Consultation item no. 1 + 2: Do you agree with this appraisal? Please comment.

ICORG Comment: ICORG would support this measure in its intention of reducing multiple submission of the same paperwork to multiple CAs but agree that it does not solve the problem of poor use of CA (and sponsor) resource currently where 10 CAs review a simple multinational study and all approve it.

A large proportion of the current EU clinical trial portfolio is composed of relatively simple low risk studies there is certainly considerable wastage of CA and sponsor resource in the requirement for these types of studies being submitted to all CAs

Would it be possible for the EMEA to run a clearing house for all CTs where a grading would occur (within a defined timeline – 2 weeks) and if a CT is given a grading indicating that it was low complexity and low risk it could be reviewed at just one CA with pan European jurisdiction.

Consultation item no. 3: Do you agree with this appraisal? Please comment.

ICORG Comment: ICORG believe central assessment to be a worthy goal with many benefits for the EU research environment. A parallel, truly harmonised, national procedure should be the objective of this amendment to clinical trials directive 2001/20/EC.

The ethics committees can continue their important role in consideration of local non-scientific issues.

The sheer numbers argument is incorrect as currently European CA assessment resource is being poorly utilised with repetitive multiple review and approval of low tech low risk studies.

If the CA assessment resource is pooled and review is coordinated centrally then it can only improve the process within the EU compared to the current status.

Consultation item no. 4: Is the above catalogue complete?

ICORG Comment: YES but would not necessarily agree with the assessments

Consultation item no. 5: Do you agree to include the aspects under a) and only these aspects , in the scope of the CAP ?

ICORG Comment: YES but would not necessarily agree that all studies require a dual assessment. Stringent timelines would be important for all new processes. Please note this suggested new process would not work unless CAs agree a unified approach to assessment.

Consultation item no. 6: Which of these approaches is preferable? Please give your reasons.

ICORG Comment: referring the matter, in this situation consensus is required it will not work if it looks like it may force a member state to allow a clinical trial which it has assessed and does not

agree with. Either the member state signs up to accept the opinion of another CA or if two reviews are carried out, centrally and in the member state disagreement will require a compromise or consensus that the reviewing member state can accept.

Consultation item no. 7: Which of these three approaches is preferable? Please give your reasons.

ICORG Comment: CAP should be mandatory, otherwise after this process you end up with a more complicated rather than more streamlined regulatory process for multinational trials.

Consultation item no. 8: Do you think such a pre-assessment is workable in practice? Please comment.

ICORG Comment: pre-assessment once prompt and accepted by all member states would be a significant step in the right direction for an improved EU regulatory environment for multinational trials.

Consultation item no. 9: Do you agree with this appraisal? Please comment.

ICORG Comment: ICORG would agree with any measures that would see the regulatory landscape in the EU be more harmonised and efficient, this may benefit from a wider definition but only in a situation where a number of significant inconsistencies in the current legislation are corrected.

Consultation item no. 10: Do you agree with this appraisal? Please comment.

ICORG Comment: As an academic sponsor ICORG would not seek exclusion from and by inference operate in a lower tier of research. As indicated before a more harmonised, practical, consistent and proportionate approach in newly designed legislation would be preferable.

Consultation item no. 11: Do you agree with this appraisal? Please comment.

ICORG Comment: Any steps to unify, simplify or clarify would be welcomed by ICORG

The directive and more particularly the *Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use* (CT-3) need to be adapted to take into account the level of risk associated with the investigational medicinal product. The CT-3 guidance was written with a standard trial of investigational drug vs placebo vs comparator as its template but not all trials are designed in this way.

Recent legislative changes i.e. Regulation (EU) No 1235/2010 and Directive 2010/84/EU have altered post-marketing pharmacovigilance so that the level of surveillance is proportional to the level of risk, e.g. periodic safety reports are no longer required for generic products and drugs whose active substance has a well established medicinal use.

The rules for clinical trial pharmacovigilance should also change and be proportionate to the risk and safety profile of the drug. The current situation where all first in man drugs in phase I trials are subject to the same rules as well established marketed products used in a clinical trial should be changed. SUSAR reporting is dependent on the assessment of expectedness and in multi-drug trials the reference document for the standard therapy is the Summary of Product Characteristics which often has a shorter list of expected events than many Investigational Brochures leading to the irony of multiple SUSAR reports associated with well-established products while newer drugs that are the focus of a trial generating few if any SUSARs.

