in respect of scientific and administrative content) is subject to a single evaluation, leading to a single clinical trial authorisation valid throughout the Community. We recognise that this would remove competency from the individual Member States and would require replacement of the Directive by a Regulation, but, given that the Member States have a long history of divergence in implementing Directives in the pharmaceutical field, believe that this is the only sure way to establish a recognisable Community standard for clinical trial approval and (more generally) regulation. Additionally, this option would link EMEA existing groups and guidelines (e.g. Clinical Trial Facilitation Group, GMP/GCP Inspectors group, CHMP Working Parties). There would be a single set of requirements across all Member States and the MSs would not be entitled to request additional documents for national use. National requirements (that do not add to the patient's protection and quality of the trial) would only apply to national Clinical Trial Applications, unless the National Competent Authorities chooses to remove them. This community approval system would need to be managed and coordinated centrally, and given the existing structure of the EMEA, this should be considered. It would also be prudent that the new system would not be limited to any particular category of product or therapeutic area. Ideally the Clinical Trial Application should be electronic, linking in with the existing EudraCT system.

Consultation item n°5: 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 paper proposes different options for EC review:

- One stop shop: This is intended to reduce the administrative burden only with national EC reviews being conducted. It is not clear what aspects of the submission would be reviewed and whether it would be a mutual recognition or centralised approach. It is not clear how this review can be undertaken in one place, since many administrative issues are subject to national requirements e.g. insurance. Since each country has implemented quite varied processes for review, this would require considerable harmonisation.
- Strengthening national networks: This provides for an optional adoption on an opinion. While this appears to be a significant step forward as it provides the opportunity for ECs in different countries to discuss and attempt to resolve issues, it may well become a forum without any concrete decision making. One key issue relates to timing: Would a single opinion, including "opt-outs" be given at a specified time? Sponsors need to know whether the study can proceed, or not, in each country. What appeal mechanism, if any, will be instituted regarding such opt-outs?

A recurring issue ECs have traditionally addressed relates to the capacity to conduct the study within the country (or at the site); sufficient clinical resource to ensure non-participants are not disadvantaged, and sufficient patients to execute the study competently. How will these be protected under this option?

Additionally, a single system capable of handling 16 applications per working day (2008 data presented) would require immense infrastructure and could potentially create a decentralised system. If so, then would the EC and RMS approvals be from the same country? Would sponsors have any influence over the choice of country for EC review?

- Clarifying the role of the EC and CA: It is agreed that there should be no overlap of responsibilities of each body. An overlap with regards to documents like Informed Consent Forms or investigator contracts seems unnecessary and leads to overlapping and sometimes conflicting comments. While review of the same document may be undertaken by both, it should be for different purposes.
- Other recommendations: ACRO recommendeds that all ECs use the EudraCT form in applications.

ACRO recognises that ethical issues should remain within the ambit of the individual Member States and therefore our preferred option is for legal clarity to be provided on the respective scope of assessment by the responsible ethics committee in each Member State and the body responsible for the single competent authority review that will provide the authorisation that is valid throughout the Community. Again, this could be achieved by means of a Regulation that could further reduce the complexity of the current situation by requiring a single ethics committee in each Member State to take direct ownership of the ethics committee evaluation rather than (as in some Member States currently) acting as a coordinating committee for multiple evaluations of the same clinical trial by different committees.

Consultation item n°6: Is this an accurate description of the situation? Can you give other examples?

The text in section 4.1 accurately describes the situation and the most important examples. An additional example would be the divergence of administrative documentation requirements in the application for clinical trial authorisation that currently exists between Member States.

Substantial amendments: It is agreed that MS inconsistently interpret the term “substantial”. Indeed, certain MS have created an additional category of amendment where documents must be submitted “for information” (this does not relate to notifying the agency of a substantial amendment that affects the EC but not the CA). One of the criteria for establishing whether or not an amendment is substantial is whether or not it impacts the conduct of the study. The Directive also effectively allows sponsors to define which amendments are substantial. Should CROs be submitting “for information” at all? Agencies tell CROs they appreciate transparency, but sometimes “for information” requests get converted to 35 day procedures by default. Additionally, we believe that:

- Greater harmony is required on the simpler notification style submissions (eg, investigator updates and other minor changes) - so that implementation strategies can be applied more universally in CT programmes.
- Greater consistency is required in the interpretation over what is substantial (e.g. France not interested in receiving shelf-life extensions; Spain interested in receiving shelf-life updates and Belgium is not).
- Conversion from notification to substantial amendment requiring approval has been experienced with the MHRA.

