



European Commission: Assessment Of The
Functioning Of The "Clinical Trials Directive"
2001/20/EC

MRC Response to Public consultation on EUCTD

January 8th 2010

Introduction

The Medical Research Council (MRC) welcomes the opportunity to comment on the functioning of the Clinical Trials Directive 2001/20/EC (CTD) with a view to indicating changes to facilitate the aims of the Directive.

The Medical Research Council is a UK-based non-governmental organisation that is funded by a grant-in-aid by the UK tax payer. The mission of the MRC is to improve human health through supporting the delivery of world class medical research. The MRC has a long-standing interest in the development and implementation of clinical trials; and is a major funder of academic clinical trials. The MRC works closely with researchers, both in the UK and globally, with the National Health Service and with UK Government Departments.

The key points that the MRC wishes to raise in response to the consultation are presented below. A more detailed response to the issues raised and the questions presented in the consultation paper follows.

This response has been compiled in close consultation with MRC-funded Units and researchers. In addition we have liaised with many partners, including the Wellcome Trust and The Academy of Medical Sciences. Key MRC funded bodies (Hubs in Trials Methodology Research) and Units (MRC Clinical Trials Unit, MRC Clinical Trials Service Unit) will also submit separate responses to the Consultation. The MRC supports the submissions from funded Units and partners as above. We hope that this input will help to inform the discussion around potential changes to the CTD.

The MRC wishes the EC well in their challenge to address the current weaknesses that have arisen from the implementation of the CTD.

The MRC response – Summary of Key Points

MRC encourages the EC to consider revisions to the Directive and underpinning guidance that would:

- develop a framework of risk-commensurate assessments;
- ease multinational sponsorship by encouraging co-sponsorship
- clarify the scope and intent of the Directive and
- improve the consistency of application of the Directive without moving to single European Authority opinions

Full response to Consultation

The MRC broadly welcomed the introduction of the CTD and continues to support the key aims of the Directives to:

- Increase the protection of health and safety of trial participants
- Increase the ethical soundness of clinical trials
- Increase the reliability and robustness of data generated in clinical trials
- Simplify and harmonise the administrative provisions governing clinical trials in order to allow for cost efficient research
- Achieve the above while promoting high-quality research in the EU and the competitiveness of the European pharmaceutical industry

However, MRC concurs with the ICREL report¹ and other sources that the last two purposes have not been realised by the current CTD and its implementation. The MRC welcomes this timely review and the opportunity to consider whether changes to the Directive, guidance or national implementation will address these issues as highlighted in ICREL report.

Key Issue 1 – Multiple and divergent assessments of clinical trials
The MRC agrees that this is an area of difficulty which causes several serious issues in the conduct of trials and particular difficulties for multinational trials.

MRC agrees that the implementation of the CTD has significantly increased the administration costs and time involved in gaining approval for multicentre clinical trials; this is often due to regulatory authorities in different member states differing in their assessment of what constitutes a clinical trial. Any amendment to the Directive or Guidance must clarify this issue in order to improve consistent decision-making across the EU. Such an improvement in decision-making would reduce the number of amendments to trial protocols and aid in reducing administrative costs and the time to trial initiation. As an example, the increased administration duties that have arisen from the implementation of the current Directive have led to the MRC Clinical Trials Unit increasing the number of trial management staff by 33% even though the number of trials being co-ordinated has not changed significantly over the past 6 years. Furthermore, as academic trials are largely supported by grant funding of a specified duration, time delays in starting trials can lead to problems of continued funding as grant support may run out before the trial is completed; this can lead to further administrative costs and delays for the investigators and increased costs for the funder. It may also put the trial at risk of not being completed.

Going forward, the MRC supports an option in line with Section 3.3.2.1(a) of the consultation in which it is proposed that a lead National Competent Authority (NCA) determines the suitability of the trial protocol with input

¹ http://www.efgcp.be/downloads/icrel_docs/Final_report_ICREL.pdf

and potential vetos from other involved NCAs. For researchers, a key issue will be the timescale of the NCAs responses which would need to be set. There would also need to be definitive guidelines and agreed terminology in order to prevent different interpretations being applied by the various NCAs. The MRC considers that the voluntary harmonisation process (VHP), recently opened up to non-commercial sponsors, has been extremely helpful for the approval of multinational clinical trials. The MRC is in favour of further streamlining of the authorisation process, however, as the majority of clinical trials do not involve more than one member state, the retention and further development of experienced national competent authorities is essential.

