European Commission: Concept Paper on Revision of the 'Clinical Trials Directive' 2001 / 20/EC

Medical Research Council (UK) response to the consultation document

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European Commission Concept Paper on Revision of the 'Clinical Trials Directive' 2001 / 20/EC[1]: Medical Research Council (UK) response

The Medical Research Council (MRC) is a UK-based non-governmental organisation 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 in the UK and internationally. The MRC works closely with researchers, both in the UK and globally, with the National Health Service and with UK Government Departments.

In preparing this response, the MRC has liaised with many partners, including the Wellcome Trust, CR-UK, the Academy of Medical Sciences and the European Science Foundation (ESF). The MRC supports the submissions from these partners. It is clear from these discussions that there is significant consensus across all these organisations as to the impediments to the conduct of clinical trials, and the potential routes to address these, while maintaining the highest standards of participant protection and confidence in medical research.

RESPONSE TO THE CONSULTATION DOCUMENT

1. COOPERATION IN ASSESSING AND FOLLOWING UP APPLICATIONS FOR CLINICAL TRIALS

Consultation item no. 1: Do you agree with this appraisal? Please comment.

A single submission for approval of multinational trials is the best option and one that the MRC strongly supports. It is important to ensure that further separate information is not required by Member States and that the content of the submission is proportionate. Implementation of this proposal will thus need to address issues of both **harmonisation** and **risk proportionality** – these emerge as strong requirements in common across many of the areas considered in the concept paper and proposals.

In the UK an effective single application system for MHRA[2], NRES[3]and other approvals has been implanted – the Integrated Research Approval System (IRAS)[4]. We would encourage the Commission to consider this system and to ensure that any new systems developed can align with national application processes to other regulators and Ethics Committees.

However, subsequent multiple assessments of single applications will not streamline the process beyond submission which must be addressed as discussed in the following items.

[1] http://ec.europa.eu/health/files/clinicaltrials/concept_paper_02-2011.pdf
[2] Medicines and Healthcare products Regulatory Agency
[3] National Research Ethics Service
[4] https://www.myresearchproject.org.uk/Signin.aspx

Consultation item no. 2: Do you agree with this appraisal? Please comment.

The MRC and partner organisations have previously highlighted the difficulties with multiple, often divergent, assessments. The preferred option for the MRC is that a lead National Competent Authority (NCA) determines the suitability of trial protocol with input and potential for veto from other involved NCAs for conduct in their country.

1.2. Single submission with subsequent central assessment Consultation item no. 3: Do you agree with this appraisal? Please comment.

The MRC does not support the option of single assessment – for most of the reasons outlined in the concept paper, including concerns about loss of UK input to authorisations involving UK sites and participants, potential costs and the difficulty of operationalising this approach.

1.3. Single submission with a subsequent 'coordinated assessment procedure'

This would formalise the current Voluntary Harmonisation Procedure (VHP) – which the UK MHRA participates in. The MRC supports this option and the designation of a 'Reporting Member State'. As with other proposals, it is important that this is implemented in a way that reduces bureaucracy and promotes harmonisation through dialogue between Regulators. A further advantage of this approach will be to increase awareness of areas of differing interpretation and discussion of these by the Competent Authorities.

1.3.1. Scope of the CAP ('Coordinated assessment procedure')

Consultation item no. 4: Is the above catalogue complete?

The MRC endorses the position that ethical issues clearly fall within the ambit of Member States and should remain there. The safety plan should be added to the catalogue in relation to CAP review which otherwise appears complete. The revision provides an opportunity to clarify which areas fall under the remit of the CAP and which fall under the Ethics Committee as there is considerable variation in this across Member States. The outline of the CAP is fairly brief in this concept paper and we endorse the need for further information as highlighted in, for example, the response from CR-UK.

Consultation item no. 5: Do you agree to include the aspects under a), and only these aspects, in the scope of the CAP?

As in the response to the question above, the MRC agrees that only matters relating to trial product and protocol should be in scope – with an approach that takes account of the risk level of the trial proposed and a proportionate review dependent upon that risk. There is also a need for the EC to adopt a risk-based approach with reduced time for approval and reporting requirements for lower risk trials. While individual nations need to retain separate Ethics Committee review, we support the need for single national opinions to be clearly given, and also for much greater communication between Ethics Committees across Europe.

Discussion of decisions in multinational studies would be a beneficial area for this communication - although such discussion must not impede the timescales and process for the specific approvals.

In order for the CAP to work optimally, there is a need for definitions to be consistently applied across Member States –for example of an Investigational Medicinal Product (IMP).

Consultation item no. 6: Which of these approaches is preferable? Please give your reasons.