Non-interventional studies: The paper states that there are divergent interpretations of the term “non-interventional”, especially with respect to “no additional diagnostic or monitoring procedure and use of epidemiological methods”. In fact, it is our experience that CAs disagree on whether or not blood tests are acceptable, despite this being clearly permitted in Volume 9A of Eudralex. It is not our experience that CAs differ on whether or not analytical methods are epidemiological in nature. It is not clear how further refinement of the wording in Volume 9A will clarify it however it is recommended that the detailed definition of “non-interventional” be included in the revised legislation. This will reduce the likelihood of inconsistent interpretation. Note: a consistent categorisation amongst CAs is required for follow-on safety studies with products that do not have a marketing authorisation i.e. interventional or not.

The paper refers to the introduction of new legislation submitted in December 2008. However, this directive only covers review procedures for protocols, amendments, the role of the Pharmacovigilance Risk Assessment Advisory Committee and the final study report. It does not address the definition of “non-interventional” and, if this is what is intended, it is not considered an appropriate place to address this. Moreover the new legislation only covers post-authorisation safety studies, not all non-interventional studies.

Consultation item n°7: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

The text in section 4.2 accurately describes the situation and the most important examples. ACRO agrees that inconsistent reporting of SUSARs leads to an increased risks of undetected factors influencing the risk-benefit balance. We also agree that divergences in applications result in an increase in administrative costs for sponsors due to the need to customize applications more than is appropriate.

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?

The paper proposes the following solutions:

- Revising the Clinical Trials directive with respect to SUSAR reporting, follow up on annual safety reports by ECs, notifying CAs of a substantial amendment submitted only to ECs (and vice versa) and CA substantial amendment review times. Other changes could also be made at the same time e.g. better define “non-interventional trial”, define “non-investigational medicinal product”. However, this does not address concerns that arise out of the divergent implementation of the EU guidance on CTA submissions, some of which might be addressed in revised legislation, possibly with annexes.
- Replacing the Clinical Trials directive with a regulation: It is questionable that a Regulation would be an adequate means to rule out different interpretations and processes at a national level, as it would have to be extremely detailed and it might still not be able to address all eventualities. A large part of this national diversity does actually arise from transposition into national law (different CTA approval processes, documentation requirements etc. In some cases, like the IMP labelling requirements in Germany, there have actually been mistakes during the transposition of EU requirements into national law.). However, to a certain degree, diversity arises from ad-hoc decisions made by NCAs as not all types of amendments which might occur in the context of a clinical trial clearly fit into pre-defined categories.

ACRO's preferred option would be to repeal the Clinical Trials Directive and readopt its content (with appropriate revisions) in the form of a Regulation. The divergent application of the Directive's requirements stem from both application on a case-by-case basis and as a consequence of how the requirements were transposed into national law. In the experience of our member companies, it is the latter that accounts for many of the divergences we encounter. A Regulation would indeed provide greater consistency and certainty, so start-up times would be more predictable. The needs for clarity and alacrity are just as important.

Consultation item n°9: Can you give examples for an insufficient risk-differentiation? How should this be addressed?

ACRO has no additional examples to add, but fully supports the concept of applying a risk-based approach to the application of common standards.

Consultation item n°10: Do you agree with this description? Can you give other examples?

ACRO agrees that a more flexible approach regarding the definition of sponsor could be helpful in some instances; however, any revised definition should clearly state where liability for the study lies. There continues to be uncertainty over the role and responsibilities of the legal representative of a sponsor that is not established in the Community. We would recommend changes to make clear in law that the sponsor of a clinical trial (even when the sponsor is established outside the EU) retains the overall legal responsibility and liability for all aspects of the trial.

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?

ACRO does not believe that a revision of guidelines alone is sufficient to address the problem satisfactorily. In many cases, the problems arise from the way in which the Directive's requirements were transposed into national laws. Revision of Community guidelines to a point that they become inconsistent with national laws will simply add to complexity and confusion.

