**Proposal for a Clinical Trial Regulation**

The European Commission has recently published its proposals for a new Regulation to replace current the Clinical Trials Directive.

The NHS European Office is seeking views on the proposed Regulation in order to assess the impact of these proposals on the conduct of clinical trials on the NHS and influence the EU decision-making process. We have identified some aspects of the proposed Regulation that are most relevant to the NHS, and would welcome your response to a number of questions on these issues set out below.

We also welcome your views and comments on any other aspects of the proposed Regulation which you consider may be problematic or could be further simplified.

**Key Questions**

**1. Definitions: Low interventional clinical trials: Article 2.3**

Are you satisfied with the definition of low- interventional clinical trials?

*A number of the responding CTUs were satisfied with this definition. However, several raised concerns (often highlighting the same issue, albeit in slightly different words) and/or suggested changes with respect to (b) and/or (c) below, as indicated below.*

*One CTU said “We fully support the introduction of a risk proportionate approach that will be employed throughout the EU. However we are concerned that the work by the MHRA, MRC and others on risk adaptation is not fully reflected within the new low-interventional framework provided by the proposed regulation. Further clarification is required on this point.*

*We believe that there is an opportunity to extend the category of low-interventional studies, perhaps through the use of a sub category, to include the low risk nature of many trials that use marketed products with a well-known safety profile, outside of their indications e.g. the use of aspirin for cancer prevention, so that this category is not limited to within licensed use. Such studies are of great importance to public health and pose very little risk to participants, so we would prefer an approach that better facilitates delivery of these studies.” This CTU went on to say “We are pleased to see the Commission’s attempt to define the scope of the Regulations in an inclusive manner, rather than the previous Directive, which relied on examples of studies that were not within scope. However, we believe that further clarity is required to ensure appropriate interpretation of scope. In particular, the definitions could be read to include retrospective studies; and in 2(e) the use of the phrase …”diagnostic or monitoring procedures” needs to be specifically defined. The term ‘low-interventional studies’ is misleading and confusing; we would suggest that it be replaced with ‘low-risk interventional trials’ or ‘low safety risk studies’*.”

*Another replied “ Although we welcome the attempt at introducing a risk based approach to the implementation of the regulation we believe that this does not go far enough. The regulation should focus on truly investigational or novel products. For example many academic trials utilise marketed products within a new indication. Often the safety profile of these drugs are well defined, however under the proposed regulation these trials would be subject to the same stringent safety and administrative burden as first in man trials. We feel that this is not appropriate. An additional intermediate risk based category should be introduced for trials of this type (similar to that employed in the UK).”*

*Two CTUs also referred to the lack of explicit mention of placebos in this definition.*

*“There is no explicit mention of trials involving placebos. The implication of Article 2(3)(a) “the investigational medicinal products are authorised” is that they are not included, but an explicit reference would be helpful.”*

*“It would seem that placebo-controlled trials can never be ‘low-intervention’ because the placebo would not be an authorised product.  We should ask that placebo-controlled trials that would otherwise be classified as ‘low-intervention’ be recognised as low-risk.  It may be that they cannot be considered ‘low-intervention’ in terms of the authorisation, but they certainly should in terms of trial conduct. “*

Would you make any changes to this definition, particularly with regards to the following wording:

3.(b) ......'standard treatment in any of the Member States concerned.'

*The collective comments indicate the need for greater clarity regarding what is meant by ‘standard’, e.g. is it for the clinical condition under investigation (regardless of whether licensed for that use/used within the terms of its MA), and in all or some of the countries participating in the trial.*

*“What is meant by ‘Standard treatment’ could be clarified and how it is standardised across the EU (e.g. what is standard treatment in one country may not be in another). It may be challenging, particularly for non-commercial sponsors, to identify what is standard treatment across all member states and (the definition) needs to consider within country variability as well.  It also needs to be clarified that it presumably means standard treatment in the clinical condition under investigation.”*

*“We are happy with this suggestion; in particular this would help in (eg) paediatric trials if the medication is not necessarily licensed for use in children but is routinely used as standard”*

*“Introduction of this definition is welcomed along with the spirit of introducing risk proportionate regulation relevant to the risk of the clinical trial compared with standard treatment practice. There may be some implementation issues with the definition around:*

* *For multi-national trials whether it will acceptable to countries where the treatment is not used in accordance with the terms of the MA and is not standard treatment that this is classed as a low interventional trial because it is standard treatment in another of the countries involved in the application.*
* *For multi-national trials where the trial would not be classed as low interventional in any member states but an additional member state later approves the trial where the treatment is standard treatment in that country; what practically would happen in terms of implementing a risk adapted approach across the whole trial and whether it would be justified.*
* *In some cases an IMP may not be used in accordance with the terms of the MA but there may be extensive class evidence of its use – if this is permitted to be interpreted as ‘standard treatment’ within a member state then it would make this definition more acceptable and ‘workable’.”*

*“Definition of low-interventional trial. When it mentions that this would be defined as “standard treatment in any of the Member States” I wonder whether as this can be so variable across the NHS (let alone the rest of Europe), would we need to seek clarification/confirmation from the MHRA with an explanation that the IMP is considered standard treatment in the NHS before we can proceed (am thinking in terms of timelines)?”*

 (c) '......' minimum additional risk.....'