Opt-out is our preferred option – however, there needs to be a balance between trying to address the issues of a dissenting State and the need to ensure a reasonable timescale and harmonisation. In practice, the sponsor may often prefer to omit the dissenting State from the study; however, there may be times when a further dialogue about the reasons for concern and veto would be valuable for the Sponsor and researchers. These discussions should be led by the Reporting Member State before the decision is made and there should be an option for the Sponsor to request further discussion if that State is deemed important for study conduct by the Sponsor.

It will be important for the EC and EMEA to maintain data on opt-out rates to monitor whether there are particular areas of divergent opinion that need to be addressed.

1.3.3. Mandatory/optional use

Consultation item no. 7: Which of these three approaches is preferable? Please give your reasons.

In the initial stages, an optional process is the preferred option. If the process is successful, then it may not need to become mandatory as States and Sponsors will opt to use it. Once the optional system has been evaluated, further consideration can be given as to whether this should be adopted as mandatory.

1.3.4. Tacit approval and timelines

Consultation item no. 8: Do you think such a pre-assessment is workable in practice? Please comment.

The MRC strongly supports risk-based approaches to regulation and approval and so reduction of timescales for these lower risk studies is certainly supported. In addition, further consideration must be given to reducing the administrative burden (and therefore costs) for such studies in reporting and monitoring requirements. The risk assessment required should be at the lowest level necessary to ensure introduction of this approach does not create additional unnecessary work for researchers.

In defining risk levels, great care must be given to definitions in order to ensure these can be applied consistently across Member States.

The MHRA in the UK is piloting work using this type of categorisation with a similar definition of type A trials. There will therefore be practical experience in the coming months as to how this approach can be used in practice.

2. BETTER ADAPTATION TO PRACTICAL REQUIREMENTS AND A MORE HARMONISED, RISK-ADAPTED APPROACH TO THE PROCEDURAL ASPECTS OF CLINICAL TRIALS

2.1. Limiting the scope of the Clinical Trials Directive

2.1.1. Enlarging the definition of 'non-interventional' trials

Consultation item no. 9: Do you agree with this appraisal? Please comment.

The MRC does not support this appraisal. We consider that the scope of the definition of non-interventional trials should be broadened to *exclude* more trials from the scope of the Directive – as for such studies the stringent requirements needed for licensing studies are not relevant and do not increase participant protection as the risks are low. It is important to consider the aim of regulating trials under the Directive – primarily patient safety – and it should therefore be recognised that certain trials pose higher risks to participants or will provide data used in subsequent licensing applications. For those trials which do not fall into either of these categories, it must be questioned why there needs to be EU level legislation over and above the requirements of all countries for EC and site review. The MRC would thus prefer the scope of the Directive to be further limited.

Interpretation of what is a 'non-interventional trial' (and therefore what is not covered by the Directive) varies across the EU. The UK appears to apply the definition very rigidly and, as a consequence, fewer trials are likely to be excluded in the UK than elsewhere. Removing the complexity across the EU only works if all Member States interpret whatever definition is included in the same way. We note and support the useful examples in the response from the Wellcome Trust.

It would be very helpful in certain circumstances to recognise that there may be a non-interventional phase of an interventional trial. Many academic trials have a primary outcome that is based on a surrogate outcome (such as a marker of treatment failure/disease progression) but also a more clinically meaningful long-term outcome (often secondary) such as clinical progression or death. Such trials often take very many years to reach the more clinically-meaningful outcome. However the cost of maintaining the CTA, as well as the pointlessness of expedited safety reporting when patients have long-since stopped trial treatment, is a major disincentive to undertake such trials, although they are in the public interest.

In summary, while the MRC welcomes and strongly endorses the move towards more risk-based assessments and processes, this is as yet unproven in practice. It is difficult therefore to support increased scope until real progress is made on reducing the current difficulties and introducing a truly risk-proportionate approach.

2.1.2. Excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive

Consultation item no. 10: Do you agree with this appraisal? Please comment.

Yes, the MRC has always taken the view that distinction between these two categories is unhelpful and does not aid protection of participants. In addition, we

are increasingly working in collaboration with industry partners and the definitions of commercial and non-commercial trials are often difficult to define.

It is level of risk of the product, the trial protocol and the site characteristics that should be the keys in relation to stratification; the first of these being of most relevance for the CA categorisation.

2.2. More precise and risk-adapted rules for the content of the application dossier and for safety reporting Consultation item no. 11: Do you agree with this appraisal? Please comment.

It is not very clear whether further annexes would clarify and also allow more scope for risk proportional approaches. More detail is needed as to what the intention of these revisions would be. Complexity is often compounded by how Annexes are interpreted.

However, we would welcome rules that allowed for implementation of a risk based approach – these would need to provide clear definitions to allow for harmonisation in adoption and also include clear consequences of risk stratification – in particular shorter time scales and reduction in reporting requirements for low risk trials. It needs to be recognised that the full requirements of ICH GCP as currently interpreted may not be appropriate for such trials and flexible approaches to some of these areas need to be adopted.

