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? **(p10)**

From the University administration viewpoint, an advantage is a greater central awareness of what studies are being conducted under University auspices. This may provide some peripheral protection.

One comment, from the lay perspective, would be to consider whether the EU Directive actually introduced increased safeguards within the UK, or whether it merely codified existing safeguards.

Consultation item n°2: Is this an accurate description of the situation? What is you appraisal of the situation? **(p12)**

The description given would seem to be reasonably accurate. However, there is a general lack of knowledge of regulatory, ethical and administrative procedures outside one's home jurisdiction, which can lead to over-optimistic and unrealistic perceptions of the issues around setting up international trials.

From the knowledge that within the EU we are all working to the same Directive, there is an assumption that procedures in other EU Member States will closely resemble those in one's own country. However, the implementation of the Directive is not identical in each member state, and requirements, e.g. for clinical trials insurance can differ. This particularly affects academic studies, as commercial pharmaceutical companies often have local representation in a number of member states, which can provide the necessary knowledge base.

The administrative burden of filing several different NCA and EC applications is quite high, and is complicated by the incomplete knowledge of procedures in other member states. Again, this is particularly burdensome for academic studies.

The adoption of a single EU NCA and EC opinion would simplify this, but may be impractical for a number of reasons. In particular, Sponsors and Participating Sites may be unsure that review in an external jurisdiction would have considered particular local issues relating to health care, and may be reluctant to conduct studies without a degree of internal review, which would cancel out the potential benefits of a single EU opinion.

Consultation item n°3: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences? **(p14)**

This as been partially answered in n°2 above.

Whilst there may be advantages in a single NCA opinion, a better situation would be greater collaboration between NCAs. An example might be that, instead of reviewing *ab initio* in each Member State, the NCA in the Sponsor's Member State could review and then share/consult with the other NCAs for territories covered by the application, before confirming an opinion. The other NCAS could then adopt this opinion also, and provide the re-assurance to Sponsors and sites that local implementations of the Directive were being met.

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? **(p16)**

From a University administration point of view option a) is the preferred option. This would require a formal mechanism, and would necessarily take longer (to allow consultation) than would be required for an authorisation in a single member state. However, it is likely to be considerably shorter, and to be easier to manage (from the perspective of the applicant) than the current system. It should also ensure uniformity of the protocol across the member states.

This would require an increase in the resourcing of the NCAs in each member state, as the negotiation and consultation process would impose burdens on staff (especially in the "lead" NCA) as they strove to reach consensus amongst the NCAs.

The NCAs would necessarily have to develop a greater knowledge of the procedures and the health care systems outside their own member state, and in particular, the insurance and indemnity provisions across the member states.

Such cooperation, leading to a single NCA, would itself be expected to lead to a greater harmonisation of procedures and definitions across the EU, e.g. in the definition of what actually constitutes an IMP and an IMP trial (see below), and also in the way Sponsorship responsibilities might be shared between institutions. However, clarification of a number of definitions would ensure that member state NCAs are using the same criteria.

However, as with all attempts at harmonisation, there may be difficulties in reconciling different perceptions of what constitutes adequate protection in different health care systems, and in ensuring that we do not further restrict the ability of EU organisations, especially academic organisations, form conducting trials

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? **(p17)**

Moving towards a single Ethics Committee opinion would be significantly more difficult than moving to a single NCA opinion. Some member states are still struggling to produce a single Ethics Committee opposition within the member state itself, let alone consistency across a number of member states.

Ethics committee's are particularly charged in ensuring that local needs and conditions are addressed, and this important protection must not be lost. Whilst there is scope for cooperation, this may possibly be best done through more formal networks of the ethics committees, as set out in (and perhaps going slightly further than) 3.4.2.

In moving towards this, it might be appropriate to attempt to split the review by ethics committees into those issues which are "global", e.g. affecting the fundamental ethical issues of the trial and protection to subjects, and those which deal more with the local implementation of those protections, such as local procedures for the keeping personal data secure.

