Revision of the Clinical Trials Directive 2001/20/EC, concept paper submitted for public consultation SANCO/C/8/PB/SF D(20114) 143488

Response from: Cancer Prevention Trials Unit (Barts and the London School of Medicine and Dentistry)

CRUK and UCL Cancer Trials Centre, London

CTRU (University of Leeds)

National Perinatal Epidemiological Unit (Oxford)

Newcastle Clinical Trials Unit (University of Newcastle)

Members of the *UKCRC Registered Clinical Trials Units Network*

This concept paper is very much welcomed at this time and covers key areas of concern and suggested amendments to the Clinical Trials Directive 2001/20/EC. Please find following a summary response from the above members of the UKCRC Registered Clinical Trials Unit Network. Other members have also responded either directly or through funding bodies such as Cancer Research UK.

Where concerns / additional comments have been raised by individual parties regarding consultation items, these are detailed separately in the Appendix.

Consultation Item 1

All parties were in agreement with the appraisal. The UK already uses a single portal for application (within the UK) and any EU system should be compatible.

Consultation Item 2

All parties were in agreement with the appraisal.

Consultation Item 3

The majority of the parties were in agreement with the appraisal.

Consultation Items 4 and 5

All parties were in agreement with the consultation items catalogue list and that those included in ‘A’ should be reviewed by the CAP. The following additional items were raised by individual parties to add to the catalogue:

- Process for pharmacovigilance
- Informed consent (while certain aspects of ethics clearly fall within the national responsibility it was considered that the adequacy of information provision should be standardised).

- Completeness and adequateness of the SmPC where used in place of the IB

In addition the following logistical issues require confirmation:

- How the ‘Lead MS’ will be determined e.g. where the Chief Investigator or Sponsor are based and if so how this would work for a global pharmaceutical organisation.
- Order of assessment

It was also highlighted that the ‘characteristics of the intervention compared to normal clinical practice’ may be difficult to assess centrally in all cases due to differences in standard practice between countries. Full consideration regarding how this would be handled would be necessary in any future process should it remain as an item listed under ‘A’ or it moved to be reviewed as part of the items listed under ‘C’.

Consultation Item 6

The difficulty of this issue was highlighted by all parties and no one process was considered to be ideal. Please refer to the appendix for full details of individual responses.

The majority of parties agreed that an individual MS should be permitted to ‘opt out’ but this came with a number of caveats:

- Disagreements could be resolved by a ‘majority vote’
- Opting out would only be from the trial being conducted in that MS, not a veto for the whole trial
- Sponsor must have the opportunity to address the concerns of any MS which is opting out, particularly where the involvement of that MS was critical to the conduct of the trial
- Where concerns were related to an ethical issue that may be relevant to patients in another MS they would have the right to know.

Consultation Item 7

Please refer to the Appendix for individual responses.

Consultation Item 8

All parties were in agreement that a risk based approach to pre-assessment was workable in practice, however please refer to the Appendix due to the differing responses to Item 7 and 8 these are not able to be summarised for all parties.

Consultation Item 9

The majority of parties agreed that it was not preferable to extend the definition of non interventional trials. The scope of the Clinical Trials Directive should not be extended. One party did not agree with this Consultation Item – please refer to the Appendix for details.

A risk based, proportionate approach to all aspects of the trial authorisation, conduct and reporting is supported. Please refer to the UK MHRA/MRC Joint Project for Risk Based Approaches when conducting clinical trials.

Consultation Item 10

All parties were strongly in agreement with the appraisal. The approach should be risk based rather than Sponsor / Funder based.

Consultation Items 11 and 12

All parties were strongly in agreement with the appraisal and some urged caution in regard to ensuring against over interpretation in particular between MS; one single approach is required across the EU. There were a number of logistical issues raised:

- The Guidance should be carefully written and considered to ensure against over interpretation where specific instructions are not able to be provided to cover all scenarios.
- How will the Annexes be implemented e.g. will there be additional questions within the CTA? Will the Annexes replace the Guidance – caution against overcomplicating things with having too many cross referring documents.
- Exemplars on how to apply risk adapted approaches would be useful

The following areas were raised where more detailed rules would be required, specifically tailored for risk adapted approaches:

- NIMPs
- Pharmacy procedures
- Monitoring requirements
- Trials with a long period of follow up taking place after the IMP has stopped being administered

Consultation Item 13

All parties agreed with the appraisal and need to improve the definitions and guidance relating to what are currently referred to as NIMPs. Any changes and implementation should be commensurate with a risk adapted approach.