*“’‘Minimal additional risk’ is open to interpretation, and who decides whether risk is minimal? This is essentially a good idea and is presumably down to the sponsor to propose, but who gets to agree the categorisation. Would competent authorities in different member states accept a lead authority’s classification (e.g. if we get a trial classified as low risk under the new MHRA approach, will that be the same for each member state?) “*

*“In principle, this is acceptable, but the definition of ‘minimal’ may be difficult to interpret (eg 5ml extra blood taken as part of an existing blood drawn vs 5ml taken on a stand-alone basis). This section could be usefully expanded to give some examples of what is envisaged as ‘minimal additional risk’*.”

*“The Q&As could be used to further define these terms in order to allow appropriate interpretation of the definitions in line with the spirit of the new Regulation.*

*The MHRA’s recent publication on Risk Adapted Approaches to Clinical Trials Management is a useful document to refer to for further practical definitions.*

[*http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/News/CON126145*](http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/News/CON126145) *“*

**2. Co-sponsorship arrangements: Article 69**

Are you satisfied with the proposal to allow co-sponsorship arrangements when conducting clinical trials?

*Views on this point were mixed, reflecting in part current practice in the CTUs and partner organisations regarding co-sponsorship.*

*““It is key to the functioning of our unit that we have co sponsorship allowed.”*

*“ We are very supporting of the inclusion of the option to co-sponsor clinical trials.”*

*Specific concerns raised are set out below.*

Do you consider the proposals in Article 69.2(a) and/or (b) would pose any difficulties, and if so why?

*“Generally OK with the idea of co-sponsorship, however agreements between co-sponsors would need to be very detailed to cover legalities; this could have a direct impact on timelines for trial set up.  What might the impact be on liability and insurance? Would it be helpful to consider developing some exemplar models of co-sponsorship as reference points to help speed the processes?”*

*“Although our Trust/university choose not undertake co-sponsored studies here, we are happy with the proposal in principle.*

*The main issue, we feel, is that article 69(2)(a) and (b) do not take account explicitly of which organisation takes on responsibility for indemnification, although we note that Article 74 does outline the “corrective measures to be taken by Member States”.*

*However, more guidance on the potential split of responsibilities with regarding to liabilities and associated indemnification would be helpful.”*

*“The Explanatory Memorandum, 3.8, explains the need for co-sponsorship by stating that clinical trial networks may have “practical or legal difficulties” in deciding “who amongst them would act as ‘single sponsor’” or “forming, jointly, one legal entity to act as ‘single sponsor’”. However, the proposal would still require co-sponsors to elect a single “sponsor who can take measures requested by a Member State, and who can give information on the clinical trial as a whole”. It is not clear how the stated practical or legal difficulties would be overcome as the co-sponsors seek to establish an overall sponsor. Also, there is a risk that responsibility will be weakened if divided between multiple sponsors*.”

**3. Start, end, suspension, temporary halt and early termination of trials: Articles 33 - 34**

Are you satisfied with the reporting times proposed for the start, and end/early termination of clinical trials?

*“General comment – throughout the document it would be helpful to be consistent and clear as to whether working days or calendar days are being referred to.”*

*“This depends on the efficiency of the reporting system, and the type and amount of data required. Timelines that are too ambitious may lead to a decrease in the quality of data.”*

Do you have any additional comments on the requirements for notifications: Articles 33 and 34?

*“It would be useful, in order to prevent any ambiguity, that ‘serious’ were added before ‘adverse events’ on line two of the paragraph.”*

 Do you consider the requirements to be adequate and/or proportionate?

