ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC

Position Statement

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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 [CTD]?

As mentioned in this report, "there is a range of internationally-agreed documents setting out universally applicable principles for the protection of clinical trial participants, independently of where the clinical trial has been performed […] Thus, there is no shortage of agreement on the general principles" (p. 29). In addition, there are fundamental rules found in the national legislation that contribute to the protection of human participants (i.e. Constitution, Civil Code, Criminal Code, regulation of healthcare professionals' education and practice, etc.). In principle, the CTD did not introduce substantial changes to the regulatory framework for the protection of human participants in Europe.

Thus, the improvement has not been as much in the identification of principles, but rather in their implementation. One first important change is that the CTD has increased the awareness of key actors as to their specific role and responsibilities as regards the protection of human participants. Members States that had not yet developed a specific legislation/regulation for biomedical research involving human participants made some concrete efforts to implement the CTD, adopting the necessary regulatory framework, designating the Competent Authorities (CA), supporting existing Research Ethics Committees (REC) or creating them when needed. Such efforts were also encouraged by the Oviedo Convention, especially in the Eastern and Baltic countries. It is in fact difficult to clearly differentiate the influence of both documents on the situation in various countries. A second important element is that academic-researchers could no longer by-pass their responsibilities in conducting research with humans. As mentioned in the ICREL report, "there was no mechanism of enforcement for compliance to ICH-GCP in non-commercial trials" (p. 20). The CTD helped to clarify the situation and academics could no longer pretend that they were not bound to follow the same rules as the research industry in protecting human participants when conducting clinical trials. A third important element is that due to the CTD there have been increased resources allocated to the protection of human participants. This allowed for instance more professionals to be trained in

research ethics and regulation, not only within the research community, whether industry or non-profit driven, but also within the CA and REC communities.

A last element that should be highlighted is that since there were no reports that documented the situation during the years preceding the CTD, it is difficult to assess whether the protection of human participants was not properly guaranteed. This is not true in other parts of the world, such as in the US where a number of independent bodies have critically assessed the human participants protection regime. Such reporting is an achievement in and of itself that should not be underestimated with the industrialization and commercialization of clinical trial.

This being said it is hard to attribute to the CTD the role of having concretely improved the protection of human participants in Europe. At least, it is hard to point out specific examples where the CTD would have played a protective role. If it did, there should be fewer abuses but such decrease of abuses are difficult to quantify.

A real concern is that as the CTD generated, or is perceived to have generated, an increase in administrative burden for investigators, sponsors, CA and RECs. There are many voices asking for simplified procedures. This shortcoming does not mean that the fundamental principles of research ethics and regulation be abandoned or forgotten for the sake of improving the attractiveness of the European research area. It should be pointed out that, on some aspects, the Oviedo Convention provides higher protection to human participants, for instance concerning research with children. Members States should keep the right to adhere to provision that provided greater protection, even if this may distort the research industry. It is important to remember that the main purpose of the regulation of research involving human participants is the protection of the participants, not the promotion of research, although these need not be in opposition.

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

The CTD raised critics right from its drafting. The fact that it allows multiple and divergent opinions/decisions from the various CA and REC is certainly one of the most important ones. Yet, this is directly linked to the nature of the directive. As an EU directive, it requires Members States to adopt the necessary provisions for its implementation, giving them relative freedom in choosing the procedures to follow, in designating the CA and the REC. This national freedom also extends to issues of liability, informed consent, legal capacity, etc (see Dominique Sprumont and Gytis Andrulionis, The importance of the National Laws in the Implementation of the European Legislation of Biomedical Research, European Journal of Health Law 11 (2005), pp. 245-267). There is a clear misunderstanding to what extend the CTD could actually harmonized the regulation of clinical trials within the EU members states.

Another problem is that the scope of the CTD is rather limited if compared to the full range of health or biomedical research involving human participants, without mentioning behavioural research and other types of research (for ex., neuromarketing). The CTD only covers clinical trials with therapeutic products. This involves no more than half of all biomedical research including epidemiological studies, research in psychotherapy or some research with human biological materials. It is therefore unavoidable that divergences occur between the various coexisting regulations applicable to biomedical research.

