



European Commission consultation on the functioning of the “Clinical Trials Directive” 2001/20/EC

MRC Clinical Trials Unit Response

Introduction

The Medical Research Council Clinical Trials Unit (MRC CTU) was established in 1998 by bringing together two existing MRC groups that conducted clinical trials, the MRC Cancer Trials Office and the MRC HIV Clinical Trials Centre. It is supported by the UK Medical Research Council, a non-governmental organisation funded by a grant-in-aid by tax payers, whose mission is to improve human health through supporting the delivery of world class medical research. The remit of the Unit is to design, conduct and analyse clinical trials and other epidemiological studies to answer questions of clinical and public health importance, particularly in cancer, HIV infection and other areas in which there are important questions, but a lack of clinical trials infrastructure or tradition of trials.

The MRC CTU undertakes a variety of clinical trials and epidemiological studies, including large cohort studies and trials of non pharmacological interventions, as well as trials of medicinal products. The clinical trials we undertake are mainly large, multi-centre (often multinational) phase III trials, which involve many collaborators. Depending on the funding arrangements and division of responsibilities, the trials conducted by CTU are sponsored either by the MRC or a collaborating non-commercial organisation. We are currently conducting 36 clinical trials that require a Clinical Trial Authorisation in Europe.

Response

Consultation item no. 1 – Benefits of the Clinical Trials Directive

From the perspective of a Clinical Trials Unit that conducts multinational studies, one of the main benefits of the Directive is that both competent

authorities and ethics committees work to common timelines for ethical and regulatory review. In terms of patient protection, the Directive has contributed to greater awareness in the clinical research community of the need for good clinical practices.

Key issue 1: Multiple and divergent assessment of clinical trials

Consultation item 2 – Appraisal of the situation

It is the experience of the MRC Clinical Trials Unit that regulatory authorities in the member states differ in their assessment of whether a clinical trial is within the scope of the Directive. For example, we conduct some multinational clinical trials comparing treatment policies in HIV infection in which the protocol allows investigators to select the particular drugs used from licensed drugs within a specified class. Differing assessments by competent authorities, with some classifying this as a clinical trial within the scope of the Directive, and others as a study that is outwith the scope, cause considerable confusion and difficulties for the authorisation and conduct of a multinational trial.

Consultation item 3

This is an accurate assessment of the situation. As well as the impact on administrative costs highlighted by the ICREL survey, the delays to trial initiation often causes considerable difficulties for the management of grant-funded studies as research grants are normally only made available for a limited duration. Grant-supported staff are required for the development and submission of the protocol and the applications for approval, but delayed start-up often results in the grant running out before the study has been completed.

Consultation item 4 – Streamlining of NCA authorisation

MRC CTU has found the voluntary harmonisation process (VHP), that has recently been opened up to non-commercial sponsors, very helpful for the approval of multinational clinical trials that we coordinate.

We would be very much in favour of further streamlining of the authorisation process, but as the majority of clinical trials only involve one member state, experienced and well-staffed national competent authorities will continue to be essential. For multinational non-commercial trials there would be considerable advantages for the chief investigator and sponsor to continue to have access to the support provided by their local NCA. We would therefore strongly support the “decentralised/mutual recognition procedure” based on the VHP, but not a completely centralised procedure.

We may not always know in advance that a non-commercial trial will be international. A trial may start in one member state and only become multinational when colleagues in other countries become interested in

participation in the trial and additional funding is secured. It would be most helpful if the mutual recognition process were able to encompass this situation.

Consultation item 5- Streamlining of Ethics Committee assessment

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, as would further clarification of the scope of the NCA and of the ethics committees, so that each focuses on their areas of expertise. For example, the review of SUSAR's is most appropriate to the expertise of the competent authorities, rather than ethics committees. Removal of the requirement that individual SUSARS are sent to ethics committees would reduce the administrative burden for both the committees and trial management staff.

Key issue 2: Inconsistent implementation of the Directive

Consultation item 6

The different requirements for the reporting of SUSARs in the member states cause considerable logistic difficulties for non-commercial sponsors. Very few non-commercial organisations have the volume of SUSARs to warrant maintaining the numbers of trained staff that would be required in order to manage an electronic system for direct reporting to the Eudravigilance database. In the UK, we are most fortunate that the MHRA accepts paper reports of safety events in UK and submits them to Eudravigilance. However, some member states will only accept electronic reports, thus creating additional logistic difficulties for multinational non-commercial trials that have to find a way to ensure that events in patients resident in those countries are reported electronically.

