The Network of Hubs for Trials Methodology Research (HTMR) is a UK MRC funded collaboration of seven trials methodology research centres. [1] The MRC Network of HTMR has been established to create a national platform for research in methodology related to the design, conduct, and analysis of clinical trials, and has strong links to local clinical trials units.

The Network of HTMR welcomes the opportunity to participate in the public consultation of the Clinical Trials Directive 2001/20/EC.

Key Issue 1: Multiple and divergent assessments of clinical trials

Consultation item 2: The Network of HTMR agrees that the multiple and divergent assessment of clinical trials is a key issue that needs to be addressed by the Commission. For example, one of our associated clinical trials units conducts multinational clinical trials comparing treatment strategies in HIV infection. The protocol allows investigators to select licensed drugs within a specified class. When this study was assessed, some competent authorities classified this design as a clinical trial within the scope of the Directive, while other competent authorities deemed the study to be outside the scope. This divergent assessment causes confusion and difficulties for the authorisation and conduct of a multinational trial.

Consultation item 3: The Network of HTMR agrees that the consultation document has captured some of the impact of the divergent assessment of clinical trials. The increased administrative costs and delays to trial initiation have made it very difficult to manage grant-funded studies as research grants are available for a limited duration. This has produced a situation in which the set up of the trial requires so much grant-funded staff resource that the grant often runs out before the study is completed.

Consultation item 4: The Network of HTMR supports streamlining the authorisation process for multinational trials. The Network of HTMR supports a formalisation of the Voluntary Harmonised Procedure in law as well as robust national procedures. Improved consistency in interpretation is required, perhaps by more specific drafting, to allow less local interpretation.

Experienced national competent authorities are essential. For multinational non-commercial trials it would be advantageous for the chief investigator and sponsor to continue to have support provided by the

[1] Birmingham Clinical trials Unit, Robert Aitken Institute; Department of Social Medicine, University of Bristol; MRC Biostatistics Unit, Cambridge; Neurosciences Trials Unit, Western General Hospital, Edinburgh; Centre for Medical Statistics and Health Evaluation, University of Liverpool; MRC Clinical Trials Unit, London; Clinical Trial Service Unit, Oxford

NCA. The Network of HTMR strongly supports the "decentralised/mutual recognition procedure" based on the Voluntary Harmonised Procedure, but not a completely centralised procedure.

Consultation item 5: Because ethics committees must reflect the cultural values of the community, a single ethical opinion would seem inappropriate. However, stronger cooperation of ethics committees with exchange of best practice and experience would be very valuable. Further clarification of the scope of national competent authorities and ethics committees is needed, so that each can focus on their area of expertise.

Key Issue 2: Inconsistent implementation of the Clinical Trials Directive

Consultation item 6: The Network of HTMR urges clarification of the definition for a 'substantial amendment'. EU member states have interpreted 'substantial amendment' differently and these differences in interpretation have resulted in increased administration. For example, in the UK (but not necessarily in other member states), adding an extra study site is interpreted as a substantial amendment, necessitating ethical review, and regulatory authorisation. When several such 'substantial amendments' occur in large multicentre trials, this generates much paperwork and is very resource-intensive.

The Network of HTMR urges clarification of definitions for 'interventional' and 'non-interventional' trials. These terms are interpreted differently across the member states, often blurring the borders between interventional and non-interventional trials. Given the difficulties encountered with the Directive with respect to interventional trials, the Network of HTMR opposes the extension of the regulations to non-interventional trials.

The Commission should also provide more clarity on the rules on SUSAR reporting. Currently, the different requirements for SUSAR reporting in the member states are confusing and burdensome, particularly for non-commercial sponsors. Very few non-commercial trials have the volume of SUSARs to warrant staff to manage an electronic system for reporting to the Eudravigilance database. Fortunately, in the UK, the MHRA accepts paper reports of safety events and submits them to Eudravigilance. However, some member states will only accept electronic reports, thus creating logistical difficulties for multinational non-commercial trials that must ensure that SUSARs are reported electronically.