Another key problem is that since the CTD is limited to therapeutic products, the national drug agencies play an important role in its implementation. This creates a problem in the sense that clinical trials are mainly run by physicians who do not normally fall under the

authority of the national drug agencies. In most countries, physicians are regulated by professional bodies that are completely independent from the drug agencies. This is problematic as in case of abuses the drug agencies are not fully prepared to sanction the physician-investigator. Such issue is not only true for the EU, but has also been raised recently in the US (United States Government Accountability Office, Oversight of Clinical Investigators: Action Needed to Improve Timeliness and Enhance Scope of FDA's Debarment and Disqualification Processes for Medical Product Investigators, GAO-09-807, September 2009).

In any case, it would be important to analyze in greater detail in which specific cases the CA and RECs reached divergent opinions. This is especially relevant in multicenter studies. If divergences are linked, for instance, to the competency of the investigator, this may be a domain where local or national authorities have better knowledge of the situation. A physician may have all the necessary training but has been recently deprived of his or her license to practice for severe breach of patients' rights or professional duties. How should a research centre be assessed to ensure it offers all the necessary safety guarantees for the participants? What type of liability insurance contract is acceptable according to the national law? Each of these examples justifies a different opinion from one CA to the other due to local contexts. Unless the CTD is modified so as to impose the same liability for all CT in Europe, opening the road for a long awaited single European liability regulation, it seems difficult to avoid divergences.

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

Not being directly active in the CT assessment procedure in the EU, we can not evaluate the figures provided. Yet, looking at the ICREL report, it would be important to compare results with those from other parts of the world, especially the US and Japan. It would also be interesting to analyze more in detail to what extent the CT per se are not more complex today in their design and implementation than they were in 2003. Other factors may also play a role in this perceived increased time frame for launching a trial. An important element to take into consideration is the delays due to sponsors and investigators themselves after they have obtained all the necessary clearance. Previous studies in Switzerland and in the US have shown that the research industry is responsible for a serious portion of the delays.

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?

If stronger cooperation between the NCA is certainly an important objective, the way to reach it may have very different consequences. The present situation is perceived as involving a heavy administrative burden for everyone. This presents a risk as the main actors, from the investigators to the REC members and the CA, may loose touch with the principles at stake in the protection of human participants and get bogged down by process viewed as rubberstamping with long meaningless checklists to be followed by junior members of the office. There is also a risk of professionalizing ethics in a way that the main actors may not feel concerned anymore by their own responsibilities in the protection of human subjects as another EU administrative body will be in charge of taking all the important decisions. A single community decision seems rather questionable in that sense. It also raises serious legal

issues as the scope of the CTD is limited compared to all biomedical research involving human subjects (see above).

A voluntary approach should be favoured as it takes into consideration the resources and willingness of all stakeholders, mainly the CA and REC. Those who are most organized can offer their support to the others and contribute in their capacity building. The process should involve everyone concerned in the assessment process. If only part of the members of the CA and REC, as well as the sponsors and investigators understand the need for applying the principles in a way that protects human participants, guarantees the quality of the research, and, ultimately promotes the European research era, the protection of human participants involved in research conducted by less motivated researchers and sponsors, reviewed by CA and REC that are less competent would be weaker. All necessary resources should be made available to prevent such discrimination in Europe. It requires improving the level of training, competency and experiences at every level, not concentrating them in the hand of a limited circle of experts.

The second option of formalizing the process by designating a lead CA is interesting if it does not require more technocracy/bureaucracy. There has been experience at the national level with such procedures (i.e. Spain or New Zealand). The implementation took a long time before becoming efficient. Yet, it could be a next step when the voluntary approach will have proved useful. One administrative problem when moving directly to such formalized coordination is to take into consideration the great disparity among CA and REC in the EU. The manpower and resources vary greatly from one country to another. It may become difficult for smaller administrations to cope with the complex procedure that is being proposed.

