REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC

CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

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Name of Organization	Country
EUCROF European CRO Federation **Secretariat** Simona Foglietta Viale dei Parioli12 00197 - Roma - Italia Tel: +39-06 807.60.72 Email : info@eucrof.eu Representatives on this matter : **Dr. Uwe Kramer** Tel: +49 - 89-893 119-28 Email: uwe.kramer@fgk-cro.de **Dr. Dagmar Chase** Tel: +49 - 89-92 92 87-0 Email: dagmar.chase@clinrex.com	**CRO Associations located in EEA:** **Belgium** **Czech Republic** **France** **Germany** **Italy** **Norway** **Spain** **The Netherlands** **UK** **plus Associated Members from** **Greece** **Portugal**

EUCROF Comments on Consultation Items

Consultation Item	
No. 1	EUCROF agrees. One “single submission” through an EU portal would greatly reduce the administrative burden, i.e. time and money. For efficiency reasons, the “single submission” concept should feature the following characteristics: • Electronic submission only • National Competent Authorities (CA) should not be allowed to request any documents in addition to a standard set of documents which is uniform to all Member States • All documents included in this single submission should be provided in English language (except label translation and Informed Consent Form, for example, which would have to be provided in the languages concerned). • No additional national application procedure should apply (see also 1.3.3, item no. 7) The best would actually be that all documents, those that will be assessed by the CAs as well as those that will be assessed by the Ethics Committees (EC), would be submitted through that portal and no additional submission to ECs is required. The EU portal (maintained by EMA) would distribute application documents to the Members States concerned and deficiency letters and approvals would also be provided through that portal. The Member States would have to see to it that local distribution (to local ECs and any other local institutions) is defined and organized. That way, only one formal validation of the submission would be necessary.
No. 2	EUCROF agrees The option of having a single submission but independent assessments would not represent significant improvements – the

	advantages would be limited to the preparation of the submission dossiers. Delays through individual lists of deficiencies/queries at different time points would remain – ultimately leading to (country specific) amendments. Not much would be gained. EUCROF trusts that, by applying a single coordinated assessment, suggestions for improvement of the study which would be raised during the coordinated assessment process by the individual Member States concerned would not get lost and therefore a single coordinated assessment would not involve higher risk for trial subjects. A single coordinated assessment involving all Member States concerned would be highly appreciated by EUCROF. .
No. 3	EUCROF agrees. EUCROF thinks that a central assessment is not appropriate for clinical trial authorization, particularly in view of the fact that only 25% of EU clinical trials are performed in more than one EU Member State and that the average number of Member State per trial is 2. To involve all 27 Member States seems to be a waste of resources of those countries that would not be involved in the clinical trial concerned. One advantage, however, of the centralized procedure would be the fact that Member States to be newly added to ongoing trials could start immediately without any additional procedure. Therefore, it will be of utmost importance to introduce a simple and straight forward procedure to add on Member States to ongoing studies when introducing the coordinated assessment procedure. Another advantage of a centralized assessment procedure could be that for innovative products, like those that are compulsory for the centralized procedure (CP) for marketing authorization (MA) (biotech products, new active substances for cancer, viral diseases etc. or orphan drugs) the EMA would be involved very early on, which might ease the cooperation later on during the CP for MA. However, EUCROF feels that this does not outweigh the disadvantages. EUCROF votes against a centralized assessment for clinical trial approvals.
No. 4	EUCROF would like to add: under a) “statistical aspects”. EUCROF trusts that under a) “in view of all anticipated benefits” (first bullet point) is meant to include the medical need and

