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Estonian Hospitals Association comments on the public consultation paper on the assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC

Estonian Hospitals Association is a non-governmental voluntary union established for representing the common interests in health care matters and arranging co-operation of hospitals.

Estonian Hospitals Association welcomes the opening of the discussion by the EC on the impact of the EU clinical trial legislation. Please find below comments to the Consultation Paper ENTR/F/2/SF D (2009) 32674.

We find this initiative timely and necessary in the light of increasing publicly funded research from one hand and from the perspective of keeping the EU attractive for good quality industry sponsored trials on the other.

Our comments to the specific Consultation Items:

Consultation Item 1, p10	We have found the legislative framework in general supportive of the protection of trial subjects. We would point to two main areas where the EU legislation has had an important impact: 1) the more uniform standards for the functioning of the Independent Ethics Committee network and 2) widening of the common trial standards to the Phase I research in the regions where this was not the case before. We also find the Directive helpful in bringing up the issues around the paediatric trials, although possibly not providing optimal solutions there.
Consultation Item 2, p12	In general it can be agreed with that the paper describes the situation in the EU trial arena well. From a perspective of a small EU member state it seems that the complexity may be over-stated by the paper or not related entirely to the EU legislation itself but its applications by the MS-s. This is important to consider, as the means to remedy the situation may well differ according to the root cause. There are also good reasons for divergent decisions described by the paper, as the aspects of patient protection may differ according to the level of standard therapy, prevalence of disease etc across the EU.
Consultation Item 3, p14	The reasons behind the increase of administrative costs needs

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	further analysis before it can be concluded that this is caused by the Directive. There are certainly other changes in the trial environment and conduct, several of these dependent on the sponsors that drive the administrative costs of the studies. It cannot be agreed that the current regulatory model of National Authorities (referred to as "patchwork of assessment" in the document) leads to patient safety issues. This is a speculation not backed up by the EC in the paper and should not be considered as a factual ground in justifying any change in the legislation. The time to the "1st patient in" does not only depend on the regulatory and IEC approval but also on the sponsor logistics and the study site/institution. A better understanding of the causes of delay is necessary before drawing conclusions on that issue.
Consultation Item 4, p16	The deliberations on the streamlining of the regulatory approval are most welcome. The starting points for this need to consider that the immediate over-sight in form of constant safety analysis and the inspections during the active conduct of the study remain with the MS-s and that the National Agencies are the best accessible information and contact points for the patients and investigators. This necessitates that the National Agencies retain a rather intimate knowledge of all ongoing trials on the MS territory. Thus, a system described based on the „decentralised model", seems workable and preferable. The model needs to keep the opportunity for input from all MS-s and divergent decisions if scientifically justified (e.g. based on differences in standard therapy across EU). The MS-s should keep the oversight and approval of study sites as this needs information accessible mainly nationally. It should also be kept in mind that the bureaucracy around the assessment and assessment report formats should be kept minimal. The scope should not be optional as this leaves an impression of potential loopholes for specific trials. The system should cover all trials performed in more than one MS.
Consultation Item 5, p17	The attempts to better define the scope of assessment of the regulators and the IECs are welcome. This should have a possible impact on the speed as well as quality of the assessment by these bodies. On the other hand, considering the objective differences among the MS-s and the whole nature of the issues considered by the IEC-s, there should be no attempt of inter-MS ethical decision-making. Further attempts to strengthen the co-operation of the IEC-s and to develop guidance documents to support these bodies are nevertheless welcome.
Consultation Item 6, p20	It is agreed that there are issues that are not handled in a harmonised way between MS-s and the divergences around the substantial amendments are possibly the most outstanding.

	Further formal agreement would be necessary here. The same applies to the regulatory issues around the SUSAR reporting, more than to the safety definitions themselves. It is very important to agree on the borderline of the scope of the directive, both in the interests of patient safety and of the feasibility of non-interventional studies.
Consultation Item 7, p20	It is not agreed that the current regulatory issues around SUSAR reporting result in actual threat to patient safety. It should be more seen as a regulatory/workload/administrative cost issue.
Consultation Item 8, p20	From a perspective of a small MS, both the further clarification of the Directive text and the clarification in the form of the Regulation are easily implementable. Reliance on non-binding guidance documents has not proven useful.
Consultation Item 9, p22	Although partially true, the implications and practicalities of the diversification of rules according to the trial specifics may prove to be more detrimental than the limitations of the „broad brush“ approach described here. There is enough flexibility and room for the scientific common sense in the current system to address this.
Consultation Item 10, p22	It is agreed that the necessities of the academic research should be addressed. Nevertheless, in the interest of patient safety a very clear responsibility distribution has to be retained.
Consultation Items 11-13, pp 23-24	There should be no double quality standard for academic research. Part of the marketing authorisation or not, research is only ethical when it is conducted to the best standards and so that the medical decisions can rely on the information generated. It is also not always possible to a priori differentiate what part of the research may end up in a MA application of a medicinal product. It seems improbable better practice can be achieved with modification of the guidance only.
Consultation Items 14-15, p26	There is little in terms of regulation that can be done. Most fruitful interventions seem rather to be training of regulatory staff, better access to scientific/regulatory advice for the industry and better co-operation/training for the IEC-s. The acceptability of the consent by a representative of the patient in emergency situations needs to be discussed and brought into the legislation, however, major difficulties can be foreseen in the view of differences in the very basic legislation in the MS-s, often on the constitution level. Another issue that has not been addressed by the EC Paper but which in our view deserves attention is the current standard of informed consent and the forms used. For legal/protectionist reasons the information provided is hardly digestible for an average reader, even less so for the patient under stress or in any other unfavourable condition. Measures to ensure that the patient is informed and not overwhelmed with masses of data need to be put in place (e.g. recommended formats, readability requirements, recommended length of the informed consent

	forms).
Consultation Item 16-17, p29-31	The issue is well covered in the paper. Considering that the GCP compliance problems are not unique to the 3rd countries but need constant gardening also in the EU itself, it cannot be foreseen that the EU have resources, obligations or right to police the world. The EU has to have a clear mission of supporting the foreign regulators in their efforts and a firm policy on the acceptability of data in the EU MA system. No real value in the assessment of the EMEA of the trials in the 3rd countries is seen. The "review of intentions" does not guarantee the standards of trial conduct in the environment of no local regulatory oversight and might give false assurance.

We hope to see the EC pursuing the review of the clinical trial legislation and are happy to provide input also during the further steps.

Yours truly,

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Chairman of the Board
Estonian Hospitals Association