House of Commons Science and Technology Committee: Inquiry into clinical trials and disclosure of data

Response from UKCRC Registered Clinical Trials Units Network*

The UK Clinical Research Collaborations Registered Clinical Trials Units Network consulted its members for feedback on the questions raised.

1. **Do the European Commission's proposed revisions to the Clinical Trials Directive address the main barriers to conducting clinical trials in the UK and EU?**

   Overall, it is felt that the European Commission's proposed Clinical Trial Regulation includes some important improvements, such as a single submission point for the EU clinical trial authorisation, the proposed co-sponsorship arrangements, greater flexibility for consent in clinical trials in emergency situations and measures to decrease trial indemnity costs within the EU. Our membership strongly endorses the points raised by raised by Professor Sir Rory Collins of Oxford Clinical Trial Service Unit & Epidemiological Services Unit in his letter to Vice President Maroš Šefčovič on 24 October 2012 [appended]. Additional concerns are set out below:

   i. Members felt that although the new regulations afford more flexibility, greater clarity is needed in obtaining consent in emergency situations including situations, for example, where the clinical condition of the patient makes it an emergency but also situations where the health service may be in an emergency state for example, during a pandemic. There is also inadequate provision for consent via postal based trials.
   ii. The definition of 'low intervention' trials would be better defined as 'low risk' and should be extended to trials testing established treatments with good safety profiles for novel uses that are not standard practice for example, aspirin in cancer prevention. The current definition of 'low intervention' trials is felt to be too restrictive and could potentially be interpreted as more restrictive than the current risk adaptations permitted within the UK under the Medicines for Human Use (Clinical Trials) Regulations which are documented in the MRC/DH/MHRA Joint Project document for Risk Adapted Approaches to the Management of CTIMPs. Article 2(3) of the new proposal defines these as trials on an authorised medicine used *in accordance* with the authorisation or in the context of a standard treatment, and that the additional intervention only poses a minimal additional risk. We propose that this definition is extended to include: trials of an existing drug (with a well documented side-effect profile) at a lower dose or for a longer duration, trials of an existing drug for a new condition (particularly where there is extensive class evidence of its safety profile), trials of food supplements or other products that can be sold without prescription.
   iii. Consideration is required for a risk based approach to pharmacovigilance once patients have stopped treatment and it is no longer necessary to actively monitor individual patients for treatment side effects (this includes the active monitoring of

individual patients for SARs and SUSARs and also the development of an annual safety report). Under the current legislation and the proposals for the new Regulation in such circumstances this can lead to huge pharmacovigilance costs for trials that are following patients up for long periods of time, sometimes over many years. It is also pertinent to note that pharmaceutical companies do not routinely follow up participants long term and therefore long term effect can be missed. Follow up may involve postal follow-up, via GPs or annual attendance at hospital and so does not necessarily involve the regular active monitoring of patients for pharmacovigilance purposes. One suggestion has been to amend the end of clinical trial definition. However, the other approach is to explore other methods of monitoring pharmacovigilance over these periods where the intervention is not being used. The European Commission's response to Professor Collins' letter stated that "Creating two divergent reporting systems would result in different levels of patient protection between clinical practice and in clinical trials." These differences already exist. Patient protection is greater in clinical trials than in clinical practice. Post marketing reporting of SUSARs is at a completely different level from SUSAR surveillance and reporting in clinical trials. The difference being the need to actively monitor SAEs and for each SAE, to consider whether or not it is a SUSAR only exists for clinical trials. The difference in these levels of protection already has enormous practical implications. As a result, decisions about the safety of drugs have to be made based on poor quality epidemiological data.

iv. The blanket reference to ICH-GCP within the new Regulation risks further embedding processes into practices that are not commensurate with the risks of the trial or treatment. The following examples demonstrate:

- "The rights, safety and well-being of the individual research subject should prevail over all other interests." This would mean that it is almost impossible to do a phase I or II clinical trial. It is felt that these rights should be preserved as far as possible, but the role of the ethics committee is to balance the risk to these against the potential of the research to save lives and improve the health of future generations.
- "Ensuring that the group of subjects participating in the trial represents the population to be treated" The issue about trial participants being representative might be acceptable for phase III trials but is unlikely to be helpful for phase I or II trials. It is also felt that even late phase trials do not need to be representative; what is important is that they are as generalisable as is reasonably possible, which is a completely different requirement. For example, it might be desirable to include larger numbers of less common types of participant to get more reliable estimates for such subgroups, in which case the trial would be deliberately less representative in order to be more generalisable. Additionally, the cost of including a very broad spectrum of patients (who may eventually receive the treatment) may delay introduction of a beneficial treatment in the vast majority of patients.

