Response on behalf of the UKCRC Registered Clinical Trials Units Network of, United Kingdom

The UKCRC Network of Registered Clinical Trials Units* support many elements of the proposed Clinical Trial Regulation and Amendments agreed in May 2013, in particular the move towards risk adapted approaches to trial conduct, the waiver or reduction of fees for non-commercial clinical trials, the provision of a national indemnification scheme for low risk clinical trials and more recent amendments to address concerns around consent in trials relating to emergency situations.

However, serious concerns remain in regard to a number of areas which do not go far enough to achieve the overall aim of reducing unnecessary bureaucracy and stimulating research within the EU. Indeed some of the proposals will instead increase the administrative burden in the conduct of clinical trials, specifically the reference to ICH-GCP as the quality standard for trials, the proposed financing of IMP(s) in low risk clinical trials, electronic archiving of the Trial Master File, blanket inclusion of sub-group analyses for gender and age, and some elements of the proposals for increased transparency. ***We request full consideration of the following key issues by the UK and the Rapporteur in order that the opportunity for the EU proposal to truly facilitate clinical research and meet its intended aims is not missed***.

1. Definitions_____

'Low risk clinical trials are often of crucial importance to assess standard treatments and diagnosis' (Amendment 9) however, unless the definition is applied widely and appropriately there remains a real risk that clinical trials research in these areas will continue to suffer. We have received direct communication from the Commission clarifying that they consider '*standard treatment*' to be a flexible definition however '*Sufficient published evidence*' remains a worryingly loose term and may be better defined within complimentary guidance. **We would consider the following types of clinical trials must fall within the low risk category**:

1. Use of placebo where it does not increase the risk in the trial (Amendments 59 and 61 - AGREED)
2. Trials of a licensed drug for a new condition, at a lower dose or for a longer duration (where there is extensive class evidence of its safety profile) (Amendment 60 - AGREED)
3. Testing established treatments and existing drugs with well documented safety profiles for novel uses that are not standard practice for example, aspirin in cancer prevention.
4. Trials of food supplements or other products that can be sold without prescription

It is unclear whether 3 & 4 would be classed as low risk clinical trials under the current definition; particularly in light of the amendments made to Recital 9 which states that low risk trials '*will only have a very limited and temporary adverse effect – if any – on the subject's health'* (Amendment 9 Recital 9 and Amendment 58 Article 2). For instance, if one considers clinical trials using chemotherapy; even standard treatment is likely to have some adverse effect on the subject's

health and this may not be temporary, but the subject is at no greater risk than they would be through routine care. However, if the Recital 9 and Article 2 principles are applied, many clinical trials in these settings will not be classed as low risk. It is also pertinent to note that the FDA already considers many of the types of trials listed above when conducted in cancer as exempt from similar regulations in the US.

REVIEW AND CLARIFY Article 2 and Amendments 9, 58 – 60: We request further clarification within the Regulation or associated guidance in order that all truly 'low risk' trials may be included in this definition.

2. Good Clinical Practice_____

As a network we are in agreement with the principles of Good Clinical Practice as described in Commission Directive 2005/28/EC. The inclusion of a blanket reference to ICH GCP (Recital 29 and Article 44) as the quality standard throughout this Regulation risks further embedding processes into practice which are not commensurate with the risks of the trial in relation to patient safety or trial integrity (particularly in relation to clinical trial management and monitoring). ICH GCP is largely considered to be an 'industry or commercial' standard and having been un-adapted since 1996 is considered over prescriptive and out of date. Risk adapted monitoring is permissible as detailed in Recital 30 (Amendment 39) and Article 45 and we strongly support these principles. We presume that the requirement to submit a risk assessment and monitoring plan with the clinical trial application will not alter the responsibility of the sponsor in deciding the nature and level of monitoring. The academic community have applied other robust methods of monitoring clinical trials than the traditional on site monitoring for many years e.g. remote statistical monitoring and it would be unacceptable for this work to be influenced by an individual Regulator or assessor's opinion.

REJECT Recital 29 and Article 44. We do not agree to ICH GCP being included as the reference quality standard throughout this Regulation.

3. Pharmacovigilance _____

The changes proposed to Recital 9 (Amendment 9) for low risk clinical trials to be '*subject to the vigilance and traceability rules governing normal clinical practice*' are welcome, however there remains some ambiguity as to what this might mean in practice which we request is further clarified to prevent misinterpretation:

- Can '*vigilance and traceability rules governing normal clinical practice*' be interpreted that for low risk trials pharmacovigilance will be via the legislation set out for marketed products outside the scope of this Regulation? Should this be the case it would negate the requirement for low risk trials to report to the marketing authorisation holder via the Agency (Amendment 209). Amendment 199 would also be in contradiction.

- We request that the wording of Amendment 201 is clarified to include the exemption of low risk clinical trials from annual reporting on the safety of each or all IMPs (Amendment 201). We suggest that following the Primary Completion Date of a clinical trial where the clinical trial includes a period

of long term remote follow up of patients e.g. for survival the active monitoring and reporting of individual events is no longer required.