*“Need to be clear if we mean randomisation or recruitment (when we refer to ‘start’). Many studies will be having screening visits before baseline and randomisation at the start, so may want to tie start to consent. (With) The advert of more flexible and adaptive designs, with the potential for multiple randomisation stages, the end can also be unclear (last consent or last randomisation). It would be helpful to be clearer in definition terms of some of these key points.*

*For both start and finish notifications it would be useful to be clear if it is first and last patients within each member state or of the whole trial that require the timeline for notifications.”*

*“Article 34(5) includes the statement: “…where the clinical trial provides for a primary completion date prior to the end of the trial…” It is not clear what is meant by the phrase ‘primary completion date’ so a definition should be provided.”*

*“Largely yes. However it would be useful to define whether the ‘last visit of the last patient’ is the last treatment visit, last visit into the hospital, last data item. Particularly in academic cancer clinical trials (assume low interventional) there may be long periods of follow up for patients (for survival only) e.g. up to 15 years and during this time it may be deemed unnecessary to actively monitor for SAEs and SARs therefore an Annual Safety Report / Developmental Safety Update Report may not be deemed necessary to generate. The understanding and acceptance of this situation within the Regulation would be desirable.”*

*“There is a specific issues with regard to the notification of end of recruitment if the 15 days commences following recruitment of the last patient. In academia multicentre trials often close at a specific time point rather than after recruiting an exact number of patients. Centres will be given advanced written notification of the planned recruitment closure e.g. one month. Dependant on the nature of the trial it is possible that few or no patients will be recruited during that month. If the calculation of the 15 days is from last patient recruited this could cause academic units to be in breach of the regulations. Hence a change in academic custom and practice may be required.”*

*“Article 33 requires sponsors to “notify each Member State concerned of the end of the recruitment of subjects for a clinical trial in that Member State” within 15 days. Due to the difficulty of establishing when a particular site has stopped recruiting, it may be difficult for sponsors or CTUs to comply with the 15-day time limit.”*

*Article 34 of the new regulation requires sponsors to notify all applicable member states of the normal end of the clinical trial within the same period as early termination, i.e. within 15 days rather than the current 90 days. (This applies to the end of a trial in each member state as well as the end of the trial per se.) This allows little time for data analysis prior to submission of the end-of-trial report. Were any non-compliance identified subsequently, this would have to be reported after notification of the end of the trial. The proposal to reduce the time limit from 90 to 15 days would appear likely to cause problems following the submission of end-of-trial reports.*

*The proposal to treat the ‘normal’ end of a trial in the same way as its early termination would not appear to be proportionate”*

*“With respect to Article 34, Reporting of results within one year from the end of the trial. The document states that the sponsor is to submit a summary of results within one year from the end of the trial. If not possible (for scientific reasons) the article states that “protocol shall specify when the results are going to be submitted, together with an explanation”. Does this mean that the trial team would need to submit an amendment to the protocol after the trial is complete? This seems little excessive to me, could we not inform the MHRA in writing or completion of an “end of trial” notification form to explain?”*

*“Article 35 - Temporary halt/early termination for safety reasons – is there a timeline for this? Serious Breaches are seven days of the sponsor becoming aware currently,”*

**4. Safety reporting: Articles 36- 42**

Reporting adverse events and serious adverse event: Article 37

Are you satisfied with the proposals for safety reporting in Article 37?

*“Article 37(2) states that the “investigator shall immediately report serious adverse events…” An explicit timeframe (eg within x days of being notified) should be given rather than ‘immediately’ which is open to interpretation.“*

Reporting suspected unsuspected adverse reactions: Article 38

Would you prefer further clarity regarding the exact periods within which SUSARS should be reported. Article 38 (1) and (2)?

*“Yes, as with the point above, explicit timelines would be very helpful.”*

*“Reporting of SUSARs by the sponsor to the agency. Could do with more clarify over the timelines for reporting SUSARs? A bit too subjective at the moment “time period for reporting shall take account of the severity of the reaction”.*

*“Yes, I would prefer further clarity as the proposed revised regulations do not specify a time frame for reporting SUSARs and use subjective terms such as “severity of reaction” and “timely reporting”. Does this mean that the previous requirements for fatal and life threatening events (reports to be submitted within 7 days and follow-up report within 15 days) and for non-fatal and life threatening events (to be reported within 15 days) still stand? There is still no specified timeframe for submitting follow-up reports for non-fatal and life threatening events? I suspect this lack of clarity will result in the MHRA deciding their own “interpretation” of timely and severity, where one clear European standard would be much more helpful.*

*Article 38, 3. – It is unclear if this provision allows the Sponsor to delegate reporting a SUSAR to another institution based in the member state where the SUSAR occurred. I am thinking of the scenario we have for trials with sites in other EU countries, where each country has a Sponsor as well as having the “overall” Sponsor in the UK. For example If a SUSAR occurred in a Spanish site, it would be very helpful if the UK Sponsor (who was co-ordinating the whole trial) could identify and prepare the SUSAR report but ask the Spanish Sponsor to report the SUSAR to the Regulatory Authority in Spain for adding to Eudravigilance. It is unclear if this would be permissible.”*

*“These are clarified in Annex III”*

*“Yes.. It is inconsistent that the time frame for reporting of SUSARs is vague given the tight time lines for reporting trial opening etc. as defined in articles 33 -34.”*

*“Yes. If the time period for the reporting of SUSARs were shorter than that which currently applies in the UK, this may make compliance difficult”*

Annual reporting: Article 39

Do you consider the proposals for annual reporting to the Agency to be workable?