A single national Ethics Committee would advance the process and reduce bureaucracy and result in a single opinion across member states.

Consultation item n°6: Is this an accurate description of the situation? Can you give other examples? **(p20)**

There is clearly a need for greater harmonisation of definitions, the key one of which would seem to be in the definition of an IMP trial itself, as set out in Example 3. The current dividing line between a non-interventional study and an interventional one would seem, to a lay person at least, ambiguous and potentially counterproductive. The inclusion of a study of an established treatment as an IMP study, merely because some additional diagnostic or monitoring procedures are included, would seem to be an actual discouragement of such studies, due to the additional administrative and regulatory burdens imposed, and this in turn would seem to actually detract form patient protection in reducing the number of these studies performed.

Consultation item n°7: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences? **(p20)**

This would appear to be an accurate description. There is a noticeable greater (and growing) administrative burden on academic trials units and their central support.

The effects of the directive increase both bureaucracy and costs. Research activity in many clinical areas has been severely curtailed as a result. The evidence suggests that the costs of publically funded trials have increased by 85% and there has been a documented decrease in the number of publically funded trials in certain areas [1].

1. McMahon AD. The unintended consequences of clinical trials regulations. PLoS Med. 2009; 3 (11): e1000131.

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? **(p21)**

Moving from a Directive approach to a Regulation approach might offer advantages in that there would be greater clarity and less room for debate on definitions, and this could also pave the way for the required greater collaboration between the NCAS and the ethics committees across the member states.

However, from the academic trials perspective, we would wish to ensure that any Regulation properly addressed the differences between academic and commercial clinical trials. Whilst a Directive gives room for discretion on the part of NCAs, a Regulation would lose the (limited) flexibility in the system, and could lead to academic studies having to be performed to the same level as commercial studies.

This in turn would further reduce the scope for academic centres to initiate and conduct trials, as their trials are usually conducted on an altruistic basis, without the prospect of future commercial return. Consequently, a Regulation based on commercial studies would not be appropriate.

It is also likely that the introduction of a Regulation would require significant changes in domestic legislation in some member states. A particular example might be in the introduction of compulsory clinical trials insurance in those member states such as the UK which do not currently have such provisions. If indemnification of clinical trials subjects were to become divorced from existing clinical negligence schemes, this could result in significantly increased costs in both commercial

and academic studies. Conversely, where a member state had to adopt a national clinical negligence scheme (akin to CNST) where none exists at present, this could impact on the member states health care budget.

A revised Directive, containing revised definitions, alongside specific guidance containing relevant examples could be a more appropriate way forward.

Consultation item n°9: Can you give examples for an insufficient risk-differentiation? How should this be addresses? **(p22)**

Clearer guidance on risk categories might have benefits in allowing for proper risk-based monitoring regimes to be devised, commensurate with agreed risk levels. This might also lead to agreed tariffs for clinical trials insurance for different categories of clinical trials.

Consultation item n°10: Do you agree with this description? Can you give other examples? **(p22)**

This describes the situation very well.

A major disincentive to academic clinical trials is the degree to which academic sponsors, with limited resources, can be expected to carry full legal responsibility across a number of member states. Although duties can be delegated by contract, ultimate responsibility remains with the Sponsor. Some member states do not permit the sharing of Sponsor responsibility (as opposed to duties), and the interpretation of Co-Sponsorship may differ form member state to member state where such sharing is permitted.

In the UK, the DoH does not permit sharing of Sponsor responsibilities on a geographical basis, only on a functional basis, i.e. a single Co-Sponsor takes responsibility for a function, such as Pharmacovigilance, across all territories where a trial is conducted.

As academic trials are normally conducted on an altruistic basis, there is a natural reluctance on the part of the academic central administration to assume legal responsibility for studies outside one's own member state, especially where the academic institution is constrained by lack of resources to adequate monitor the conduct of the study in another member state.

