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Comments on:

Revision of the "Clinical Trials Directive" 2001/20/EC
Concept paper submitted for public consultation

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Abbreviations	
CAP	Coordinated Assessment Procedure
CTA	Clinical Trial Application
CT	Clinical Trial
EU	European Union
GCP	Good Clinical Practice
HSC	Hospital Scientific Committees
IMP	Investigational Medicinal Product
MAH	Marketing Authorisation Holder
MS	Member State
NCA	National Competent Authority
NEC	National Ethics Committee

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B 1.1.	3	Consultation Item no. 1	We agree with this appraisal.	Provided that the NCAs do not request additional documentation to be submitted locally, single submission would reduce the administrative workload of sponsors. For this purpose provisions may be included to the revised Clinical Trials Directive that NCAs shall not impose any additional obligations on sponsors for the documentation of CTAs that are submitted through the single “EU portal”.
B 1.1.	3	Consultation Item no. 2	We agree with this appraisal.	A separate assessment by each MS would retain acknowledged difficulties deriving from independent assessments.
B 1.2.	3	Consultation Item no. 3	We agree with this appraisal.	Despite of some advantages of this option (i.e. a great variability of views are being included and this facilitates the detection of points of “weakness” in a CTA; elimination of the phenomenon of countries to be chosen for assessment as being more indulgent), central assessment would not be practicable since: - Very few clinical trials are rolled out in more than five or six MSs and a central assessment hinders viewpoint of the concerned MSs to be eminent. - Different perspectives in ethical and local aspects as well as differences in clinical practice in MSs need to be addressed and this would in any case lead to a parallel, national procedure.

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B 1.3.1.	6	Consultation Item no. 4	We consider the catalogue complete.	
B 1.3.1.	6	Consultation Item no. 5	We agree to include only the aspects under a), in the scope of the CAP.	Ethical and local aspects should be subject to assessment by the NECs and the HSCs in each MS separately due to local perspectives. Though, it has to be noted that the assessment of ethical aspects of a CT is performed in conjunction with the risk-benefit assessment. Both approvals of NCAs (via the CAP - where each NCA should issue a separate approval of the CTA) and NECs should be mandatory in order to proceed to the CT in a MS. Critical changes to the CT should be introduced via the substantial amendments of CTA i.e. both new CAP produced NCAs and NECs approvals should be issued.
B 1.3.2.	6	Consultation Item no. 6	An individual MS should be allowed an “opt out”, if justified on the basis of a “serious risk to public health or safety of the participant”.	Provided that the raised issues by a MS could not be resolved through the CAP, It would be inappropriate for a MS to be “forced” to approve a CTA to which it disagrees on the basis of a “serious risk to public health or safety of the participant”. Therefore, decision by simple majority or at EU level (by the Commission or the Agency) should not be enforced.

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B 1.3.3.	6	Consultation Item no. 7	The CAP should be mandatory for all multinational CTAs	Though mandatory for all multinational CTAs, the CAP should also be optional for national CTAs. The optional role for national CTAs would contribute (in some cases) to the decrease of the cost for the sponsors. In other cases (e.g. an Investigator initiated study in one clinical center) national procedure may be more appealing. Nonetheless, CTAs regarding orphan drugs, pediatrics, biologicals or advanced therapies should always be subject to assessment by the CAP, in order to harmonize CTAs for those products.
B 1.3.4.	7	Consultation Item no. 8	We do not think that such a pre-assessment is workable.	A “tacit approval” would not be applicable within the CAP assessment. Timelines set should be preserved. Existing timelines are not long and introduction of “type A trials” pre-assessment would only result to a limited time gain. Therefore, the need to introduce “type A trials” is not well established. Furthermore, such a categorisation would result to a tendency to downgrade the risks involved in the CTs in order to characterise CTs as “type A trials”. In addition, there are reservations concerning the definition of “type A trial” as cited in §1.3.4. For example, conditions that refer to “part of a standard treatment in a MS” as well as “interventions [that] do not pose more than insignificant additional risk” are dubious. Clinical practice and standard treatments may vary through MSs and a certain therapy may be considered undertreatment or overtreatment in different MSs. Moreover, the vagueness of the “interventions [that] do not pose more than insignificant additional risk” condition, would require several additional guidance/Q&As as to be clarified.

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B 2.1.1.	9	Consultation Item no. 9	We agree with this appraisal.	Our opinion is that in introduction of §2, no clear justification is provided as to propose to limit the scope of the Clinical Trials Directive. We think current definition of “non-interventional CTs” should be preserved and revised Clinical Trials Directive should apply to all clinical trials falling within the scope of the present Clinical Trials Directive. A separate directive for all other types of CTs may be introduced if harmonisation of requirements among the EU is desired thereto.
B 2.1.2.	10	Consultation Item no. 10	We agree with this appraisal.	Reasoning under 2.1.2. is adequate and profound.
B 2.2.	10	Consultation Item no. 11	We agree with this appraisal.	Detailed provisions (concerning the content of the CTA dossier and safety reporting) to be annexed to the basic legal act would enforce their impact for greater harmonisation in the EU.
B 2.2.	10	Consultation Item no. 12	No other key aspects are deemed necessary.	However, as it is described under the reply/comments to Consultation Item no. 14, minimum and maximum insurance and indemnisation fees among MSs may be annexed to the revised Clinical Trials Directive (please refer to comments on Consultation Item no. 14).