	the targeted benefit of the proposed treatment over currently used treatments.
No. 5	EUCROF agrees. Aspects under b) and c) should remain within the responsibility of ECs. However, EC procedures need to undergo harmonization as well, otherwise not much is gained. It appears that EC procedures are a main reason for the diversification of clinical trial protocols in multi-national studies. In addition, the majority of adjustments to study documents are made to documents under b) and c), i.e. the EC procedures are the main drivers of the workload for getting approvals. On the other hand, it seems that the majority of proposals in this concept paper for the modification of the EU Clinical Trials Directive focus on the authorization procedure by the CAs. EUCROF thinks that it is of utmost importance that the EU Clinical Trials Directive sets out a clear set of rules regarding the harmonization of EC procedures (adherence to one single opinion per Member State, time of submission, adherence to timelines, opinions based on scientific and factual grounds) in order to pursue the goal of making the EU /EEA a more attractive place for clinical research. A European accreditation of national ECs including inspections might help to reach this goal. As ECs review data protection aspects and insurance/indemnity requirements, these topics – in the context of clinical trials - should be considered for harmonization as well. As mentioned above, EUCROF favors the approach of limiting aspects under b) and c) to EC review, however, this might be in contrast to the Declaration of Helsinki which asks for EC review of the trial protocol. If and how the Declaration of Helsinki should be referenced in the EU Clinical Trials Directive might be another point of consideration.
No. 6	EUCROF prefers the first option, i.e. a Member State should be able to “opt out”. In more detail, an individual Member State should be allowed to opt out: • if this is justified by serious risk to public health or by safety of the participant based on scientific and factual

	grounds – and only then (health and wellbeing of the trial subjects should have the highest priority) • if the protocol does not comply with the standard of care in the specific Member State (e.g. local treatment guidelines represent a higher medical standard than the proposed treatment in the study protocol) • if the study indication is not sufficiently represented in the population of the Member State The reasons for supporting the "opt out" option are: • It would allow starting the study in a timely manner in those Member States which accept the protocol. However, there should also be a possibility to appeal against the negative decision of single Member States, but this should not hold up the study start in the other Member States. • It would provide transparency. The applicant would know which Member State(s) has/have a problem with the trial protocol as well as the reason for rejection. This might not be the case with a majority vote (option 2). Moreover, the majority approach may become a problem in the case of an even number of Member States concerned. There would have to be reasonable rules for getting a vote in situations which result in a tie. Referring to the Commission or the EMA for a final decision would for sure impact the timelines and costs in a negative way. In addition, there is no obvious reason for the third option to guarantee better and safer trials compared to the first option. .
No. 7	EUCROF prefers the first option, i.e. the CAP should be mandatory for all clinical trials. EU procedures to get clinical trial approvals should be simple, straight forward and unambiguous. To offer more than one possibility will result in confusion. "One system fits all" approach is preferred by EUCROF. However, in case of only one Member State being concerned, the timelines for receiving the assessment results should be shorter since no coordination is required. Also, as already mentioned, a clear procedure will be needed to add on member States to ongoing trials. There is some experience with the Voluntary Harmonisation Procedure from which it is important to learn for a future CAP procedure. In one Voluntary Harmonisation Procedure a trial was rejected even by countries that had no issues, simply because some of the other countries had concerns. It was furthermore not possible to get a harmonized answer because none of the Member States was volunteering to take the lead in the process. Thus, a long unconsolidated list of requests from all participating countries was provided in on one day. It was difficult to differentiate the questions and to find a single