Several parties were concerned that there was the possible intention to extend the current scope of the NIMP definition further and queried whether auxiliary products should be included at all for lower risk trials where safety and traceability issues are covered through the pharmacovigilance procedures and accountability procedures and standard hospital systems.

Consultation Item 14

Please refer to the Appendix for details of individual responses.

Consultation Item 15

The majority of the parties agreed with the appraisal, subject to the provisos given.

Consultation Item 16

The majority of the parties agreed with the appraisal.

Consultation Item 17

The majority of the parties agreed with the appraisal that the fundamental rules of GCP should be applied across all countries including the specific proposal relating to point 2.7.2.4.

Consultation Item 18

Please refer to the Appendix for details of individual responses.

Contact details for all contributing parties are held by the UKCRC Clinical Trials Units Network Co-ordinator, CTRU, Leeds, LS2 9JT. Comments, queries and requests for further information should be made through the Network Co-ordinator.

Compiled and submitted on behalf of the afore named organisations by Gillian Booth, Operations Director, CTRU, Leeds. G.Eddison@leeds.ac.uk and Svet Mihaylov, TMN Co-ordinator, CTRU, Leeds, S.I.Mihaylov@leeds.ac.uk

Appendix

Table 1. Individual CTU Responses (not covered in the summary)					
Consultation Item	**Newcastle Clinical Trials Unit (Newcastle University)**	**Cancer Prevention Trials Unit (Barts and The London School of Medicine and Dentistry, London)**	**National Perinatal Epidemiology Unit, Oxford**	**CR UK & UCL Cancer Trials Centre, London**	**CTRU Leeds**
1	There is an inherent risk that this approach would requiring working to the most rigorous interpretation (across the member states) of the Directive, in terms of the documents required for the submission. Clarity would also be required as to whether the single portal should be used only for trials spanning more than one member state, or for all trials (single and multi-country) being conducted within the EU.		NPEU does little work in the EU outside of UK because of past difficulties with some nations and this would not necessarily be changed by a single submission. It is assumed that despite the proposal (appraisal 17) to register trials in "third countries" on the EudraCT system, that such trials would not be forced to use any single submission procedures. This would not be a positive step.	An assessment of impact on infrastructures and timelines would be needed.	
2	Agree in part, separate assessment by each member state may still be required, at least in the short term, but suggest that there could be an opportunity for these individual assessments to go back through the portal and be re-assessed in an 'over-arching' fashion with ultimate responsibility to harmonize being at the portal level. Sharing and reviewing assessments in this way might, in the medium to long-term, lead to a reduction in differences in interpretation and application of the Directive across member states.				

3	We disagree with this appraisal. A single submission with subsequent central assessment would be the ideal. We think this could be workable; there is no compelling reason in principle why ethical issues and perspectives should not be uniform throughout the EU. In practice, it may be the case that current ethical frameworks and views differ so much across member states that this would be very difficult.	However, we were in support of the idea of a single scientific committee whose scope would not include ethical issues or national aspects/rules and thought it did not need to involve all MS for all trials. There could be a very large number of members who could potentially be assigned to a scientific committee. Only a small proportion of these members would make up a single committee for any particular trial and they not necessarily need be from a participating MS.		Agree would not be workable for reasons given, in particular resource implications for all, although centralising could enable standardisation of decision-making process. (Such a committee could be useful for arbitrating and be the basis for the EU level decision in section 1.3.2). In appraisal, what is "national and local perspectives" referring to? A parallel national procedure would only be required for ethics. Other national issues should be discussed as a committee, or at least centrally (as in CAP). This can only lead to increased harmonisation.	
4		We agree that the CAP should cover the aspects under 'a' (ie, key issues critical for a trial) and not the ethical and local/national issues, with one exception. We thought that one of the key CAP issues, ie, 'charateristics of the intervention v local practice' might better be considered under 'c' – the local/national issues (since local practice will vary amongst MS).		Catalogue appears complete. With some queries: - Reference is made to "under the CAP, it would be up to each MS to divide the tasks between CNA and EC" – which tasks is this referring to, as remits of ECs are already clear? This appears to be in contradictions to other plans, by introducing potential for further variations in interpretations. - Unclear if would be a 'single decision' under the CAP areas when assessed centrally (ie to feed into the 'single decision' per MS mentioned) and how the CAP decision would be achieved/managed.	
5	We agree that all items under (a) should be included in the CAP. We also consider that items under (b) could be				