The guideline on IMP labelling and CTA contents should be revised to align national requirements, and the guideline on CA submissions in its current format does not adequately reflect national diversity as it does not even list all additional national requirements (like local application forms, additional memos, etc.).

Further, the proposal seems to imply that different standards might be applicable for commercial and non-commercial sponsors, because data from the latter are not necessarily included in clinical trials. It is critical that common standards are applied, regardless of the nature of the sponsor. The purpose of the legislation is to protect trial subjects and generate good quality data. The extent of protection required is independent of the intended purpose of the data. Subjects are entitled to the same level of protection regardless of how the resulting data will be used. Similarly, subjects agreeing to participate in a trial have the right to expect that the quality of data generated through it will be of the same high quality, regardless of how that data will be used. It should also be noted that the final use of data is not dependant on the whether or not the sponsor is commercial. Large numbers of interventional clinical trials are conducted with marketed products, where the sponsor is commercial. If different standards are to be applied, this should not be dependant on the nature of the sponsor.

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 previously mentioned, many of the problems associated with the Directive's implementation stem from how its requirements were transposed into national law. ACRO does not believe that revision of the Clinical Trial Directive will overcome this issue satisfactorily but, rather, we support the replacement of the Directive with a Regulation that will be binding on the Member States.

Additionally, ACRO recommends an amendment to the section on psychiatric patients. The text of the directive mentions that "In the case of other persons incapable of giving their consent, such as persons with dementia, psychiatric patients, etc., inclusion in clinical trials in such cases should be on an even more restrictive basis. Medicinal products for trial may be administered to all such individuals only when there are grounds for assuming that the direct benefit to the patient outweighs the risks." Moreover, in such cases the written consent of the patient's legal representative, given in cooperation with the treating doctor, is necessary before participation in any such clinical trial. In some EU countries, this paragraph was transposed into the local legislation in a sense that the ICF should be signed by a legal representative for all psychiatric patients. No difference is made between types of

psychiatric disorders. Considering that not all psychiatric patients have a legal representative (patients with certain types of disorders, or certain stages of disorders), as they can decide for themselves, an adaptation of this paragraph would be needed.

Consultation item n°13: Would you agree to this option and if so what would be the impact?

ACRO does not agree that "academic" sponsors should be excluded from the rules established for clinical trials in the Community. We believe that all clinical trials (with the exception of non-interventional studies) should be regulated in the same way and in accordance with common standards to ensure the quality of clinical trials and to safeguard trial subjects. We also believe that the way forward is to have a risk-based approach to the implementation of those standards. This would necessitate a common understanding (by all stakeholders in the regulatory process) of the risks associated with clinical trials and their implications for implementation of the common standards. We refer to the EMEA guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical trials with Investigational Medicinal Products (EMEA/CHMP/SWP/28367/07) as a good example of a risk-based approach to the implementation of common standards. There are a certain percentage of academic clinical trials (10-20 %) which are conducted in more than one country, and their conduct would possibly be negatively affected if (probably diverging) national legislation would apply.

If "academic" sponsored clinical trials were to be excluded from the scope of the Directive, patients, academic investigators, sponsors and CAs would need to be assured that the differential applied to "academic" studies did not result in commercial disadvantage to "commercial" studies, or to a covert selection bias. Further, transition arrangements would need to be specified as ACRO member companies have seen a number of recent examples of MAAs being approved based on trials which began life as "academic" studies.

Consultation item n°14: In terms of clinical trials regulation, what options could be considered in order to promote clinical research for safeguarding the safety of the clinical trial participants?

This is an extremely controversial area. Regarding clinical research for paediatric medicines, existing legislation in most countries differs relating to requirements for consent and assent, and the requirement to respect the decision, especially the refusal, of a minor to treatment. Even within the UK, the legislation in Scotland differs from that in England & Wales. Clinical trials legislation will need to be framed very carefully indeed to assure that patients' rights are not lessened as a result of participation in trials.

Additionally, ACRO would welcome a Guideline on how to consent patients into paediatric or emergency trials which is available in all MS.

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?