- The option for the Sponsor of submitting a single safety report on all IMPs used in the trial in the case of a clinical trial involving the use of more than one IMP (Amendment 202). We seek further clarification on whether there is any intention of making annual safety report information publically available during the course of the clinical trial (Amendment 203).

- We question the additional burden of including ethics committees in the assessment of SUSAR reports (Amendment 207)

We cannot support the following amendments to the Regulation:

- Amendment 204 page 107 Article 39a (new) – it would not be possible, other than through comparison of the control arm of a trial with that of another trial, to gauge whether there is an observed efficacy defect related to an authorised medicinal product. This would normally be commented upon at the time of publication if a noticeable difference was seen but could not be identified through individual patient review or interim analyses.

- Amendment 209 page 109 Article 41 para 1 – the amendment requires safety information to be presented by gender and age group which is possible but the amendment justification suggests that the requirement is for an analysis of safety data for gender and age effects. The scope of the annual safety report should not be data analysis and interpretation. Any decision to analyse safety data for gender and age effects should be made on scientific grounds on an individual trial basis at the time of analysis and should not be a requirement for all trials.

REVIEW AND CLARIFY Amendments 9, 202, 203, 209, Recital 26, Article 37 and Amendment 198. There remain inconsistencies and ambiguity in the text in regard to pharmacovigilance requirements for low risk clinical trials

REJECT Amendments 204 and 209. We do not agree with these amendments.

4. IMP Management

Pharmaceutical 'support' of academic trials through the provision of IMP free of charge is not an un-usual situation within the UK, as such the proposed Amendment to Recital 60 (Amendment 51) could have serious negative consequences for many academic trials within the UK.

REJECT Amendment 51. We strongly oppose this Amendment. It would have major financial consequences for the NHS, charitable and government funders within the UK.

5. Archiving _____

Archiving of the TMF indefinitely in electronic format after end of the trial will have major cost implications particularly for academic sponsors which do not have the resource to scan large volumes of paper documentation and format into an easily accessible format. Practical consideration must also be given to changing technologies over time. Given the reason for this proposal is in case of a sponsor being under investigation for misconduct we would seriously question the value of this additional work versus the likelihood of misconduct happening.

REJECT Amendment 223. We cannot comply with this Amendment.

6. Statistical Analysis Plan _____

We do not support submission of the full Statistical Analysis Plan at the time of authorisation; this document will not be available at this time and is typically amended / developed during the trial. We suggest instead that a description of the statistical methods to be employed, including the timing of any planned interim analysis(ses) may be more appropriate.

REJECT Amendment 271. We do not support submission of the full Statistical Analysis Plan at the time of authorisation.

7. Patient Population _____

There are several references to ensuring that the data generated is relevant as well as reliable and robust and we welcome the opportunity to justify this in the clinical trial application if this is not possible (Amendments 17, 18 and 91). The use of over-prescriptive language within the Recitals (Amendment 1) in regard to this is unnecessary.

REVIEW AND CLARIFY Amendments 92 and 272. We have serious concerns with these amendments which suggest an intention to power all trials for a pre-specified sub group analysis by gender and age. This is strongly opposed because it could have significant implications for overall sample size and therefore cost. Such decisions must be made on scientific grounds.

8. Informed Consent _____

Prior interview and provision of information

We welcome the amendment to Article 28 (Amendment 158) to recognise that recruitment for clinical trials also takes place via correspondence. However the emphasis on provision of information both orally and in writing remains in both Recital 24 (Amendment 34) and Article 29 (Amendment 164) which we feel is misplaced; information should be provided in the best format to optimise understanding of that particular

trial in that target population; this is also in contradiction to the amendments made to Article 28. We request further amendments to these Articles.

Clinical trials in emergency situations

The amendments made to Article 31 (Amendment 190) placing greater focus on the urgent need to treat rather than legal representative's availability as the requirement for deferred consent is essential to the continuation of clinical trials research in the emergency setting. We welcome the changes to this Article and note that resulting amendments to Recital 23 (Amendment 33) are now required to bring this in line with the amendments to Article 31.

AGREE Amendment 158. REVIEW AND CLARIFY Amendments 34 and 164 which are in contradiction to those amendments made to Article 28 (Amendment 158). Inclusion of provision of information both orally and in writing is misplaced and will halt recruitment into clinical trials using postal consent methods.

AGREE Amendment 190. REVIEW AND CLARIFY Amendment 33

9. Transparency_____

We support the international efforts to improve the transparency and unbiased reporting of all clinical trials. We would be happy to participate in the development of common guidelines on voluntary data sharing and the content of the lay persons' summary.

The proposals included in the Regulation including the requirement to register clinical trials in a publicly accessible database and appropriate content of the end of trial report are pleasing to see and it is also encouraging to see the addition of a number of processes which many academic trials units already employ including obtaining prospective consent for the use of data for other research purposes and making the outcomes of the trial accessible to participants. We feel that to avoid ambiguity further clarification is required in some areas. We strongly suggest that the EU Portal should allow the uploading of a pdf report or tables of analyses generated from the study database rather than requiring re-entry of individual data items as was the case in the pilot of the EudraCT v9.0 database; re-entry of data is very time consuming, discourages complete reporting and greatly increases the risk of error.