	included in the CAP; with regard to (c) only suitability of the investigator and site need to be considered locally; insurance and personal data could be included in the scope of the CAP.				
6	Our preference would be for disagreements relating to the assessment done under CAP being ultimately resolved by member states 'opting out' on an individual basis. This would prevent long delays in relation to appeals etc.		National opt-outs will defeat the object of a co-ordinated assessment. A referral to "commission" level is not specific enough for comment. –What body would assess? What would the timelines be? How will their decision be made binding on dissenting states?	A decision to opt out (and the concerns raised) should be passed on to EU Commission/EMA. Unresolved issues should be referred for EU level decision, and heard by independent body. Such a body could be part of the monitoring and oversight of the conduct of CAP.	
7	We consider that the CAP should be mandatory for all multinational clinical trials. 120 trials per annum is manageable in terms of administration. The majority of these trials will be conducted by pharma companies who have the resources to pay fees to support the infrastructure. High fees would however be more problematic for academic trials.	Regarding whether CAP should be mandatory or optional, we would prefer mandatory for all clinical trials if it means there will be greater consistency in the EU Directive, and if the application process remains consistent whether one MS is involved in a trial or several. For example, if it would mean applying through a single EU portal, possibly with an application form covering key trial issues covered under CAP, and then routed back to the concerned MS (even if this is just one MS).	The co-ordinated multinational facility of the CAP will mainly benefit commercial companies; there is little benefit to the non-commercial CTUs who more often work in a single country only. The option to use a national application route should be preserved for these trials.	Mandatory for all' is preferable, however would require significant resources and support. 'Mandatory for all multi-national'/'optional' could both perpetuate differences and potentially lead to two-tiered system. In addition, this would mean that a national trial approved according to national procedures would then have to revert to CAP at amendment in order to become multi-national.	The CAP should be used only in multinational trials (option B)
8	We note, however, the potential for variable and over-cautious interpretation of the provision that the IMPs be 'either authorised in a member state in accordance with Directive 2001/83/EC or Regulation 726/2004, and	However, we would hope that this would not result in the assessment of lower risk trials taking priority over higher risk trials.	Provided there is a robust and widely accepted assessment of the risk as minimal; national regulatory authorities vary widely in this regard. An EU equivalent of the FDA "Generally Recognised as Safe" category is also strongly recommended for "IMPs" that are	Additional comments: - In (a), for clarification, does standard treatment refer to any indication? - ie are IMPs used within 'broad' indication (eg in 'cancer' - use in one cancer for first time, but licensed and used as standard in another) included?	The MHRA/MRC Risk Adapted Approach within the UK should be followed with the CAP used only in multinational trials 'Standard treatment' may differ between countries, a clear process / decision tree for how

	used within the authorised indication; or part of a standard treatment in a member stated concerned' (our emphasis). In the situation that an IMP is used outwith its authorised indication but is (part of) a standard treatment in some but not all of the member states concerned, an over-cautious interpretation might mean that the trial was not classified as Type A.		essentially food additives or similar.	- 'standard treatment' differs between countries. - The wording in (b) may need clarifying. In particular: How is it decided what is significant? The term 'interventions' is used, how is this defined in this context? - as a change is proposed to include 'non-interventional' trials within the scope of the directive (point 2.3), what affect will this have on 'non-interventional' trials currently falling outside the Clinical Trials Directive?	cases such as this would be handled without necessarily changing the trial from a 'type A' trial would be required
9	Do not agree with the appraisal. We believe that a wider and consistent (across member states) definition of 'non-interventional trial' should be addressed, thus limiting the scope of the Clinical Trials Directive. The approvals process outside the EU Directive is sufficiently robust to ensure that these studies are conducted safely, as local independent risk assessments are carried out.		Whatever the outcome of this consultation exercise, non-interventional will trials still require: oversight from a data protection perspective and assurance of adequate data quality . Therefore they should be subject to those aspects of the clinical trials directive.	Extending the definition of 'non-interventional' trials and including within the scope of the Directive would imply that the scope will need to be redefined, as non-CTIMPs currently not falling under the Directive will then need to be included. What would be the intention here? Would it be preferable to have an absolute definition of an interventional trial, so anything falling outside of the definition is automatically non-interventional?	We agree - A wider definition of non interventional trial is not supported A risk based approach to working is fully supported as per the UK MHRA/MRC approach
10	What the academic community objects to is having standards developed for early phase and pre licensing studies applied to post marketing or extended indication studies. Industry can withstand the application of the same standards across all their trials but this approach has had a major adverse effect on the ability of academia to perform studies and led to an				