ACRO agrees that the subject of emergency clinical trials should be addressed in future legislation. The definitions surrounding legal capacity to consent are enshrined in civil and criminal law, and vary substantially amongst countries. The Directive addresses the principles for trials for incapacitated adults, but no such text exists for emergency situations. In some instances, the emergency may be associated with incapacitation, such as being unconscious; however, there are other circumstances where the emergency does not result in such incapacitation (although this might depend on the definition of incapacitation). Similarly, incapacitation can be associated with non-emergency situations such as that associated with mental incapacitation; therefore, separate legislation should be

included to address this. Consideration might be given to defining emergency, incapacitation and legal representative in the CT Directive. However, the latter two terms may already be defined in MS legislation and may be challenging to revise. Similarly, each MS currently manages the consenting of unconscious adults differently (possibly in legislation) which may also be challenging to amend. For example, the UK legislation defines a hierarchy of persons who should be consulted in the consent for a minor or incapacitated adult in an emergency, when the responsible parent/legal representative is not available. The need also to obtain parent/legal representative consent when possible is also addressed.

In our experience, the most appropriate mechanism to reconcile patient's rights and the peculiarities of emergency trials is one where there has been prior approval from an ethics committee so that, if prior informed consent is not possible, a patient may be entered into the trial in an emergency situation prior to provision of informed consent on condition that consent from the patient or their legal representative is obtained as soon as is practical after entry. Additional safeguards can be added to enable the ethics committee to apply specific conditions to the use of such an approach.

Consultation item n°16: Please comment? Do you have additional information, including quantitative information and data?

Pharma companies utilise third countries for clinical trials for a number of reasons, such as the need to accelerate recruitment of patients, the required number of which is increasing. The data are also used in marketing applications for those third countries, where locally generated data is required. There are a wide range of benefits from such studies:

- Large populations
- Treatment naive patients
- Ethnic diversity
- Wide range of indications
- Good recruitment and retention
- Regulatory framework
- GCP, ethics and protocol compliance
- Qualified and experienced site staff
- Fewer competing trials
- Established infrastructure
- Strong investigator-patient relationships
- Often good standards of medical care
- High quality data

The legislation in third countries is developing and evolving thus, for example, Latin American countries are already revising their CT legislation and the Middle East is currently drafting theirs. In addition, India requires CROs to be registered (something that is required currently in the EU only in Italy) as well as fingerprinting of volunteers. Countries are implementing appropriate parts of ICH, under the umbrella of the Global Co-operation Group in ICH, which recently began to include a number of regulatory authorities in its discussion. ICH GCP E6 has been implemented in, for example, Latin America and Asia from the 1990s to early 2000s, with GCP compliant ECs in operation. Arguably some third countries apply more controls than EU/EEA countries, with respect to requirements of the Declaration of Helsinki, 2000, that were not adopted by the EU/EEA (or the USA). Thus, in Brazil, use of placebo may be justified only if there is no alternative treatment, although (as in India) supply of post study drug is usually mandatory for indications such as HIV and oncology. Moreover, while EU/EEA countries permit first in man studies, Indian (currently) and China do not, unless the sponsor is a domestic one. In addition to ICH E6 GCP requirements, companies implement local requirements. Thus, in addition to requesting patient informed consent, informed consent

of a village chief, such as in Africa and certain parts of India, or of a female patient's husband, such as in Saudi Arabia, is also requested.

In light of the dramatic increases in clinical trials conducted in emerging markets over the past decade and the concern expressed by some regarding their quality ACRO commissioned a report by VOI Consulting, Inc. to address these issues. On July 21, 2009 ACRO released this report, entitled "*The Case for Globalization: Ethical and Business Considerations in Clinical Research*" (Executive Summary attached as Appendix A). The report has several key findings:

- **Global trials speed drug development** – The report concludes that globalized trials can reduce development time by half while lowering costs and maintaining quality and safety. For example, phase III cancer trials are conducted three times as fast if both U.S. and global sites are used, compared to U.S.-only sites. What takes 5.8 years to enroll takes 1.9 years when a global trial is implemented.
- **Research quality standards must be met worldwide** – The report found that trials in emerging countries, such as China and India, are subject to the same standards as those conducted in the Western Europe and the U.S. CROs train research staff around the world in good clinical practice (GCP) principles and proof of compliance is required by drug regulators in every major pharmaceutical market.
- **Clinical research improves local economies** – Clinical research offers advantages for host countries, including an influx of advanced equipment, trained personnel and high-paying jobs. The presence of CROs also results in improvements in local health systems. Clinical trial sponsors in Poland, for example, fund 30 percent of hospital cancer therapy.
- **Emerging market equals growth market** – CRO activity in Central European countries, South Korea and Taiwan is very robust, medical infrastructures are advanced and capabilities are just about on par with Western Europe.