*“Whilst the information should be to hand, we have concerns that for non-commercial organisations the resources to collate such a return may not exist to the same degree as for commercial organisations. “*

If not, what problems do you anticipate would occur when aiming to comply with the requirements?

*“Need to consider what happens if there is a trial run, then a hiatus and then another trial run using the same IMP. Does the reporting just restart? Could a sponsor become retrospectively non-compliant (because it has a new ‘last trial’ and a cessation of reporting from the previous ‘last trial’). This seems to reflect the pattern of research in industry rather than the non-commercial sector. Article 41 is better phrased as reporting requirements are tied to each individual trial.”*

*“The Development Safety Update Reports (DSURs) can be difficult for non-commercial organisations to compile swiftly, maintaining accuracy. Also, for large research-active trusts, there may be more than one trial using the same IMP, but the organisational structures/resources may not allow for rapid cross checking between trial DSURs to pick up any IMP-specific issues.”*

*“Article 39, 1. – Appears to be aimed at Marketing Authorisation Holders (MAHs), where is would make sense that an Annual Report (DSUR) would be required for the drug they manufacture and have, or have had, a clinical trial programme for. Therefore safety reports should include all the available information for the product. However I do not think non-commercial organisations and how they function has been considered. Non-commercials more often are not taking a drug to license, do not have a programme of clinical trials for one drug, but often have multiple trials looking at different IMPs and IMP combinations, often with the IMP provided by a Pharma company.*

*Currently we submit DSURs per trial. Some of our trials include multi-drug regimens. If Article 39 .1 comes into force then we will have to produce a separate DSUR for each IMP for each trial, meaning having to produce multiple DSURs for the one trial. Apart from the resources required to do this (we don’t have them), it does not make sense from a safety perspective as it is the safety of the combination of the IMPs for that trial that should be looked at. So for the common scenario I have outlined, I see this requirement as a waste of limited non-commercial resources to produce many reports when one report to discuss the safety of trial participants would better protect participants. It would be very useful if this article had some proviso for organisations who are not manufacturing the IMP.”*

*“The requirement in terms of content and preparation of DSURs has been difficult for academic sponsors in the main because they do not focus their research activity on certain IMPs, rather disease areas. Examples being; DSURs have been required to be reported for one IMP being used in several different trials all in very different disease areas; pharmaceutical organisations not willing to collaborate to receive information from academic trials for integration into their DSUR reports, DSUR reports requiring reporting until the Notification of End of Clinical Trial which in some cases is many years after the last patient received the IMP (e.g. cancer trials where patients are followed up for survival). The Annual Reporting detailed in Article 39 remains centred around reporting for an individual IMP which will not resolve the problems experienced in implementing the DSUR.*

*Possibly a simple template for low interventional trials could be considered for annual safety reporting to the Regulator rather than the DSUR.”*

*“The Regulation states that annual reports must be produced for IMPs for non-authorised products and products that are used outside the terms of their licence. The inclusion of products used outside of their licence raises certain issues for reporting safety, which mainly concern the fact that marketing authorisations are rarely kept up-to-date with standard practice:*

*The regulation states that a report on the safety of each Investigational Medical Product (IMP) should be submitted annually. It is not clear whether this is one report per trial or one report per IMP. It is often difficult for academic organisations to report on an IMP basis. Many NHS and University’s do not have the resources available to create and maintain a central organisational adverse event database. In addition, many academic trials include combinations of IMPs which make it very difficult to report on the level of individuals IMPs. In the UK the MHRA allow academic sponsors to report on a trial specific basis. A similar provision for academic organisations should be included in the regulations.*

*Clarification regarding the procedural process is required before the full impact of these changes can be properly assessed. For example:*

*1. No mention is made of using the recently introduced Data Safety Update Report as the template for providing the annual report. Will the use of this template continue?*

*2. It is unclear what the mechanism for electronic reporting will be. If this is via EudaVigilance this may be problematical for NHS and academic sponsors.*

*3. The current guidance defines the timelines for the annual report data freeze date and allows 60 days for the preparation of the report. Clarification is required as to whether this will still apply.*

*“Annual reporting by the sponsor to the agency. What about reporting for “low-interventional” trials (products that are being used within their MA?) to the Agency? Or will they now just be reported to the MA holder as per article 41? I found this a bit confusing.”*

Annual reporting by the sponsor to the marketing authorisation holder: Article 41

Do you consider the proposals for annual reporting to the marketing authority holder be workable?