Within the UK, the role of Ethics Committees is seen as separate and reasonable clarity exists as to functions of MHRA and RECs, although in some individual cases this has been difficult to navigate. MRC is supportive of the option suggested in Section 3.4.1 of the consultation. A 'one-stop' for submission already exists in the UK (Integrated Research Application System, IRAS) and this could be extended to cross-Europe trials. Strengthening the networking of national ethics committees across the EU would be welcomed however, this would require resources to be made available to support effective networks and learning.

MRC does not support a move towards a single EU body for ethics review as national views on ethics will remain crucial e.g. countries vary widely on views regarding embryonic stem cell research and embryo research.

Issue 2 – Inconsistent implementation of the CTD

The aim of the CTD at European level was to achieve a comprehensive harmonisation of the regulatory framework for clinical trials. It has been acknowledged in the consultation that the Directive has achieved only limited harmonisation which it attributes to 'inconsistent application'. However, the consultation leaves open the question as to whether the difficulties of implementation lie in application of national legislation, rather than in the European Directive itself.

It is agreed that the current situation gives rise to risks of insufficient patient protection due to inconsistency in implementation and also to increased administrative costs due to over reporting.

The MRC supports greater clarity regarding 'substantial amendments' and the definition should be reviewed to ensure that it is fit-for purpose without being disproportionate. There is a risk that researchers may not amend protocols to achieve optimal trials, due to the excessive bureaucracy this entails. The consistent interpretation of what is considered a 'substantial amendment' is crucial as differences in interpretation result 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. If several such 'substantial amendments' occur in large multicentre trials, this generates a large administrative burden and is resource-intensive.

Similarly, a consistent and clearer approach to SUSAR reporting across countries needs to be developed and adopted. These changes should counter excessive reporting and help to ease the concerns that current practice in relation to SAs and SUSARs leads to serious cost burdens without significant patient benefit. The administrative burden would be significantly reduced by rationalising the divergent requirements for safety reporting. Developing a system that would allow a sponsor to submit a single SUSAR report to one central place, and for that report to be automatically accessible to all relevant regulators would greatly reduce the administrative burden for multinational studies, and improve patient protection by reducing duplicate records.

Another issue for non-commercial sponsors is that there are different reporting requirements for SUSARs across the member states. This causes logistical difficulties for multinational non-commercial trials who do not have the resources or need (due to the small number of events) to maintain an electronic system for submitting in Eudravigilance. Please also note the comments from the MRC Clinical Trials Unit in this regard.

Across the EU, the definition of IMPs is open to interpretation (e.g. PET ligands used in trials; see Example 1). MRC considers that including non-IMP in the CTD would have significant negative implications in both costs and times; even if such trials were treated as low-risk. MRC considers that trials that compare the effectiveness of different standard treatments will normally be of no greater risk to the patients than normal care. We would support clearer and more consistent application of guidance at the EC level as to definition of IMPs (see Example 2).

The MRC considers that clarification of provisions within the Directive is a more attractive approach rather than repealing the entire Directive (4.3.1) which could lead to a considerable hiatus in improving this area. The MRC acknowledges that Community Regulation would increase harmonisation across the EU which could be helpful in some situations (e.g. reducing time-lags for authorisation between Member States). However a note of caution may also be required as a 'one size fits all approach' may not be appropriate, particularly if this were seen to affect 3rd country trials.

Example 1: Within UK academia, there is confusion as to whether a compound used in specific circumstances is an Investigational Medical Product (IMP) or not. This situation appears to have arisen, in part, because most academics do not have sufficient access to the type of specialist regulatory support provided in the industry sector and is also due to differing interpretation by NCAs. A researcher reported that his group were advised that the use of a specific PET tracer compound came under the governance of a Specials Licence for one application (because it was a proof of principle or a mechanistic study), but another, very similar proposal, in another disease process was classified as a clinical trial of an investigational medicinal product. The general confusion over these sorts of issues and the time and resources required to sort them out means that PET research groups in the UK often proceed on the assumption that they need to meet full IMP standards for every compound.

Example 2: This example highlights the inconsistent classification of studies across experimental medicine and early clinical trials. A UK-based research group researcher has previously performed 5 studies exploring the effects of various licensed agents in healthy volunteers which had previously all been classed as not falling under the remit of the Directive; they submitted a similar protocol (to assess the effects of a different licensed chemical) with the same outcome measures to the MHRA for confirmation study but the protocol was judged by the MHRA to be a clinical trial. According to the researchers, this protocol differed in no substantial way from the previous or subsequent protocols which were judged not be clinical trials under the Directive. The researchers considered that the proposed study had no direct clinical implications and that the results would not change the known efficacy or safety assessments of the chemical. This type of issue inevitably leads to delays in starting research and in this particular case a student's first 8 months of funding were spend dealing with the issues related to this decision before the researchers reluctantly decided to discontinue the study.