ACRO encourages the Commission to review the full report which can be accessed at www.acrohealth.org/globalization. As a stakeholder in the clinical trials process, the global CRO industry is committed to assisting the Commission in the harmonisation of clinical trial conduct through the application of good clinical practice. Global CROs apply these principles uniformly, helping to ensure compliance with good clinical practice in clinical trials performed in third countries.

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

Broadly speaking, we support the concept of ensuring that all participants in clinical research – no matter where they live or the environment in which research takes place – be protected by the same level of safety and ethical considerations, and that they be afforded the same standard of care, including adherence to the GCP principles promulgated by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Further, all clinical trials conducted outside the EU, which are submitted to support authorisations in the EU, should be conducted scientifically and ethically in accordance with EU principles and standards. From the strict regulatory point of view of ensuring compliance with EU standards for trials that provide data that is used in EU applications, we would again favour a risk-based approach to enforcement based on the contribution of the data to the EU dossier. Where these data make a significant contribution to the dossier's pivotal clinical trials on which EU regulatory decisions will be based, we agree that legally required additional information about the trials would allow for better

control and enforcement. However, such detailed information may not be needed in the case of non-pivotal trials, except where the non-EU data make a significant contribution to the evaluation of the safety of the product concerned. In the overall context of the use of non-EU data to support EU applications, control and enforcement of standards is not the only regulatory issue and we would suggest that measures are also needed to ensure that clinical data gained in populations outside the EU are relevant to the EU population.

Regarding the options presented in the paper, Section 7.3.4, "Optional assessment of 3rd country clinical trials by the EMEA," seems to be the most robust approach, and would do much to allay criticism from the US and the FDA. Section 7.3.6, "Strengthening scrutiny of clinical trials results of which are submitted to the EU, or which are financed in the EU," proposes a "clock stop" which seems sensible, yet will it correspond to an increased patent duration, or will it simply erode the patent life further, thereby partially defeating the intent of such trials?

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?

To ensure better regulation principles are taken into account, ACRO emphasises the need to establish a single regulatory framework for clinical trials that is administratively simple and applies a risk-based approach to the implementation of common standards throughout the Community to ensure the quality of trials and the well-being of trial subjects.

Additionally, the paper does not address responsibilities of the ECs and CAs to patients enrolled into trials. Both have clearly defined responsibilities regarding approvals, but few relating to conduct, and to communication to patients when conduct has been inappropriate, e.g., the recruitment of ineligible subjects into trials, especially those who may have gone on to experience serious adverse reactions. Another example may arise in "academic" studies, in which insurance provisions may not be evidenced so strongly, and Information Sheets and Informed Consent documents may be more reflective of the normal clinical standards of information provision, rather than "trial" standards.

Further, the paper's definition of "subject" in clinical trials is not precise. In some countries subjects are defined as those who signed ICF, however in others they are defined as those who are randomized. This inconsistency has implications when study insurance is established and enrolment per country is defined during CTA preparation.

Finally, ACRO suggests the addition of a definition of protocol deviation and protocol violation with direction what and in which case it shall be reported to EC/CA. Currently there is no clear understanding of direction and each EC has its own requirements or preferences.

III. Conclusion

ACRO is grateful for this opportunity to provide comments in response to the Commission's Consultation, and we welcome further dialogue on these critical issues. Please feel free to contact ACRO at any time for additional input.

Appendix A:

The Case for Globalization: Ethical and Business Considerations in Clinical Research

July 21, 2009



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Executive Summary

As clinical trials have become increasingly globalized over the past ten to fifteen years, the possibility of conducting studies that offer adequate subject protection and yield reliable results in emerging countries has understandably attracted considerable attention. In this analysis, we examine the facts regarding the current state of clinical research and the role that biopharmaceutical companies and their clinical research organization (CRO) partners play in ensuring that the dual goals of trial safety and quality are met.