Concerning the last option of a single body to act as the CA in the EU, we have mentioned above the main issues it raises. At this stage, it would be contrary to the objective of the CTD in protecting human participants to introduce it. Even more, care must me taken not to presume that centralization reduces bureaucracy. Experience shows in others fields that the transfer of power does not necessarily reduce paperwork.

In any case, it is of great importance to study in greater detail the various strategies encouraging Members States to become more involved in the process. Some form of assessment should remain at the national level but some mechanisms to improve exchange of information and experiences are needed. This should be done more at the procedural level while maintaining the responsibilities of the CA and REC.

For the scope of the proposed streamlining, it seems prudent to be rather restrictive. At least, the system should not become compulsory until a real involvement of all stakeholders is guaranteed.

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?

It has been suggested that if all REC would have proper training and resources, they would reach the same conclusions thus avoiding the present situation characterized by discrepancies between REC assessments of multicenter studies. The same could be said about the judicial system that generates in each country various answers to similar questions. Yet if the variability in the REC decision process may in part be influenced by a difference of training and resources, it should be underlined that such variability is also linked to the very nature of the ethical, legal and scientific debate. Perfectly valid but differing opinions can coexisted on

major ethical, legal and scientific issues. One could refer for instance to the Council of Europe Court of Human Rights decision on the status of the embryo to underline the difficulty to reach an agreement in a multicultural, multilingual and multireligious community such as Europe (see the case Vo v. France, 8 July 2004, *Application no. 53924/00*). To avoid all divergences among REC seems therefore a wrong objective and gladly this is not what is suggested by the consultation paper.

The various options are certainly interesting and complementary. To be clear, we should analyze them based on the principle that they would apply only at the national level (see comments above on a single competent body as CA at the EU level).

The idea of a one stop-shop for submitting a proposal has been applied for several years in Switzerland where forms have been developed to facilitate the submission to the various authorities depending on the nature of the trial (see http://www.swissmedic.ch/org/00064/00067/00330/00849/index.html?lang=en). This is a cost effective process that is rather simple to set up when the CA and the REC work closely together. The EU could most likely offer support, for instance through templates and technical support to the national authorities. This should be done in parallel with the third option of clarifying the role of the CA and the REC. Such process is indispensible and requires a dialogue between them. This implies that the CA respects the work of the REC and the opposite.

Historically, the RECs have usually been active before the national drug agencies started overseeing clinical trials. Their responsibilities and authority go usually beyond the scope of therapeutic product clinical trials. Even if this is not true everywhere (see the case of France where the Loi Huriet was not built on the existing network of RECs but created a new system of control and surveillance of biomedical research), it has some importance in the way CA and RECs are working together. In most countries, RECs have strong links with the university hospitals and the medical faculties. They enjoy a strong independence from the authorities, either the Ministries of Health or the Ministries of Sciences and Education. In fact, it proved sometimes difficult for the RECs to realize that their role has changed with the adoption of specific regulation and legislation at the national and European level. This brings us to the proposal on the strengthening networks of national Ethics Committees involved in multinational clinical trials.

In some countries, this type of network not only exists, but is recognized as representative by the RECs themselves. This is not true everywhere. Several factors may explain this difference, among them their historical development. The RECs sometimes lack the incentive to collaborate more closely. This is due in part to their jurisdiction as defined by the law and the regulation. When the scope of responsibilities of a REC is limited geographically, a REC may be reluctant to accept another REC opinion as binding if this is not specifically authorized by the law. The CTD has certainly improved the situation on that aspect by introducing the single-opinion procedure for multicenter trials. Yet, this also had the consequence of encouraging some form of “forum-shopping”, the research industry selecting the most efficient REC (meaning sometimes the fastest or the less demanding) to submit their multicenter trial in a given country. This may not have a positive impact on the protection of human participants. In any case, REC networks should be better supported.