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B 2.3.	11	Consultation Item no. 13	The new definition for IMP is clearer than the old one but still there are misunderstandings (please see comments). The approach described for “auxiliary medicinal product” would indeed help to simplify, clarify and streamline the rules for medicinal products used in the context of a clinical trial.	The new definition for IMP may still lead to misunderstandings. For example, in a randomised clinical trial with 2 patient groups where study’s objective is to compare efficacy between the 2 groups and prove group A non inferior to group B, the groups being: Group A: combination therapy of drug X plus drug Z (this combination therapy being the standard treatment for the disease) where the novel drug V is being added. Group B: combination therapy of drug X plus drug Z (this combination therapy being the standard treatment for the disease) where placebo is being added. In the above described example, IMPs according to the new definition is understood to be the novel drug V and the placebo. Combination therapy of drug X plus drug Z is considered to be the background treatment. In the same clinical trial, if placebo is not possible to be administrated, the Groups will be as follow: Group A: combination therapy of drug X plus drug Z (this combination therapy being the standard treatment for the disease) where the novel drug V is being added. Group B: combination therapy of drug X plus drug Z (this combination therapy being the standard treatment for the disease).

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B 2.3.	11	Consultation Item no. 13		In this case it is not clear, even with the new definition, which products are being considered IMP's. The critical question in this case is whether the reference is the background treatment or the "nothing" that is added to it. In the first case, drug V and drug X and drug Z will be considered IMP's and this would have great impact to the management and monitoring (including safety monitoring) of the CT. In the second case, only drug V will be considered an IMP and this will resemble to what was expected in the former CT design (where a placebo was also introduced). The existing as well as the proposed definition introduces conflicts on safety issues, since requirements in the design and monitoring of CTs also change. Adverse events related to IMPs are managed in a different way than adverse events related to other products used in the context of a clinical trial.
B 2.4.1.	13	Consultation Item no. 14	None of the proposed policies is considered appropriate	Indeed, the risk for a trial subject varies considerably. It is the responsibility of insurance companies to estimate the risk and adapt the insurance cost accordingly. Removing insurance/indemnisation requirements for low-risk trials is not considered to be a proper solution, since: - Issues raised in Consultation Item 8 for "type A trials" are also applicable herein. - A trial subject is still possible even in a low-risk trial to be exposed to risks and subsequently be harmed. Thus, the possibility to ask for indemnisation should be maintained.

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B 2.4.1.	13	Consultation Item no. 14		Optional indemnisation by MS is neither considered to be a proper solution, since: - Damages paid till the present moment may correspond to a minimal burden on national budgets. Yet, this is difficult to be projected to the future, since safety awareness is continuously enhanced, for example with the provisions for Direct Patient Reporting implemented in the new EU legislation. - Liability for indemnisation taken away of sponsors and be attributed to MSs may pose sponsors to underestimate risks involved in CTAs and in correspondence may lead NCAs to overestimate the risks, both resulting to rejections of CTAs. - In addition, “Optional indemnisation by MSs” is not clarified in the §2.4.2.as whether would be optional for CTs in a case-by-case scenario (per CTA), or optional for each MS (that would lead to MSs providing indemnisation for all CTs conducted in their territory and MSs who would not follow this policy for any CTA). As it concerns the effort to minimise costs for estimating the insurance amounts needed (as indicated in §2.4.1), we propose to harmonise the minimum and maximum insurance and indemnisation fees among MSs (i.e. by annexing them to the revised Clinical Trials Directive).

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B 2.5.	14	Consultation Item no. 15	We agree with this appraisal.	Reasoning under §2.5. is adequate and profound.
B 2.6.	14	Consultation Item no. 16	We agree with this appraisal provided that conditions set would be fulfilled concurrently.	In view of these texts (Declaration of Helsinki, Convention on Human Rights and Biomedicine of the Council of Europe, Guidelines on GCPs), the conditions set by the §2.6. should all be in force at the same time in order to harmonise procedures for Informed Consent in the case of emergency CTs. Conditions as described in §2.6. are not necessarily linked with each other. This would be clarified with the addition of the word “and” at the end of each condition, so as: - “The trial subject is not in a state to give informed consent; **and** - The physical or mental conditions that prevents giving informed consent is a necessary characteristic of the research population; **and** - Because of the urgency of the situation, it is impossible to obtain informed consent from the parents/legal representative (in case of adults) in accordance with the Clinical Trials Directive, and it is impossible to give the information, as provided in the Clinical Trials Directive; **and** - The trial subject has not previously expressed objections known to the investigator.”

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B 3.	16	Consultation Item no. 17	We agree with this appraisal.	In addition, we propose that the EU authorities should add a requirement to the MA application dossier, specifying that all studies presented as supporting documentation for granting the MA were conducted according to GCP. Furthermore, a separate statement may be needed to assure that the CT complies with any regulations set by the public registry of the 3rd country (if applicable).
B 4.	16	Consultation Item no. 18	We do not have additional information to contribute.	Concerning the issue of insurance cost per patient per annum in different MSs, it is not of great value to compare overall average cost (if this is the case in §7.2.), due to discrepancies in the risk assessment among different CTAs (the risk assessment is critical for the definition of the insurance cost). Therefore, a comparative conclusion is only possible to be drawn when the insurance cost for the same CTA among different MSs is compared.