Although concerns have been raised about the globalization of biomedical research, the reality is that emerging countries play a vital role in the advancement of medical science. Clinical trials in these countries, particularly those with industry sponsorship, are conducted at the high standards necessary to obtain regulatory approval in major markets. In addition, the investments made by trial sponsors, which are frequently implemented by CROs, are a major contributor to improving the health systems and economies of the developing world.

Among the key findings of this report:

- Increased demand for clinical trial subjects combined with lower participation rates in developed countries has the potential to dramatically slow the progress of medical science. Indeed, VOI Consulting estimates that it would require approximately 5.8 years to fully enroll all currently open Phase III cancer trials if only U.S. locations were used as compared to 1.9 years using both U.S. and global trial sites.
- While trials in emerging countries have received an enormous amount of attention in recent years, the vast majority of clinical research continues to be conducted in countries with well-established infrastructures. A few statistics point out just how big a role the U.S., Western Europe and other developed regions continue to play:
 - Member companies of the Pharmaceutical Research and Manufacturers of America (PhRMA) spent approximately 96% of clinical phase dollars in developed countries during 2007.
 - In its September 2008 report on CROs, Frost & Sullivan estimates that North America has a 49% share of global R&D spending while Western Europe had a 37% share. The share for Asia Pacific, a region that includes established markets such as Japan and Australia as well as

well emerging centers such like India and China, is approximately 13.5% and the rest of the world has only 0.5%.

- Seventy-six percent of all Phase I studies take place in just three countries, the U.S., Canada and the Netherlands.
- Analysis of data from ClinicalTrials.gov shows that 51.8% of all newly registered industry-sponsored trials in 2008 had at least some U.S. activity; the exact same share as in 2006. This compares with India's 2.7% participation rate, China's 1.8%, Russia's 3.3% and Mexico's 2.4%.
- Trials in emerging countries are subject to the same standards that prevail in the developed world. This is especially true of industry-sponsored trials as these are ultimately aimed at gaining regulatory approval for new products. To engage in unethical or poor quality research is to run the risk that the product will be rejected and the sponsor left with no way to recoup their R&D investments. The power of the market to correct improper practices is shown by a 2009 incident in which a U.S.-based commercial Institutional Review Board was forced to close due to client losses just one week after receiving an FDA warning letter.
- Regulatory and cultural norms regarding clinical research in emerging countries are often more, rather than less, strict than in developed regions. Examples of this include the difficulty of conducting early phase studies in India and placebo-based studies in Latin America. Patients in these countries may also seek greater input from friends and family before deciding to enroll in a trial.
- Clinical research plays an important role in improving the health systems and economies of emerging countries. In Poland, for example, 30% of hospital cancer therapy is funded by clinical trial sponsors.
- The term "emerging market" disguises a wide range of experience levels. After 15 years of experience with clinical trials, capabilities of the larger Central European countries are considered to be very nearly on a par with those in Western Europe. Other countries, such as South Korea and Taiwan, have advanced medical infrastructures and should be considered "emerging" only in the sense that their trial activity is growing rapidly.
- Working with CROs offers a number of advantages for sponsors involved in emerging country trials. In addition to the benefits of reduced costs and faster time to market, CROs provide standardization of operating procedures (SOPs) and, at the same time, are more likely to have a deeper understanding of local language, culture and norms, qualities which lead to better relations with investigators and improved trial execution.

- The presence of CROs benefits host countries as well. They provide advanced equipment and trained personnel, offer high paying jobs in areas where employment opportunities are scarce and have been instrumental in harmonizing research norms in emerging countries with developed world standards.

Although legitimate concerns have been raised in the past about clinical trials in emerging countries, the ability to conduct high quality studies in these locations has been enormously improved over the previous ten to fifteen years. Rather than placing further barriers to drug development, efforts should be focused on enhancing the progress that has already been made while continuing to train and monitor researchers throughout the world to ensure their compliance with the highest standards. As this report demonstrates, much of this is already being done as part of the normal business practices of biopharmaceutical companies and CROs, all of whom have a major stake in a strong and improving clinical research environment.

To view the full report, please go to www.acrohealth.org/globalization.