The Network of HTMR highlights an additional issue for consideration by the Commission. Currently, the MHRA interprets 'extemporaneous preparation' of medicines in a pharmacy as manufacture which requires a clinical trial manufacturing licence and Qualified Person release. Industry is increasingly interested in the use of 'industry verified' preparations of this type which might be acceptable to EMEA but would require clinical trial licences if prepared in the UK (but not in many other EU countries). This has lead to confusion about what aseptic pharmacy preparation units

can do without a clinical trial licence. This inconsistency across the EU should be addressed.

Consultation item 8: The Network of HTMR notes that divergent requirements for safety reporting are a major problem. The Network of HTMR believes the Commission should remove the obligations of sponsors to report SUSARs to Ethics Committees. Instead, a system should be developed that allows the sponsor to submit a single SUSAR report to one place and for that report to be automatically accessible by all relevant regulators. This would greatly reduce the administrative burden for multinational studies, and at the same time improve patient protection by reducing duplicate records.

We do not consider that a regulation is an appropriate way to address the problem of divergent implementation of the EU directive across Member States.

Key Issue 3: The regulatory framework is not always adapted to the practical requirements

Consultation item 9: The Network of HTMR agrees that there is currently insufficient risk differentiation in the application of the Clinical Trial Directive. An appreciation of and agreement about different levels of risk is needed so that risk-adapted approaches to medicinal product labelling, safety reporting procedures and trial monitoring are agreed and implemented. The source of the problem is not always the Directive itself, which allows for some risk adaptation, but rather the expectation of the inspectors. Guidance on acceptable risk adaptations would greatly assist chief investigators and sponsors, particularly in situations where the trial is a lower risk trial. For example, investigational medicinal product documentation is a particular issue for pragmatic trials of treatment policy. Trials that compare the effectiveness of different standard treatments are of no greater risk to the patients than normal care. There is no justification for additional documentation of dispensing or special labelling other than that which is required for high quality normal clinical care.

Consultation item 11: Revision of some of the guidelines would be very helpful, in particular those for safety reporting, SUSAR reporting and IMP labelling, However, this would not address sponsorship issues and insurance which are currently substantial obstacles to multinational non-commercial clinical trials. The HTMR supports an amendment to the CTD to allow a sponsor in each Member State.

There is also lack of clarity about how the requirement of the GCP Directive that “the necessary procedures to secure the quality of every aspect of the trials shall be complied with”, should be applied in practice to trials with different levels of risk for participants. It is the “every aspect” part of the GCP Directive that is difficult to interpret for a low risk trial. Guidance is required to clarify the GCP Directive in relation to lower risk trials.

Consultation item 12: The Network of HTMR believes an amendment of the Directive and the guidance documents would be preferable to the long delays that would be involved in developing, passing and implementing a new regulation. A new regulation has the potential of unintended negative consequences that would then be difficult to change.

Consultation item 13: The Network of HTMR supports a risk-based approach to the regulation of academic trials. This would include a risk-based approach to clinical trial monitoring, including on-site monitoring. We urge that this is genuinely based on risk, with the level of monitoring appropriate for the actual risk, rather than the perceived risk. For example, in a trial of an accepted standard treatment being used with children, the level of risk should be considered low based on the use of a standard treatment rather than high based on the fact that the trial involves children.

The Network of HTMR opposes the exclusion of academic/non-commercial trials from the scope of the CTD. We oppose the idea that different regulations should apply to commercial and academic trials. It is important that academically sponsored trials are viewed as meeting the necessary quality standards. If a two-tiered system was adopted, this could imply that academic trials are of less value and generate less robust data than commercially sponsored studies. We feel that true harmonisation across Europe will not be achieved if academic trials are excluded. The level of risk, rather than the identity of the sponsor, should determine how the regulations are applied.