For multi-drug trials the SUSAR reporting could be altered to be proportionate to risk by the standard therapy drug (s) being classified as auxiliary medicinal products with different regulatory requirements to the IMP as described in Section 2.3 or by accepting one adverse reaction assessment and one expectedness assessment for an event that occurred when a patient was taking multiple drugs.

Consultation item no. 12: Are there other key aspects on which more detailed rules are needed?

ICORG Comment: A unified approach to standard of care medications and procedures would make the EU a more attractive research location, great variation currently exists between member states. Also a unified approach to the levels of approval required, in some EU countries it is simply 3 layers CA, ethics and hospital approval required in others it can be as many as 7 separate applications.

Consultation item no. 13: Do you agree with this appraisal? Please comment.

ICORG Comment: Yes, we agree with this appraisal. We would like to see a distinction made between the medicinal product that is the object of the trial and other medications that are used in the context of the trial but are not the focus of the trial.

As well as the examples of challenge agents, rescue medication and background treatment we would like the definition of auxiliary medicinal products to include standard chemotherapy used in oncology trials with an investigational medicinal product.

Currently standard chemotherapy drugs are defined as IMPs because they are study drugs and are administered as described in the protocol. However, it is questionable if they meet the current definition of an investigational medicinal product: *'a pharmaceutical form*

of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated

or packaged) in a way different from the authorized form, or when used for an unauthorised indication, or when used to gain further information about the authorized form' when they are not being tested, used as a reference, not used or assembled in a way different from their authorized form, not used for an unauthorised indication and not used to gain further information about the authorized form but instead are used because it would be unethical to offer oncology patients a novel treatment without the standard care treatment. We would support the redefinition of an IMP to: '*A medicinal product which falls within the definition of Article 3(3) of Directive 2001/83/EC, and which is being tested or used as reference in a clinical trial.*'

We also agree with the concept that 'Auxiliary medicinal products' could be subjected to a proportionate regulatory regime, which would be separate from IMPs. Under the current regulatory regime all drugs used in a multi-drug oncology trial are subject to the same adverse reaction and expectedness assessments as outlined in CT-3. As the reference document used for chemotherapy drugs is the Summary of Product Characteristics a lot of adverse reactions to these drugs are assessed as unexpected with the result that a high proportion of SAEs (up to 60%) in oncology clinical trials are classified as SUSARs with associated preparation and reporting of SUSARs. This is a misuse of sponsor, regulator, ethics committee and site staff resource. As well as a poor use of manpower, monitoring of safety signals is impaired by the high background noise of these SUSAR reports from standard chemotherapy. The current system is highly disproportionate with drugs like cyclophosphamide – which has been used by millions of patients in over fifty years of post-marketing exposure - regulated in the same manner as a novel recombinant humanised monoclonal antibody.

Consultation item no. 14: Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

ICORG Comment: We feel strongly that both of these options should be implemented. Clinical research is a relatively low risk endeavour, the insurance process and costs take up a disproportionate quantity of scarce resource and funding, the academic sector would benefit greatly from mandated member state indemnification. The existence of such would also reduce the related delays in protocol start-up times.

Consultation item no. 15: Do you agree with this appraisal? Please comment.

ICORG Comment: Yes but only in an environment of better cross community harmonisation

Consultation item no. 16: Do you agree with this appraisal? Please comment.
ICORG Comment: ICORG would agree with this appraisal

Consultation item no. 17: Do you agree with this appraisal? Please comment.

ICORG Comment: ICORG would fully support the requirement to register all third country studies planned for registration at study start-up.

Consultation item no. 18: Do you have any comments or additional quantifiable information apart from that set out in the annex to this document?

ICORG Comment: It is obvious from these figures that the EU is not yet an attractive location to carry out multinational trials be they academic or industry sponsored, worryingly there is a strong trend in all sizes of multinational trials for a significant year on year drop in the already weak numbers.

This would seem to indicate that significant change is required in the regulatory and other hurdles faced when trying to carryout pan European trials.

If the directive had succeeded you would expect a reasonable percentage of the 4000+ trials to be possible on a pan European basis instead the 'nearly' pan European trials (14,15,16) member state studies are in the single figure range and therefore less than 0.25% of the total European clinical trial portfolio.

If so, you are invited to submit them as part of this consultation exercise.