Those networks should be offered the necessary resources to realize their objectives of federating the REC, facilitating the exchanges of information and experiences, running training programs for their members, liaising with the CA as representative of the RECs. In parallel to these networks or directly linked to them, there should be an administrative body that supervises them, developing common standards and doing the necessary surveillance to

maintain the quality of their activities. So far, some CA and national authorities have not shown great interest in achieving this oversight function. There is a great disparity from one country to another. This may explain in part the difficulty to launch a network of the RECs at the European level as illustrated by EUREC's slow progress. Thus the problem does not lie at the level of the RECs themselves, but at the level of national authorities that need to better recognize and encourage the REC networks.

The third option of clarifying the respective scope of assessment of NCA and RECs is of great importance and should be done in parallel with the implementation of a single-shop for submitting proposals. For example, the Swiss drug agency and the Swiss RECs Association have developed a checklist defining the role of both the CA and RECs in assessing proposals. Again, this requires a dialogue that is much needed and that could also contribute to the capacity building of RECs networks at the national and European level.

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

Example 1: Substantial amendments

The issue of the substantial amendments is mainly a problem of interpretation not only by the CA but also by the sponsor. As mentioned in the consultation paper, sponsors tend to announce more amendments than necessary. It is likely that this problem will be partially solved over time when the practice of the CA will be better developed. Of course, stronger guidance on what amendments should be considered substantial and also better training of the sponsor and CA collaborators could help improve the situation. As for other issues, it would also be interesting to know the evolution in other parts of the world that may experience the same kind of problem.

Example 2: Reporting of SUSARs

For the SUSAR, the problem is not completely the same. It is important to remember that their announcement plays an important role in assessing the risks for human participants involved in clinical trials. The concerns should not be the number of SUSARs to be announced but the capacity to properly use this information for the sake of the participants. The potential for harmonization of the NCA practice in this field is high to avoid multiple and over reporting. In that sense, RECs should not receive directly this information as they do not usually have the capacity to assess those data and take the necessary measures.

Example 3: Scope of the Clinical Trials Directive

We have raised before the issue of the CTD scope. It is not limited to the distinction between interventional and non-interventional clinical trials. The fact that a study is non-interventional does not mean that it does not present ethical, legal or scientific dilemmas. In some countries, the legislation is not limited to drug trials but cover all biomedical research involving human participants, including epidemiological studies that usually can be considered as non-interventional. It would mean a weakening of the protection of the human participants not to acknowledge the legitimacy of those legislations. Thus, even if the CTD is clarified on that issue of non-interventional studies it should not prevent Members States from maintaining control on those studies based on a broader and valid understanding of the protection of human participants.

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

As mentioned above, we agree that the present situation with the SUSARs is not satisfactory. More efforts should be made to ensure that relevant information is processed properly for the best interest of the participants.

For the increased administrative cost for academic/non commercial clinical trials, this should be interpreted as a clear improvement in the protection of human participants. Before the CTD, this research was not necessarily done according to the required standards and therefore put human participants at risks. The change introduced by the CTD was not anticipated by academics thus creating a momentary crisis. As they have now caught up with the international standards, it is likely that the administrative workload is going to be stabilized. It should be underlined that important efforts have been done by research foundations to fill the gap, especially national science foundations. The creation of Clinical Trials Units in university hospitals is an example of these efforts. It starts to pay back as there are signs that the number of academic/non commercial clinical trials could be increasing in Europe, a situation recently experienced despite prevailing fears to the contrary (see Paolo Bruzzi, Non-drug industry funded research, BMJ 2008; 336:1-2). It should also be mentioned that the pressure on academics is not limited to Europe (see for instance, Infectious Diseases Society of America, Grinding to a Halt: The Effects of the Increasing Regulatory Burden on Research and Quality Improvement Efforts, Clinical Infectious Diseases 2009; 49:328–35). Again, it seems important to keep a broader view on the situation.