The MRC, in common with many other partners, researchers and patient groups would welcome the opportunity to discuss and review such proposed documents in more detail.

Consultation item no. 12: Are there other key aspects on which more detailed rules are needed?

No further aspects have been identified.

2.3. Clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products' Consultation item no. 13: Do you agree with this appraisal? Please comment.

The MRC welcomes the recognition that the definition of IMP causes difficulties and there are divergent interpretations of this across EU States. However, the proposed approach raises two issues:

Firstly the inclusion of 'reference' products in a trial as IMP may lead to a need for amended labelling, manufacture etc for these products which would be disproportionate and an extension of the definition.

Secondly, the introduction of another category needs careful consideration; it might be that better definition of NIMPs would fulfil this need. However, we support the need to clearly identify those products in a trial which do not need the level of regulation imposed on IMPs, in particular to recognise that this is not required for background medication.

The key aim in this must be to clearly define IMPs and ensure that disproportionate requirements are not being set for products that are licensed and/or are being used in accordance with usual standard of care. Considerable

excessive costs and delays to trial conduct follow from requirements being imposed for products that are being used in the same way in patients not in trials, with no benefit for patient protection or data integrity.

2.4. Insurance/indemnisation

Consultation item no. 14: Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

Removal of requirements from low risk trials is not supported as there may be unforeseen consequences of participation and it would be most undesirable to remove potential compensatory mechanisms for these. Such events are very unlikely and so insurance or indemnity risks should be assessed as very low for these trials. If insurance companies continue to provide such cover (as opposed to state indemnity), it is critical to engage them to ensure premiums are set at a realistic rate in relation to this risk.

The MRC is in an unusual position as we operate with state indemnity for harm for trials that we sponsor, rather than requiring insurance. However, as a sponsor of multinational studies, we are aware of the difficulties that differing insurance requirements pose. However, extension of state indemnity to all trials, regardless of sponsor is likely to be problematic. It would give rise to a further system in each country for the State to assess and control risks in trials being indemnified – in particular where these are not sponsored by public bodies. It seems unlikely that States would provide indemnity without some oversight on conduct and review of protocols etc. This would therefore potentially add additional burdens to trial conduct.

There is a need for clearer understating of the indemnity available through employer liability, product liability and indemnity schemes for negligent and non-negligent harm.

The major issue for international trials is that insurance practice and legal liability varies is not the same across the EU and thus interpretations of what is required and who is responsible for providing it differ, either based on fact or perception. It is not clear whether amending the Directive would address this much bigger issue.

2.5. Single sponsor

Consultation item no. 15: Do you agree with this appraisal? Please comment.

The MRC does not support Option 1 – and does not agree with this appraisal.

The MRC supports the ability to divide responsibilities between cosponsors – this occurs successfully in UK and could occur across multinational trials. It would resolve some issues, for example regarding indemnity. In practice, this approach works well so long as all parties agree and document responsibilities. In relation to the appraisal above, specific roles would still be undertaken by named sponsors, joint sponsorship does not prevent this. It is our view that joint sponsorship in multinational studies increases clarity as to responsibilities and accountability for these.

Allowing for co-sponsorship would also carry significant benefits for collaboration outside the EU, for example with the US or with developing countries where some aspects of sponsorship cannot be undertaken locally.

2.6. Emergency clinical trials
Consultation item no. 16: Do you agree with this appraisal? Please comment.

This situation is allowed for in the UK and dealt with as described in the concept paper. This has enabled conduct of critical trials in management of acute coronary events and stroke. The MRC strongly supports this approach being implemented across the EU.

3. ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES Consultation item no. 17: Do you agree with this appraisal? Please comment.

This appraisal appears to focus on countries with lower capacity for trials that in the EU and where the frameworks for research and regulation are perceived as weak. There are many countries outwith the EU where this is not the case, including for example the US and Japan.

There is a need for continuing global discussions on harmonisation and MRC welcomes the current OECD Global Science Forum working group on this which is currently underway.

We appreciate that there are different requirements when results of trials in third countries will be submitted for EU marketing authorisations.

Consultation item no. 18: Do you have any comments or additional quantifiable information apart from that set out in the annex to this document? If so, you are invited to submit them as part of this consultation exercise.

This response builds on the previous submissions from the MRC to the Commission on difficulties and solutions to these in relation to the EU Clinical Trials Directive. In our submission of January 2010, we encouraged the Commission to adopt mechanisms 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.

In conclusion, the MRC is very supportive of the work of the Commission in this important area for medical research and appreciates the complexity of some of the issues raised. If any further input would be of assistance, please contact Dr Catherine Elliott: catherine.elliott@headoffice.mrc.ac.uk.

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