	exponential increase in cost with arguably no discernible improvement in patient safety..				
13	We do not feel that any other key aspects relating to risk assessment are needed as the application dossier appears to be extensive and comprehensive.	In terms of a risk adapted approach, we would like more detailed guidelines/exemptions on 24hr-unblinding, AE reporting (not SAE), site set-up, and close down of trial sites (there used to be a draft EC guidance for non-commercial trials, but this document has now been withdrawn).	Agree, provided that clear guidelines are set out for what is required in an Investigator Brochure and IMP Dossier for low risk trials.		
13		The EU Directive hardly mentions SmPC, although there are many references to the IB, so more on SmPC would be useful, as well as more detailed general IMP guidelines (not only on auxiliary medicinal products).	However, if a reference is a compound with an existing marketing authorisation, it should not require the same level of IMP dossier as an experimental compound.	The appraisal refers to dossier requirements and labelling for 'auxiliary medicinal products', there are currently no labelling requirements for NIMPs, it would be important not to extend this. Please can NIMP guidance be updated – in particular to ensure any requirements for accountability are commensurate with nature and status of the product, and in particular where the NIMP is licensed product in routine use that standard hospital practise may apply.	Agree but it would not be desirable to increase the level of monitoring, labelling etc for 'auxillary products' where the trial is of a low risk i.e. comparable to standard care.
14	**<u>Our preference would be for obligatory indemnisation by Member States</u>**, regardless of the risk level of the trials. The indemnisation should, as proposed, take into account the national legal system for liability. **We feel that the word 'optional' in the second bullet point is confusing, since the paragraph then**	With regards to insurance/indemnity, agree with having both options	Disagree. Removing the indemnity requirement for low risk trials is dangerous. In the event of an incident on a trial, it will leave organisations open to legal action for negligence on the grounds that the trial should not have been categorised as low risk. There may be a case for guidelines on	Either option involves risk to MS, which would need to be a national choice, and may depend on existing national health care systems and national indemnity schemes. Could be concern that if indemnity/insurance not required, or is met by MS, rather than Sponsor/Institution there is less	Agree with Option 2. Strongly disagree with Option 1. There is no justification for removing the requirement to have insurance in place; this would mean that in the event of an incident an organisation would be open to legal action and would have no indemnification.

	goes on to say 'This policy option would put Member States under an obligation to provide for indemnisation…'		what sum is adequate, but this is considered to be a national issue. Passing the indemnity liability on to (effectively) national governments of member states is unlikely to meet with favour from national legislators.	onus on institution and investigator for due diligence. EC should clarify/stipulate required terms of clinical trials insurance policy.	
15	We would also add that greater clarity is required in respect of the definition, role and responsibilities of "sponsor's legal representative in the EAA". The most acute difficulty/issue for academic trials seems to be the legal relationship between the sponsor and EAA. This is straightforward for companies but we have some concerns that the relationships and contracts between an EU academic organisation as legal representative and an academic sponsor external to the EU (e.g. a US University) may not be sufficiently robust in terms of what the EU CTD expect. A key issue is for the EU to define very clearly what aspects, activities and responsibilities, if any, should be delegated to the legal representative and what the implications in respect of indemnisation are.				Disagree with the appraisal. Option 2 is the preferable option. Option 1 relies strongly on a number of provisos including truly harmonising all MS and sharing the necessary information to support multinational research
16			Strongly disagree. The condition "The trial participant has not previously expressed objections" is potentially widely subject to misinterpretation. The		

			need for retrospective consent in emergency situations is recognised, but this should be dealt with on a trial-by-trial basis, not by high level legislation.		
17	Supporting capacity building in third countries appears fiscally impractical. **However, as currently applied, there is over-emphasis within GCP on process issues, rather than core ethical issues.**	No comment	Qualified Agreement Registering the trial with EudraCT is worthwhile, but this must not add to the regulatory burden, it should be a registration only and not subject to any kind of approval from European bodies	However, it would be difficult to enforce the requirements of EU MS if they are above those of the national regulatory body, particularly in countries where a local sponsor is mandated by national regulations.	
4. Figured and Data	Broadly speaking, we think the time and cost estimation for initial submission is low but other costs in the Annex under sections 6 and 7, appear to be realistic			None to present.	
Comments received from/additional input	Elaine McColl, Director NCTU, The response, has input from Newcastle upon Tyne Hospitals NHS Foundation Trust as the sponsor of the majority of NCTU non-commercial trials.	Dr Ann Gerrard Quality Assurance Manager Cancer Prevention Trials Unit (CPTU)	Edward Gosden	Comments from: Nicole Gower – Regulatory affairs manager CR UK & UCL Cancer Trials Centre Roisín Cinnéide – Pharmacovigilance Coordinator – CR UK & UCL Cancer Trials Centre	Comments from: Julia Brown (Director), Vicky Napp (Operations Director), Gillian Booth (Operations Director)