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 review of the CTD to clarify some of its aspects such as the reporting of SUSARs or the notification of substantial amendments is likely to improve the situation. Yet it may be questionable that such measures would indeed need a revision of the CTD as these are mostly issues of implementation. We agree with the suggestion that the present divergent applications are rather the consequences of the concrete application of the CTD in a case-by-case basis than of its transposition in national laws.

The adoption of the CTD as a regulation would be catastrophic as it would impose the pharmaceutical model as the single option for regulating biomedical research involving human participants in Europe. Such model is not adapted to all types of research and the resulting distortion would have a negative impact outside the scope of the pharmaceutical research industry. A “one-size-fits-it-all” approach in regulating biomedical research should be avoided at all costs as it will weaken the overall attractiveness of the European research era more than anything.

It should be underlined that no country has so far created different RECs to assess biomedical research. Thus if a REC reviews different kinds of research then only part of the RECs activities are conducted under the CTD provisions. Other legislations, some at the international level such as the Oviedo Convention, also apply to them. Moreover the move from a directive to a regulation will not solve difficult issues such as the CA, or the different regimes that apply liability and liability insurance from one country to another. These questions seem difficult to solve on a single basis without interfering with the legislation of

other types of researches. As mentioned above, harmonization is certainly a noble objective but it should be carefully assessed to what extend it can be achieved. For industry, competitiveness is the single issue, but it should not be at the cost of disturbing the rest of biomedical research in Europe while weakening the protection of human participants.

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

In principle, the present rules allow already a differentiation of the clinical trials depending on their potential risks. This is an issue of implementation. The fact that the CA and the REC – as well as the investigators and sponsors - do not make better use of those possibilities demonstrates in part their lack of confidence or fear of liability. This could be improved by training and improved communication among all stakeholders, rather than by formally creating subcategories of researches with different requirements for each one. Such an approach was experienced briefly in Switzerland but was quickly abandoned and even rejected by the Swiss Federal Tribunal.

A better risk-differentiation of clinical trials can be done but this should not be translated into creating subcategories of research with specific requirements in each case. This will only create more bureaucracy with little or no impact in the assessment procedure.

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

Such problem is not limited to drug trials but all occurs for the management of consortiums in the 6^{th} or 7^{th} FP. In Switzerland, the submission form differentiates the sponsor from other sources of funding. The key issue is to clearly identify who is taking over the sponsor's responsibilities while acknowledging the fact that other partners may be involved in the clinical trials. As such, this is not a problem created by the CTD itself but by the nature of multicenter trials.

Consultation item n°11: Can a revision of guidelines address this problem in a satisfactory way? Which guidelines would need revision, and in what sense, in order to address this problem?

As mentioned in the consultation paper, those guidelines are very technical. They certainly present an important margin of improvement, especially for a better risk-differentiation. Yet, it seems inappropriate in principle to assess that academic/non commercial clinical trials should be considered per se as potentially less risky for the participants. It seems dangerous to create a priori a double standard in the protection of human subjects that does not rely on strong scientific and medical evidence. The fact that a trial is conducted by an academic or a non-profit organization does not have a direct influence on its level of risks.

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?

To put it simply, if the regulation of research involving human participants is to be adapted to meet the practical necessities of investigators and sponsors, there would be no regulation of research. Historically this regulation was adopted in reaction to abuses by researchers and this

was not done without resistance from research communities (see Andreas Frewer & Ulf Schmidt (eds.), History and Theory of Human Experimentation: The Declaration of Helsinki and Modern Medical Ethics, Franz Steiner Verlag, Stuttgart 2007). It is important that the revision of the CTD be done in a way that does not weaken the protection of human participants. As mentioned above, improvement can be effected on technical issues, for instance by limiting and facilitating exchanges of information and the administrative burden. A key issue will be to what extent a Member State should maintain the authority to impose a higher level of protection without being considered in violation of the CTD. If the revision remains on the technical aspects there should not be a problem.