We agree that observational studies should not be the basis of a marketing authorisation, but we believe that it should be possible for relevant data from a well-conducted non-interventional study to be used as supporting data for an application for a marketing authorisation.

Consultation item 7

The increase in administrative costs for non-commercial clinical trials is unquestionable. At the MRC Clinical Trials Unit, the number of clinical trials that we coordinate has not changed over the past six years, but the number of trial management staff has been increased by a third because of the additional workload.

Consultation item 8

Of the issues listed, the one that causes most difficulties to the MRC Clinical Trials Unit is the divergent requirements for safety reporting. It should be possible to achieve a system 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 cannot comment on whether a regulation is necessary to achieve this rationalisation.

Key issue 3: Regulatory framework not always adapted to the practical requirements

Consultation item 9 – Insufficient risk differentiation

MRC CTU strongly agrees that there is currently insufficient risk differentiation in the application of the Directive to different types of trial. The same high standards should apply to all clinical research, whether commercial or non-commercial, but a real 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 facilitated, and public resources are not squandered. The source of the problem is not always the Directive itself, which does allow for some risk adaptation, but rather the expectation of the inspectors. Authoritative guidance on acceptable risk adaptations would greatly assist chief investigators and sponsors of low risk trials.

In addition to the areas highlighted in the consultation document, the requirements for IMP handling and documentation cause serious difficulties 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 routine care. There is therefore no justification for additional information on temperature control, different handling requirements, documentation of dispensing or special labelling other than that which would be the norm in high quality clinical care.

Consultation item 10

We strongly agree with this description. Large-scale non-commercial trials are commonly the result of international collaborations between several organisations, often with more than one funding body. For a non-commercial sponsor in one member state, often a university or hospital in the UK, to take on all the responsibilities and liability of sponsorship in other member states is a real barrier to such trials.

The definition of a sponsor given in the Directive would seem to allow for the division of responsibilities, and the regulations that transposed the Directive into UK law allow two or more bodies either to take joint responsibility, or to allocate responsibilities of the sponsor between them. Absolute clarity and formal agreements that specify how the responsibilities are divided between sponsors are essential, but we believe that it would be of benefit to patients and the public to allow such arrangements to be made.

Consultation item 11

Revision of some of the guidelines might be helpful, in particular those for safety reporting, SUSAR reporting and IMP labelling.

In addition, the GCP Directive requires that “the necessary procedures to secure the quality of every aspect of the trial shall be complied with”. Practical guidance is urgently needed on how this requirement can be achieved while at the same time implementing sensible and appropriate risk adaptations. (see response to item 9 above on insufficient risk differentiation).

Although these changes would be helpful they would not address the sponsorship and insurance issues which are substantial barriers to the initiation of multinational non-commercial clinical trials in Europe.

Consultation item 12 – Amendment of the Clinical Trials Directive

If the concerns expressed in the consultation document can be addressed through amendment of the Directive and the guidance documents, it would be preferable to do that since the development, passing and implementation of a new regulation would inevitably result in long delays and uncertainty which would cause further damage to clinical research in Europe.

Consultation item 13 – Exclusion of trials with academic sponsors

MRC CTU strongly opposes the idea that different regulations should apply to commercial and academic trials. Both may include trials with very different levels of risk, from “first in man” to pragmatic comparisons of licensed treatments. The level of risk should determine how the regulations are applied, rather than the identity of the sponsor. MRC CTU designs, conducts, analyses and reports trials which aim to improve patient care and public health. Data from our trials are often used to support a marketing authorisation or to extend the indications of a licensed product, and all our trials are designed to contribute to the evidence base on which medical decisions are made. To achieve our goals it is essential that our trials are recognised as meeting the necessary quality standards; a two-tier system that would lead people to believe that academic trials are of less value than commercially sponsored studies would not be in the public interest.

Consultation item 14 – no comment

Consultation item 15 – no comment

Key issue 5: Compliance with GCP in clinical trials in third countries

Consultation item 16

MRC CTU collaborates in several clinical trials in third countries, both in resource-rich and resource-limited settings, but only when the study is directly relevant to the population involved. While it is essential that trials are conducted to the same standards wherever they take place, the promotion of risk-based procedures would help to alleviate unnecessary burdens for participating centres. The training in and monitoring of good clinical practices can provide valuable capacity development for resource-poor communities.