This, and the corresponding reluctance to take responsibility in one's own member state for a clinical protocol not devised by one's own staff, is a major barrier to academic clinical trials in the EU.

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? **(p23)**

A review of guidelines would be welcome, as would clarification as to the extent to which an academic sponsor is held to be liable for the conduct of a trial conducted outside its own member state. A system whereby academic studies could have multiple, national sponsors, would be welcome.

The suggestions for revision of implementing guidelines given in section 5.4 are all valid, and necessary, but these themselves do not in my view constitute the main barrier to academically-led

international trials, which is the ability of academic institutions to take legal responsibility for the conduct of a EU-wide trial.

Even where an academic institution is willing to take on this responsibility, the requirement for insurance provision in each member state (most of which have compulsory insurance) may well be prohibitive. Even where a national coordinator may meet the insurance costs for indemnification of subjects in a particular member state, the Sponsor will still have, in the current guidance, residual legal responsibilities requiring further insurance.

The points mentioned in section 5.4.1 are worth addressing, and harmonisation here would be welcome. In time, with increase knowledge and familiarity with regimes across the EU, these will become less of a barrier, but revised guidelines could speed this.

Against this, it must be noted that the timeline for revising Directives is lengthy, and there is a question as to whether Guidance (rather than a revised Directive) would be held as legally valid across the EU.

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? **(p23)**

An amendment allowing for sharing of Sponsor responsibilities on a geographical basis in academic trials would be particularly welcome.

This, in conjunction with a simplified insurance/indemnity scheme for academic clinical trials across the EU would remove barriers.

Consultation item n°13: Would you agree to this option and if so what would be the impact? **(p24)**

Academic trials are run on an altruistic basis, without expectation of future commercial benefit. Consequently, academic studies cannot afford the level of monitoring and auditing that a commercial trial requires in order to gain a Marketing Authorisation. A clear recognition of the differences in the two types of trial would be welcome, as would guidelines on appropriate approaches to risk-based monitoring.

Consultation item n°14: In terms of clinical trials regulations, what options could be considered in order to promote clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants? **(p26)**

It is clear that special provisions are required for emergency medicine and a number of other types of studies, including paediatric, geriatric, and "orphan conditions".

Trials have been hindered by inconsistent interpretation and application of the requirements under the Directive, such as qualification requirements which are not always proportionate and hinder the ability to undertake trials.

The wording of the directive with respect to children is also very restrictive. This was criticised during the consultation phrase but unfortunately advice was not heeded and the predicted effect has

materialised – it has become more difficult to conduct trials in paediatrics. This is clearly to the detriment of child health.

A reduced regime, aimed at making it easier to initiate such trials would be welcome.

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? **(p26)**

The directive has restrictive wording regarding patient consent and this has greatly impeded the conduct of trials in areas where it is difficult to get consent, such as emergency medicine.

A reduced regime, aimed at making it easier to initiate such trials would be welcome.

Consultation item n°16: Please comment? Do you have additional information, including quantitative information and data? **(p29)**

Trials in third countries should be conducted to at least the same level of ethical safeguards as we would for a study in our own member stat, albeit paying attention where necessary to cultural sensitivities. Where such attention to cultural sensitivities however preclude access to specific groups, e.g. women. Then greater care must be taken in design of the study to ensure that ethical issues are addressed.

From the academic trials perspective, there may be particular difficulties in monitoring due to financial constraints, which may be in part offset by partnering, mentoring and training relationships with academic institutions in third countries.

Consultation item n°17: What other options could be considered, taking into account the legal and practical limitations? **(p31)**

No suggestions here. Suggestions above would fall under "capacity-building" i.e. 7.3.1

Consultation item n°18: What other aspects 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? **(p32)**

The regulations are suitable for early phase and commercial trials.

Whilst there should be no suggestion that patient protection be reduced in academic trials, there should be recognition that resource constraints will limit the extent of monitoring that can be carried out in an academic trial. To this end, EU-wide guidance on risk-assessment and risk-based approaches to monitoring should be developed and published.