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

We can not support such proposal. Such option would be a severe step backward in the protection of human participants by creating a double standard. Should this category of research be excluded from the scope of the CTD, would send the wrong message. It would mean that all the efforts that were made during the last decade will be partially wasted. It would also raise the issue of the limited power of the EU in the field of regulating biomedical research. In fact, such a step backward could have little impact in practice as other international instruments and national laws have been adopted since the entry into force of the CTD. Academic research is now clearly subject to the same requirements as industrial sponsor driven research.

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

Per se, the clinical trials regulation is not aimed primarily at promoting research but at protecting human participants, assessing ethical soundness of research and guaranteeing the quality of research and the results obtained. For research in emergency situations, several Members States have adopted specific rules that can be interpreted in a way that is not necessarily in contradiction with the CTD. This brings back the issue of the limited scope of the CTD. For research in emergency situations, the CTD could be clarified to avoid the possibility that it could be interpreted as prohibiting it. For research in paediatrics, it is hard to imagine how the CTD could be revised to promote such research. There have been other initiatives that encouraged them. More resources should be made available. The industry should receive more incentive to conduct trials with children. Yet this is beyond the scope to the CTD. It would be the wrong approach to adopt more lenient rules when indeed children deserve stronger protections given their vulnerability.

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?

Under provision 56 of the Swiss law on therapeutic products:

> "In exceptional circumstances, clinical trials may be carried out in a medical emergency:

a. if a procedure, approved by the competent ethics committee, permits within a useful time period:

1. the obtaining of the consent of the legal representative of the minor or person under judicial disability;

2. the establishment of the willingness of the trial subjects, in particular in consultation with their relatives;

b. if there is no indication to suggest that the trial subjects would refuse to participate in the trial;

c. if the trials are expected to produce important knowledge concerning the status, illness or suffering of the trial subjects, and if this knowledge will bring long-term benefits for the trial subjects concerned or for persons suffering from the same illness or presenting the same characteristics;

d. if a doctor not participating in the trial provides the medical care for the trial subject and defends his or her interests."

There are similar provisions adopted in several Member States. It would indeed be useful to include such an equivalent provision in the CTD. A possible solution would be to opt for article 19 of the Council of Europe Additional Protocol to the Convention on Human Rights and Biomedicine on Biomedical Research that reads as follows:

Article 19 – Research on persons in emergency clinical situations

1 The law shall determine whether, and under which protective additional conditions, research in emergency situations may take place when:

i a person is not in a state to give consent, and

ii because of the urgency of the situation, it is impossible to obtain in a sufficiently timely manner, authorisation from his or her representative or an authority or a person or body which would in the absence of an emergency situation be called upon to give authorisation.

2 The law shall include the following specific conditions:

i research of comparable effectiveness cannot be carried out on persons in non-emergency situations;

ii the research project may only be undertaken if it has been approved specifically for emergency situations by the competent body;

iii any relevant previously expressed objections of the person known to the researcher shall be respected;

iv where the research has not the potential to produce results of direct benefit to the health of the person concerned, it has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same category or afflicted with the same disease or disorder or having the same condition, and entails only minimal risk and minimal burden.

3 Persons participating in the emergency research project or, if applicable, their representatives shall be provided with all the relevant information concerning their participation in the research project as soon as possible. Consent or

authorisation for continued participation shall be requested as soon as reasonably possible.

One key element is that the provision does not create a waiver for informed consent but a deferred consent either from the human participant himself or herself or by a legal representative.

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

It is critically important that the CTD does not allow for a double standard in the protection of human participants. This would occur if researchers could use data that were obtained in third countries with less stringent rules either in the conduct of research within the EU or when applying for a marketing authorization. This is a matter of principle.

At all costs procedural requirements such as that the USA OHRP CFR now requires should be avoided. These regulations, which apply to all foreign countries holding US government research grants, are extremely burdensome to RECs, costly, and most importantly replace debate with compliance concerns. Local conditions do not undermine principles but they may influence how those principles are applied in certain settings. This should be left to the discretion of each REC and not procedurally cast in (foreign) stone.