	answer to one topic. Clearly, the CAP should offer a consolidated list of questions and not just presenting all questions of all countries concerned.
No. 8	The pre-assessment procedure is not totally clear to EUCROF, therefore EUCROF is hesitant to agree to a pre-assessment at this point. If the pre-assessment is an additional obligatory step there might be the danger of prolongation of timelines, which would not be appreciated by EUCROF. If it will be obligatory, it must be ensured that pre-assessment, CAP and national adoption do not exceed the 60 days evaluation period (or a respective shorter period, if applicable). It must be defined who would be responsible for the pre-assessment. It should be guaranteed that the classification of the study is regarded as valid upon approval of the CT application and will therefore not become a point of debate during an inspection. EUCROF prefers that the pre-assessment is not obligatory but voluntary and independent of the assessment itself. The sponsor should have the choice of going through pre-assessment or not. The sponsor should be able to self-categorize the study concerned on the basis of a simple algorithm (based on a clear definition of insignificant additional risk). Only in case of doubts, the pre-assessment should be an option for the sponsor (in the sense of a scientific advice). In EUCROF's opinion, adding a mandatory additional step makes the processes more difficult and increases the need for follow-up activities and resource allocation.
No. 9	EUCROF agrees, however, there is an urgent need of clear guidance regarding non-interventional trials (NITs) at an EU/EEA level. Some EUCROF members even were of the opinion to include NITs under the EU Directive just to have some framework rather than not having any framework. For example, in some Member States questionnaires are considered to be interventional, whereas in other Member States this is not the case. This shows how important it is to come up with a clear set of rules around NITs. In the light of the need to show additional therapeutic value of new therapies (effectiveness versus efficacy) it is even more important to create the appropriate framework on an EU/EEA level for NITs.
No. 10	EUCROF agrees.

	Patient protection should be the main concern, rather than the nature of the sponsor. It is important that the scope of the Clinical Trials Directive is as broad as possible and that all clinical trials are covered by harmonized and proportionate requirements. Clinical trials that are not subject to these requirements, offer the possibility to escape essential rules, which presumably increases the risk for trial subjects. Subjects must have equal rights and protection regardless of the type of the sponsor. Simplifications should apply to Type-A trials – no matter who is the sponsor. Furthermore the switch from a non-commercial trial to a commercial trial will be eased if the rules for the trial do not depend on the type of sponsor.
No. 11	EUCROF agrees. As the Detailed Guidance Documents (CT-1 through CT-3) have not proved to harmonise procedures in the different Member States, the only way to reach harmonization seems to be by legally binding documents. As Annexes to EU Directives are legally binding, EUCROF votes for this option. With respect to SUSAR reporting, a simplification of rules would be welcome: a) Expedited reporting of SUSARs to Competent Authorities only b) ECs and investigators to be informed periodically, whereby the length of the period depends on the risk of the study c) Clear and well-organized forms to be used by everybody in every Member State
No. 12	EUCROF suggests more detailed rules on the following key aspects: • Documents to be submitted to ECs and CAs (through single portal) • Working procedures for ECs and CAs • Procedure for communication of protocol deviations and serious GCP breaches to the EC and CA (if, what, when and how) • Studies with specific patient population (children, dementia patients, intensive care patients, emergency patients). • Insurance requirements (see also issue no 14)

	• Data protection in clinical trials (i.e. what does pseudonymization and anonymization mean for clinical trials) • Importation notification and requirements • Labeling of the IMP and other medicines used in clinical trials (NIMPs). • Definition of reconstitution: to confirm that the substance(s) used as vehicle might also include already another active substance • Final batch release The most important issue is the clear procedures for the work of Ethics Committees.
No. 13	EUCROF agrees. This could help to simplify the use of non-investigational medicinal products in the frame of (multinational) clinical trials and would make clinical trials less expensive. It is very important to harmonize definitions of investigational medicinal products and auxiliary medicinal products and respective requirements regarding submission, importing, batch release, labeling and safety reporting. Requirements should be minimal (or absent) in order not to overload the clinical trial with procedures which are related to auxiliary products The suggested definition for Auxiliary MP should include a statement that the definition relates to the respective trial only as the NIMP for one trial might indeed be IMP in another trial.
No. 14	EUCROF prefers the second option, i.e. indemnification by Member State. EUCROF is in favor of requiring insurance for all clinical trials (i.e., interventional trials). To exempt low risk trials from insurance requirements would result in lower protection of trial subjects in the future as compared to the current situation. This cannot be the intention of future legislation for clinical trials and would disseminate an unfavorable message to the public. We would rather suggest dividing clinical trials into low and high risk ones (maybe trials A and B as per article 1.3.4.) and to define the premium for an insurance according to the risk. Also a low risk is a risk and patients need to be covered. Usually