REVIEW AND CLARIFY:

- **It MUST be made clear that when using the agreed CSR template as suggested in Annex IIIa there will be no mandatory requirement for 'data sharing' within the Regulation (Amendments 48,49, 253)**
- **Amendment 194 – there may be legitimate reasons for a clinical trial to be temporarily halted for longer than 12 months; in these circumstances we suggest that the reasons for this and anticipated date of re-opening are submitted to the EU database rather than reporting of the 'data' to the EU database.**
- **Amendments 29 and 152– will the registration of previously conducted clinical trials be mandatory**

and if so, how far back will this go?

- **Amendment 151 – how is 'prior to their start' defined? The ICMJE Editors require registration prior to the recruitment of the first patient – is this the intention here?**
- **A number of amendments continue to refer to the availability of 'Results' or 'Data'; when in relation to provision of information to participants we consider the term 'Outcomes' to be more appropriate.**

We question the value to patients of providing public access to detailed technical documentation in regard to the clinical trial application and authorisation processes and in particular do not agree with making inspection reports publicly available (Amendments 238 and 241). Transparency can be achieved through the careful presentation of relevant information in an appropriate way for the audience. As such we seriously question whether the proposals to provide access for the public via the EU Portal are proportionate and will achieve the goal of giving patients greater information or understanding about their treatment and how this has been developed. We do however agree that the EU Portal would be a sensible central location for patients to access information in regard to the outcomes of the trial (Amendment 168).

REJECT Amendments 238 and 241. We do not agree with the principle of making inspection reports publically available. The potential for misuse and misinterpretation, particularly by the media is a major risk.

10. Data Protection_____

We have a number of concerns in regard to the recent proposed amendments to the new DP Regulation including how the right to be forgotten clause would work in the clinical trials setting. In particular, is the intention in this Regulation to permit subjects to have previously submitted data (to which they have consented) erased? (Amendment 252) How in practice would this work in maintaining an audit trail?

11. Authorisations / Amendments_____

We welcome the amendments to allow the assessment of Part I and II of the application simultaneously and note that the overall authorisation will be given following agreement to both Parts. There is some concern that allowing individual nations to decide which sections of part I and II are reviewed by the REC will lead to differences in administration across nations but the requirement that application and approval are communicated through the EU Portal will presumably streamline the currently divergent processes across the nations of the EU.

REJECT Amendment 66. We are not in agreement that '….including a change in number of subjects participating in the clinical trial….' should be specifically added. We do not agree that any change to

numbers of participants is always a substantial modification in terms of impact on the safety or rights of the subjects or the reliability and robustness of the data generated in the clinical trial

REJECT Amendment 90. *'…..including the anticipated benefits for the subjects,…..'* this is not congruent with the nature of information given to patients and the reason that the trial is being conducted in the first place.

REINSTATE Amendment 149. '*principles equivalent to this Regulation*', clinical trials conducted in 3rd countries cannot be required to have 'complied' with this Regulation.

CLARIFY Amendment 66. How is '…..any other change to any aspect of the trial that is otherwise significant…..' defined?

CLARIFY Amendment 148. What does '*conducted prior to date of application of this Regulation*' mean in practice; for instance does this mean started before or started and ended before.

***11. Further Points of Clarification*_____**

We suggest a small number of amendments, mainly for points of clarification to the following sections of the Regulation:

Quality of Life

There are several amendments adding the term 'Quality of Life' to the Regulation. It is not clear what the operational definition of this term in when used in the Regulation and a definition or further clarity is requested; for instance does it imply that a validated measure of quality of life should be used? (Amendments 90, 93, 155)

End of Trial

The '*End of Trial'* could more appropriately be defined as the last data item expected from the last subject – the current definition does not make appropriate provisions for clinical trials with long periods of remote follow up of subjects for disease progression and / or survival which may not require on-going routine 'visits'.

***List of responding CTUs:**

Barts CTU
Bristol Clinical Trials and Evaluation Unit
Cambridge CTU
Cancer Clinical Trials Unit Scotland (CaCTUS)
Cancer Research UK and University College London Cancer Trials Centre (UCL CTC)
Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham Newcastle CTU
Centre for Healthcare Randomised Trials (CHaRT)
Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), University of Oxford
Imperial CTU
Intensive Care National Audit & Research Centre (ICNARC)
Keele Primary Care Musculoskeletal Trials Unit
King's Clinical Trials Unit at King's Health Partners CTU
Leeds CTRU
Leicester CTU
Liverpool Trials Collaborative
Medical Research Council CTU at UCL
North Wales Organisation for Randomised Trials in Health (& Social Care) –NWORTH
Northern Ireland Clinical Research Support Centre
Nottingham CTU
Oxford Clinical Trials Research Unit (OCTRU)
Primary Care Clinical Research and Trials Unit (PC-CRTU), University of Birmingham
Sheffield CTRU
Tayside CTU
The Institute of Cancer Research Clinical Trials & Statistics Unit (ICR-CTSU)
University of Southampton CTU