The MRC/DH/MHRA Joint Project document mentioned previously sets out standards for risk adaptation that are permitted within the current legislation. This is helping to reverse the trend in excessive bureaucracy and over-interpretation of Directive 2001/20/EC and 2005/28/EC which is currently seen in the conduct of clinical trials, but can only go so far.

In Summary, whilst the proposal offers the promise of a more facilitatory environment for trials, unless the concerns identified are addressed, there is risk that the current obstacles will become a greater impediment to clinical research.

2. What is the role of the Health Research Authority (HRA) in relation to clinical trials and how effective has it been to date?

v. Whilst the Network welcomes the spirit of the HRA, there is yet to be a demonstrable impact in practice on the operations of clinical trials units. The impression is that a pragmatic approach is being undertaken to adapt procedures to facilitate high quality clinical research.

3. What evidence is there that pharmaceutical companies withhold clinical trial data and what impact does this have on public health?

vi. There are a number of systematic reviews published which show that there is a significant difference in the proportion of trials published with pharma involvement that show a positive finding compared to those trials published with no pharma involvement. This has been taken to be evidence that pharma must be avoiding publishing negative studies. However there is little distinction made between early and late phase trials in these discussions and it is possible that more phase 3 trials are positive if there is a better decision making process made at phase 2. However if those early phase trials are not published then this still distorts the picture of what products are successful when we come to have an overview of the evidence in a systematic review.

vii. We recommend that this scrutiny of evidence should not be restricted to pharmaceutical companies, but should include all clinical trials (for example, devices, surgery, talking therapies and complex interventions).

4. How could the occurrence and results of clinical trials be made more open to scrutiny? Who should be responsible?

viii. Full prospective registration of trials in a publicly accessible database should be mandatory before recruitment of the first patient. There would then be a public record of the study, what participants will be recruited, what interventions compared, and what outcomes collected. This is the essential first step in making trials more open to scrutiny. This would make an impact if this was a condition for ethics approval rather than registration prior to ethics submission in case approval is denied. Prospective publication of the trial protocol, preferably in an open access journal should also be strongly encouraged. Protocols can change during the course of a trial and ideally reasons for protocol changes should also be registered.

ix. There should be commitment to publishing the full findings of trials, whether positive or negative, wherever possible with open access.

x. Strong concerns were expressed about the possible introduction of requirements that complete individual patient data be made publicly available, without access control, at the end of a clinical trial, as a means to achieving greater transparency.

Consideration should be given to: potential compromise of patient confidentiality in small trials where such details might allow the identification of particular individuals; potential for data dredging and inappropriate re-analysis; risk of exploitation (including selective analysis and reporting) by commercial parties for publicity purposes. While we are committed to the principles of data sharing (and this is a requirement of funding for many non-commercial trials), we feel it is essential to control access to data via an explicit data sharing agreement, to ensure that the data are shared for a set purpose, that the specified purpose is in line with the original informed consent provided, and that there is an agreement in place that the secondary user does not try to link the clinical trial data to other data sets in such a way that might result in the identification of individuals, compromising confidentiality.

xi. Good clinical practice in Phase III academic trials already have robust systems for external scrutiny through the Independent Data Monitoring Committees (IDMC) and independent members of the Trial Steering Committees. These could easily be strengthened and made more transparent through minor modifications to the IDMC and TSC charters, by requiring that both committees sign off the main trial publication prior to submission. This would provide assurance that the protocol and statistical analysis plan had been followed, or if not that deviations were explained in the report and that the paper was a true reflection of what happened in the course of the trial and of the data. Making sure this was in place would be a responsibility of the Sponsor. Whether these governance structures could be adapted to work for commercial trials would require some thought, but of course they already have IDMCs.

5. Can lessons about transparency and disclosure of clinical data be learned from other countries?

xii. It is felt that this is a global issue, one which has not been resolved by any one country, not least because evidence doesn't stop at our country's borders.

***Responding CTUS:**

- Barts CTU
- Cardiff Haematology CTU
- CRCTU, Birmingham
- CRUK/UCL Cancer Trials Centre
- Institute of Cancer Research Clinical Trials & Statistics Unit
- Kings CTU
- Leeds CTRU
- Liverpool Trials Collaborative
- London School of Hygiene and Tropical Medicine CTU
- Medical Research Council CTU
- Newcastle CTU
- Nottingham CTU
- Oxford CTSU
- South East Wales Trials Unit
- Wales Cancer CTU