Issue 3 – Regulatory Framework not always adapted to practical requirements

The CTD is widely considered not to match practical considerations and requirements.

The MRC strongly supports a risk-based approach to clinical trial regulation and inspection and stresses the need for a system that will deliver a real decrease in the administrative and resource burden for lower risk trials (see Example 3). It must be recognised that some academic sector trials will be of high risk, but many are lower risk and are not intended to form the basis of a marketing authorisation (e.g. the low risk of trials investigating the use of bed-nets to reduce malaria transmission in Africa as contrasted with the higher risks of investigating the efficacy of new vaccines in infants).

The MRC strongly encourages the development of a genuine risk-commensurate approach as opposed to an artificial distinction between academically and commercially sponsored or funded trials. The latter division will give rise to difficulties defining the terms and ignores the fact that academic sector trials can also be higher-risk. MRC supports the view of the MRC funded Clinical Trials Unit which, in its separate submission, highlights that:

‘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.

Recognising that it is the primary aim of the CTD to protect patients, the MRC strongly advocates that it is the nature of the trial that should be assessed and not the type of sponsor when gauging risk. It is essential that both academic and commercial trials are recognised as meeting the necessary quality standards; a two-tier system would not be in the public or patients interest.

In addition, as stated above, MRC strongly supports revision of the Directive or Guidance to allow co-sponsorship of trials across EU countries to reduce the administrative and financial burden on academic trials MRC.

Currently, rules in the UK allow the co-sponsorship of national trials. The introduction of such arrangements requires the setting out of clear responsibilities between sponsors but such a change would greatly aid multinational research and encourage cross-EU collaboration.

Example 3: The current system is having a profound effect on academic trials across Europe but particularly in the UK (Langstrom et al in EJMNM). This is particularly evident in radiopharmaceuticals that may have been in use in one member state and not in another requiring full justification for a clinical trial and an IMP process (e.g. Fluorocholine, C-11 choline, methionine, FLT etc). These types of studies involve a very low risk to the patient/volunteer involved in radiotracer studies. The radiotracer is normally in the microdose range when administered particularly for PET tracers but also for nuclear medicine tracers. The whole raison d'être for tracers is that they do not perturb the system they are studying. The subjects are studied with 1 or 2 non-pharmacological doses delivered to patients with known disease under medical supervision in hospitals with a known quantifiable risk from the radiation dosimetry. The legislation is also impacting on the development of biomarker studies using radiotracers (radiopharmaceuticals) to support developments in Molecular targeted therapies. These types of developments are being slowed down, and indicate the need for the processes involved to be commensurate with the risk involved in administering agents that have no pharmaceutical activity.

Issue 4 – Adaptation to peculiarities in trial participation and design

Paediatric trials are essential for the development of safe medicines for children. As above, a risk-based approach is required in this area. Recognition is also needed of the differing information that may be appropriate for clinical trials protocol submission and consent in paediatric settings.

With regards to clinical trials in emergency situations the MRC highlights the need to define a consistent approach to be used across Europe. The issue of consent has been dealt with in England and Wales through the provisions of the Mental Capacity Act 2005². This Act does not apply in Scotland, where there can be considerable difficulties conducting clinical research in emergency situations.

Issue 5 – Ensuring compliance with GCP in trials performed in 3rd countries

The MRC is a funder of academically-led clinical trials and strongly endorses the principle that the safety of clinical trial participants is paramount. It must also be recognised that the resources involved in monitoring a clinical trial should be commensurate with the potential risks of the intervention.

In relation to the question of trial registration, the MRC is in favour of encouraging mandatory registration of all trials and this is already a requirement of all MRC funded trials.

² Mental Capacity Act 2005 http://www.opsi.gov.uk/ACTS/acts2005/ukpga_20050009_en_1

MRC has a long history of funding clinical trials in resource poor countries; where the scientific question being addressed is appropriate to the population being targeted. MRC has in place its own guidance for GCP in clinical trials which is applied to all trials in MRCs' portfolio. Due to the nature of the majority of these trials (i.e. academically-led; non-marketing authorisation trials e.g. DART, STOPMAL), the governance model MRC most often uses involves self-regulation by EU-based sponsors.

MRC considers that the EC should consult the secretariat of EDTCP to discuss real examples of how such trials can be conducted to high standards works in practice.

Conclusion

The MRC welcomes this review and as a large public sector funder of clinical trials is very willing to discuss any of the above, or indeed, any other areas further.

Please contact Dr Catherine Elliott or Dr Jane Fisher for any further information or assistance in this regard.

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