With regard to developing countries holding EU grants, a system of equivalence needs to be developed, rather than requiring simple conformity/compliance with EU CTD. Granting of equivalence need not, and should not, support accusations of double standards, but at the same time it should grant recognition to REC procedures where countries have put these in place. It is very difficult in some developing countries to comply with fairly rigorous national regulations and guidance now enacted for all RECs, AND to comply with US OHRP CFR regulations. This takes a lot of REC time for very little added protections to participants and huge burden for under-resourced developing country RECs.

It should be mentioned that the CA in the South are also willing today to take a closer look at the way clinical trials are conducted in their jurisdiction. The African Vaccine Regulatory Forum (AVAREF), including representatives from NCA and RECs from 19 African countries has recently reaffirmed during its fourth meeting in Abuja, Nigeria on September 21-25, 2009, its willingness to make sure that clinical trials are conducted in Africa according to the international standards and are assessed at the national level. Such initiatives deserve strong support from the EU, for instance through funding agencies such EDCTP as this is already the case.

Concerning the level of training in research ethics and regulation in Africa, we conducted a needs assessment (see "Training Needs Assessment in Research Ethics Evaluation Among Research Ethics Committees Members in Three African Countries: Cameroon, Mali and Tanzania", Ateudjieu Jérome, Baume Cédric, Joyce Ikingura, Marie Hirtle, Alassane Niaré and Dominique Sprumont, *Developing World Bioethics*, online November 12, 2009). Based on this needs assessment, an online training program was developed: http://elearning.trree.org. It is a multilingual (English, French, German), open and free access program. What is interesting is that RECs from the North have expressed their interest in using TRREE, such as in Switzerland and Germany. This demonstrates, if doubts persisted, that there is a common understanding of the minimal ethical and legal requirements that should be applied in the North and in the South. This should encourage the authorities to not accept double standards in the field. What the FDA has recently done with the Declaration of Helsinki is therefore definitely not an example to follow.

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

As mentioned above, initiatives such as AVAREF should receive direct support. Similar initiatives in other parts of the world should also be identified and supported. A key element is to strengthen the scrutiny of clinical trial results of which are submitted to the EU, or which are financed in the EU. That would imply first a double evaluation in the North and the South prior to the start of clinical trials in the South with European participation or support. This could be done at the level of the REC. Guidelines have been developed in that direction in Switzerland (see http://www.swissethics.ch/fileadmin/user_upload/Dokumente/2008_012_152.PDF). Second, research conducted in third countries should be subject to regular inspections in collaboration with the NCA and REC where the studies are conducted.

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?

One central element is a better understanding how the CTD is articulated with other rules at the national and international levels. As discussed above, the scope of the CTD is limited but its impact goes much further than those borders. There is a need for a better conceptualization of what level of harmonization can actually be achieved under the present situation.

CTD must at all costs avoid falling into the endless proliferation of tiny procedural stipulations that now characterise the US CFR. There is no evidence at all that compliance with all the procedural details meaningfully adds protections to participants, but the proliferation of procedural requirements continues. This creates the impression that there is nothing to be debated by RECs or investigators, and that compliance with a checklist simply ensures protections.

The CTD raised great expectations from the research industry. It therefore created frustrations of the same amplitude. In any case, it could prove counterproductive for the European research area if the regulation of biomedical research follows exclusively the therapeutic products approach. More attention should be given to other approaches such as the Oviedo convention. A key issue is finally how to make sure that the rules are applied in practice. As shown by the critics from the academics, it is not so obvious for some that they should follow the same standards in protecting human participants. This requires more effort in training, already at the bachelor's and master's level for the healthcare professionals, not only in the continuing education programs. This also requires more resources in helping researchers cope with the requirements. The Clinical Trials Units are good examples to follow in that sense, not only by offering the professional support that is needed but also by improving the overall quality of the research capacities in Europe.