*A number of responses cross referred to the prior response by that CTU re Article 39, indicating that the same concerns and issues applied.*

*One respondent noted “This is in principle a good idea but would be difficult to comply with.”*

If not, what problems do you anticipate would occur when aiming to comply with the requirements?

*“For early phase trials where the IMP is unlicensed, we are already informing the MAH of SUSARs. However we have a few late phase multicentre trials where the IMP is licensed and where the IMP comes from the sites own “off the shelf supplies”. Often these drugs are produced by multiple manufacturers and the site uses drug from locally agreed manufacturers. So the Sponsor will not necessarily know who all the MAHs are. We have one trial of over 200 sites all using of the shelf IMP manufactured by different MAHs. Checking this with the sites would be very cumbersome. As we are required to report SUSARs to the Regulatory Authority surely it would make more sense for the Regulatory Authority to inform the manufacturers of SUSARs as the Regulatory Authority is the organisation who grants and therefore knows which organisations hold an authorisation to manufacture the drug, and the organisations details?*

*It will be very difficult to inform MAHs in other countries where we would have to contact them in their local language. Another requirement that impacts on resource!”*

“*In many low interventional trials ‘off the shelf’ IMPs are used in combination with the IMP under investigation (e.g. adding a new chemotherapy agent to an existing regimen). In such cases these IMPs may be available as a generic product which is ordered independently by the individual NHS organisation – therefore there is no direct link between the Sponsoring organisation and the manufacturing authorisation holder. The responsibility for reporting to the marketing authorisation holder is that of the Sponsor – co-ordinating this for many sites (in a large national or international multi-centre trial) would be a significant amount of work and very difficult because the individual supplier would need to be collected for each dose of IMP given to each patient.”*

“*It is not clear what type of medicinal product this regulation applies to. This needs to be clearly defined. It would be extremely burdensome to the NHS and academia to report SARs for auxiliary investigational medicinal products.*

*In the NHS and academia authorised investigational products may be dispensed “off the shelf” from hospital pharmacy stock. Multiple brands can be used within a trial. The brand name or manufacturer may not be available to the sponsor. Hence it will be very difficult for sponsors to comply with this clause in this situation*.”

***“****Article 41 requires the sponsor to inform the MAH of all SARs where they are using an authorised medicinal product (presumably both IMPs and auxiliary medicines) within the terms of the MA.  I can imagine that this might be extremely difficult and onerous (if not impossible sometimes) where you are using off-the shelf generic products.  Indeed in strategy trials you often would not know which particular product was being used.”*

*“Annual reporting by the sponsor to the MA holder “sponsor shall inform annually the marketing authorisation holder of all suspected SARs”. Not sooner for SUSARs? What about timeframes? Will there be a standardisation for reporting to the MA holder? I this could be very variable otherwise.”*

**Other areas**

**5. Protection of subjects and informed consent: Articles 28 - 32**

Do you consider the proposed new rules for obtaining consent in emergency situations are satisfactory. If so, would you propose any changes?

*“Broadly, these are satisfactory but we would welcome guidance re the definition of ‘minimal’ risk/burden used in Article 32(1)(e) “the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject” in the context of ‘clinical trials in emergency situations”’.*

 *“The use of the term ‘prior interview’ implies that there has to be face-to-face interaction prior to consent. In some settings this may not be feasible.*

*Emergency settings justification is OK, but the issue which has been raised by other studies is where a consideration was made that a set time window could be used to gain legal consent, but the delay of that time window (e.g. 4 hours) was shown to be detrimental to the patient. Does this section need to relate to the risks to the individual of delaying treatment (even if experimental)?”*

“*A clinical trial regulation that would facilitate harmonised emergency care consent procedures across Europe would be welcome. However, as currently written the criteria would once again stop emergency care research. The proposed regulations specify that information about the clinical trial may be given after its start, and informed consent obtained subsequently to continue the clinical trial, provided that* ***all*** *of the following conditions are fulfilled:*

*(a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, it is impossible to obtain prior informed consent from the subject and it is impossible to supply prior information to the subject;*

*(b) no legal representative is available;*

*(c) the subject has not previously expressed objections known to the investigator;*

*(d) the research relates directly to a medical condition which causes the impossibility to obtain prior informed consent and to supply prior information;*