	insurance companies take already the level of risk into consideration when calculating a premium for a specific study. Thus, EUCROF prefers the second option. There should be an indemnification via the Member States, as coverage for health damage is different within the Member States, and dependent on the public health system. Member States could compensate for costs incurred for the insurance cover by charging a fee to the sponsor as part of the clinical trial application assessment fee. Arguments against the indemnification by Member States might be: • It could be that indemnification by the Member States might be less accepted by trial subjects as they might expect it to be more problematic to actually get compensation. • If the Member States are responsible for the insurance coverage this may interfere with the approval of the clinical trial due to the financial risk. An idea might be to develop an EU wide system for insurance/indemnification for clinical trials. A "clinical trial fund" in which Member States, the EU, sponsors, and insurers contribute in one or the other way. From a sponsor perspective the level of contribution to the fund could be depending on the risk of the clinical trial.
No. 15	EUCROF votes for option 1, i.e. one single sponsor carrying all sponsor responsibilities. From a CRO's perspective, to maintain several contracts with several sponsors depending on "who is responsible for what" is a highly undesirable scenario. Rather, it has to be unambiguously clear who carries sponsor responsibilities. This concept avoids loss of information and confusion. The concept of multiple sponsors, leading to an increase of interfaces, bears the risk of vagueness of responsibilities. A single-sponsor-concept is the preferred – if not the only - way to facilitate appropriate quality management in clinical trials, and thus ensure protection of subjects and validity of trial results. The existing requirement regarding a third country sponsor having a Legal Representative on the EU/EEA territory is a way for ensuring clear responsibility of the sponsor in EU/EEA toward regulatory authorities: What if there were several third country sponsors – could there be several Legal Representatives?

No. 16	EUCROF agrees to bring the EU regulatory framework in line with internationally agreed texts. Harmonization and certainty is required and should be part of the revision of the Directive 2001/20/EC. It would be very welcome not to discriminate subjects that are not able to give their consent at the time of commencement of the trial. The following should be considered: - Competent Authorities of each Member State should maintain special attention for this type of clinical trial. - The definition of a legal representative for a trial subject must be clear. - For the protection of potential trial subjects, an independent physician should confirm in writing that an emergency case is indeed given. The definition of "independent" should be clear and practicable.
No. 17	EUCROF agrees. Any trial data used for EU applications for marketing authorizations should be obtained from studies which were conducted in compliance with GCP. This is absolutely necessary to protect human rights and to avoid discrimination. For this purpose, clear, straightforward and transparent guidelines are necessary. However, we suggest that registration in EudraCT (➔ EudraPharm) or any WHO primary registry, even after the end of the trial should be possible and should be succeeded by publishing the trial results. Ex EEA sponsors bringing their products to their own market will most likely not think of entering their studies into EudraCT, however such studies might be submitted for EU Marketing authorization later on. It is questionable whether registration really prevents the trial from being unethical. In addition to registration it is very important that all stakeholders support capacity building in third countries where the regulatory framework for clinical trials is missing or weak. It should be considered that the protection of vulnerable people is hard to achieve in third countries where the people are

	poor and where in most cases there is no alternative treatment, so the choice is participation in a clinical trial versus no treatment.
no. 18	EUCROF would like to comment as follows: Item 6.1: These figures reflect the workload in one EU Member State and cover only the efforts for the Competent Authority. Each additional EU Member State adds approximately 20 h per CA application in the respective Member State. The workload for one central Ethics Committee is 32 h, with 10 h per additional local Ethics Committee in the same Member State. Item 6.4: This is the workload for only one Member State Item 6.5: € 45 per hour is definitely at the low end. Costs of € 60 seem more realistic. Item 7.1: The workload is rather 4 hours per clinical trial application in one country, with additional 2 hours for each additional Member State.