*(e) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject.*

*Criteria (a) and (b) could be conflicting. Criteria (a) clearly specifies that it is the urgency of the situation that prevents the informed consent process from occurring. However, criteria (b) states that if a legal representative is available then deferred consent could not be used, even in an urgent situation meeting criteria (a), as a representative would have to provide consent prospectively.*

*This does not take account of the practicalities of emergency care research and the need to consider the impact of delaying treatment to obtain informed consent from an available representative, or on the ability of that representative to understand trial information and make a decision under intense emotional strain and severe time pressure[*[*3*](#_ENREF_3)*,*[*4*](#_ENREF_4)*].*

*Analysis of data from the Medical Research Council (MRC) CRASH Trial, a multicentre randomised controlled trial of corticosteroid administration in acute severe head injury, provides an estimate of the delay associated with the requirement for written consent[*[*5-7*](#_ENREF_5)*]. The authors convincingly argue that the need for urgent trial treatment, even in patients who are conscious and whose relatives are available, by itself excludes the possibility of fully informed consent. They conclude that seeking consent in emergency care is actually unethical if consent procedures delay the start of trial treatment resulting in obscured or reduced treatment effects.*

*In patient and carer surveys, deferred consent has been found to be acceptable to the majority[*[*8*](#_ENREF_8)*,*[*9*](#_ENREF_9)*]. Deferred consent raises ethical dilemmas such as how to handle the situation where the patient dies before deferred consent can be sought; and the potential that the decision to decline is associated with a patient’s outcome, which could create bias in the trial results and conclusions[*[*10-12*](#_ENREF_10)*].*

*The proposed regulations should focus on the urgent need to treat as the requirement for deferred consent with the removal of clause (b), which relates to the presence of a legal representative. Further regulations should consider the ethical dilemmas raised above, and additionally, questions about data collected prior to deferred consent and whether the consent is for continuing in the trial only, or to allow use of the data collected to that point.*

***References***

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*11. Jansen TC, Bakker J, Kompanje EJ (2010) Inability to obtain deferred consent due to early death in emergency research: effect on validity of clinical trial results. Intensive Care Med 36: 1962-1965.*

*12. Nichol G, Powell J, van Ottingham L, Maier R, Rea T, et al. (2006) Consent in resuscitation trials: Benefit or harm for patients and society? Resuscitation. pp. 360-368."*

*" We share the concerns expressed by Colin Wilsher (BARQA Quasar Magazine, No.121, October 2012, p.30), that Article 32 (1,e) may be “challenging as frequently emergency research may involve more than minimal risk, precisely because of the emergency nature of the case”.*

*"* *Changes to the EU Directive to enable informed consent to be obtained after the start of the clinical trial if certain criteria are met are welcomed, and should make obtaining approval for and conducting emergency medicine trials more straightforward. The final condition (e) would prevent any trial of an intervention with more than a minimal anticipated benefit for incapacitated patients presenting with a medical emergency. Trials are only ethical if the potential risks and benefits of the intervention are in equipoise. A trial of an intervention that only posed a minimal risk to the patient would only be in equipoise, and therefore ethical, if the potential benefit of intervention was also minimal. If the potential risks were minimal and the potential benefits were substantial there would not be equipoise. Many important interventions for incapacitated people with medical emergencies have substantial potential risks and benefits. For example, neurosurgery to urgently remove a blood clot from the brain or clot-busting drugs for stroke or heart attack. Condition (e) would prevent trials of these important emergency interventions and limit trials to interventions where the potential risks and benefits were both minimal."*

*"Article 32 (1 e) Consent in emergency situations. “Clinical trial poses a minimal risk to, and imposes a minimal burden, on the subject”. This is quite subjective in terms of what would be classed as a “minimal risk”. In our (non- CTIMP trial) in an emergency setting, the wording is more along the lines of … if the benefits of the trial/study could outweigh the risks… which makes more sense to me.*

*Article 32 (2a) Information given to subject as soon as possible (following consent from the legal representative) is retrospective consent obtained too?*

*Article 32 (2b) Other subjects – who does that include?"*

*"There are potential problems with 32 1b and 1e:*

*b) A legal representative can be available - but it would be inappropriate to consent e.g. you are doing a cardiac arrest trial - what do you do? In trauma - the patient takes over an hour from injury to get to hospital (he had to be cut out), relative arrived, how long do you spend to obtain consent (the regulation is not saying assent or brief information here - it is the full 20 element GCP requirement....)!*

 *(e) minimal risk in critical and emergency care......this would be a problem in many cases - e.g. you want to treat septic shock which has a 50% mortality - you might have to try interventions which might not be of minimal risk - what we can do is minimise the risks.*

**6. Compensation for damages and national indemnification mechanisms: Articles 72 -73**

Do you consider the proposals for introducing national indemnification mechanisms for non-commercial sponsors to be helpful?

“*Yes, this will be helpful particularly for international studies*.”

*“Does this relate to both the NHS and HEI as sponsors? What would happen if a study was funded by industry, but as an investigator initiated study (not to be used for licensing) and then subsequently used for a licensing application? Does the fee get applied retrospectively?”*

*“We agree that low-interventional clinical trials should NOT require the same level of scrutiny in this regard.”*

Do you anticipate any problems or difficulties with the introduction of these mechanisms in either the UK or other Member States?

*“It may be difficult for the Sponsor Organisation (where they are non-commercial) to ensure that all Member States have provided appropriate level of compensation. For non-commercial studies, sponsor insurance policies are typically based on the level of compensation required in the Member State in which the sponsor is based; if higher levels of compensation are required in other Member States participating in the trial, this can be a challenge and an expense.”*

“*The only difficulty, as with many of the other aspects of the Regulation will be in convincing organisations to review their processes and ensure they are risk commensurate. The Regulators and other national bodies will be key in providing reassurance and guidance to Researchers and Sponsoring organisations to ensure that the spirit of the Regulation as well as the letter of the law are followed.”*

“*Clarification is required as to whether UK patients would be covered by NHS indemnity and whether this also negates the requirement of academic organisations to hold indemnity for the development and management of the trial.”*

**7. Are there any other aspects of the Regulation that you wish to comment on, and/or do you consider there are any other areas of the proposed Regulation that may be problematic, or could be further simplified?**

*“Article 52: Investigator’s Brochure (IB) – provision of the IB (and annual updates to IB, as opposed to the SmPC) can be challenging for non-commercial organisations (especially if the drug used is off-patent)*

*Article 55: Archiving of the clinical trial master file – “The sponsor shall appoint individuals within its organisation to be responsible for archives. Access to archives shall be restricted to those individuals”. Physical restriction to the identified person may be difficult (could this be limited to an agreed process, rather than a specific individual?)*

*Practical concerns re the database to be used – portal-access has not historically been good and we would be concerned with regard to the management of the database itself; for example, licensing requirements for access, etc.”*

“*The Regulation does not include reporting of Serious Breaches (which is a UK addition to the Directive when it was implemented into the Clinical Trials Regulations within the UK); it would be helpful to know whether this will be an ongoing requirement once the Regulation is implemented.*

*It would be helpful (possibly in the Q&As once written) to have further detail around risk proportionality for IMP handling (in terms of tracking and drug recalls) for low interventional trials. The Regulation makes provision for this but this would be a key relevant area for risk proportionality.”*

“***Terminology***

*Changes in terminology (e.g. Auxiliary Medicinal Product i.e. non-investigational medicinal product; substantial modifications i.e. substantial amendments etc.) should be avoided as there is the potential to cause confusion and updates to quality management documentation will be burdensome with no apparent benefit.*

***Single European Portal***

*There is concern that popular member states may be swamped with applications which may be to the detriment of national studies.*

*There is concern that access to the portal and reporting database will be limited to one or two individuals within the sponsor organisation. Within many NHS and academic organisations the governance resource is not sufficient to support central reporting. To avoid delays in reporting access should be available to the coordinating trial team.*

*Will the single portal be compatible with IRAS?*

***Data Submitted in the Application Dossier***

*Article 25, 3 states that non-clinical data will be required to be based on EU Good Laboratory Practice (GLP) studies and clinical supporting data should be based on trials registered in a public register. Academic studies often draw data from publications by third parties where it may not be possible to determine if they have been run in accordance with full GLP and/or may not be in a public database. This issue may hinder academic studies from taking place.*

*There is also concern that more data will be required.*

***Decision of a Clinical Trial***

*Article 8, 2a stipulates that non-reporting member states may disagree with the reporting member state if they deem that there are significant differences in normal clinical practice which would lead to patients receiving inferior treatment. Normal clinical practice differs significantly across Member States and therefore there continues to be scope for Member States not to participate in multinational trials. This is particularly problematic for trials in rare cancers in which there is little or no evidence base on which to base a definition of normal practice. Sponsors should ideally be able to check what constitutes normal clinical practice in different Member States to help streamline the application process.*

***Assessment Report – Aspects Covered By Part 1***

*Article 2, 1a suggests that scientific review of protocols is being undertaken. The majority of NHS and academic trials will be peer reviewed extensively by funding bodies. Reassurance is required that this will be taken into account during the regulatory review.*

***Definition of an Investigational Medicinal Product***

*The definition of an IMP has not been changed. However one of the fundamental issues with the directive has been in the interpretation of this definition. Under the Regulation, reference products which are used to compare the efficacy or safety of the test treatment are still to be defined as an IMP even if their use is standard clinical practice. We believe that reference products in a trial should not be classified as IMPs if their use is standard clinical practice. The inclusion of the concept of “authorised” and “non-authorise” IMPs only makes this more confusing.*

***Labelling***

*The Regulation appears to require additional information for labelling an IMP, we would want to ensure that labelling requirements are proportionate and supportive of patient safety.*

***Other reporting obligations relevant subject safety***

*Sponsors are required to report ‘unexpected events which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions’. It is unclear as to what these events would be if they are not suspected unexpected serious adverse reactions. In addition, non-serious unexpected adverse reactions would fall into this category. This could lead to significant over reporting.* ***The Reporting of Serious Adverse Events After Trial Closure***

*The annex of the Regulation states that serious adverse events must be reported by investigators to sponsors after the end of the trial. Currently, investigators are only required to submit suspected unexpected serious adverse reactions. Extending reporting to all serious events has the potential to place a huge administrative burden on investigators and academic sponsors and it is unclear as to what the purpose of this requirement is. It will not enhance patient safety.*

***Reference Safety Information***

*With regards to the Development Safety Update Reports the Regulation has not taken the opportunity to remove the contradictory guidance regarding Reference Safety Information (RSI) contained in CT3. It still stipulates that the RSI must remain for the reporting period but use the most recent for SUSAR reporting.*

***Submitting substantial modifications***

*The guidance on what qualifies as a substantial modification provides less clarification than that of a substantial amendment in the previous Directive and guidance. The lack of a clear definition of what constitutes a non-substantial amendment is a concern.*

*We believe that the Regulation possibly reduces the responsibility of a sponsor to assess whether a modification to a trial should be considered substantial. Due to unclear definitions and processes, sponsors may feel that they would need to submit all changes to the trial protocol to be assessed by the regulator whether it is considered substantial or not. This would create significant amounts of extra work for Member States, sponsors and trialists and would cause delays and additional bureaucracy. We believe that the definition of a substantial modification is intended to be more limited under the Regulation, which is welcomed, but the definition itself and the decision and assessment process under the proposed legislation are now unclear and potentially problematic.*

*Further issues arise from the short timelines for response if additional information is requested from the sponsor. The current Regulation states that requests for information must be met within six days, this could represent a serious challenge for academic trials units.*

***Presumed approval***

*Throughout the document there is an assumption that approval (e.g. for an amendment or initial application) is granted when a Member State does not respond within stated timelines. However, we would prefer to have confirmation of approval in order to maintain a proper paper trail.*

***Declaration of Helsinki***

*The explanatory memorandum preceding the Regulation refers specifically to the 2008 version of the Declaration of Helsinki. The use of this version of the statement may be problematic due to the requirement listed in Article 35 of the Declaration which requires patients to ‘be assured of access to the best proven intervention arising from the study’. If mandated, this may cause significant problems for running clinical trials.*

***Paediatric trials***

*We need to understand if this Regulation is going to supersede existing guidance relating to paediatric trials and what possible relationship they could have. The issues highlighted in this document are confounded by the fact that most paediatric treatments, especially in Cancer, are not used within their licensed indications. There are also substantive differences in standard treatment/clinical practice across the Member States.*

*We are also concerned about point h in Article 31 which states that a paediatric trial must have some direct benefit for the group of patients involved. This is a concern as diagnostic trials or similar studies do not immediately confer a benefit on the participants but will help to build knowledge to support care in the future.”*

*“There is a lack of clarity in articles 91 and 92 of the new regulation concerning the length of the transitional period during which trials may continue to be governed by Directive 2001/20/EC.*

*On a positive note, the proposal to establish a single EU portal for clinical trial applications and reporting should simplify procedures for any future trials involving other member states. Similarly it is to be expected that the establishment of the EudraVigilance database will simplify safety reporting.”*

To view the text of the proposed regulation, please see the link below.[**http://ec.europa.eu/health/files/clinicaltrials/2012\_07/proposal/2012\_07\_proposal\_en.pdf**](http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf)

The NHS European Office has produced a briefing which outlines the main changes in the proposed Regulation and this together with our responses to European Commission consultations on the revision of the Clinical Trials Directive may be found below.

<http://www.nhsconfed.org/NationalAndInternational/NHSEuropeanOffice/influencingEUpolicy/clinical-trials/Pages/Clinical_trials_directive.aspx>