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Professor Robert Souhami CBE FMedSci
Foreign Secretary

21 December 2012

Sandor Beukers
Medicines and Healthcare Products Regulatory Agency (MHRA)
5th Floor
151 Buckingham Palace Road
London SW1W 9SZ

Dear Mr Beukers,

The Academy of Medical Sciences welcomes the opportunity to respond to the Medicines and Healthcare Products Regulatory Agency (MHRA) consultation on the European Commission's proposals for a Clinical Trials Regulation (CTR). The proposals are an improvement on the current Clinical Trials Directive (CTD). We are particularly pleased that the CTR takes a more proportionate approach and that it formally introduces co-sponsorship for clinical trials. The ambitious assessment times described in the proposals would do much to speed the translation of research into benefits for patients. We also welcome the MHRA's efforts to engage stakeholders around the CTR and the increasingly facilitative approach the MHRA is taking in the implementation of the CTD.

Our outstanding concerns about the proposals for the CTR focus particularly on its impact on multi-state trials and include:

- We welcome the introduction of a single application portal with a single application dossier but would like European institutions to outline their plans for creating and implementing the requisite IT systems to take these plans forward.
- The Academy welcomes efforts to make clinical trials more transparent but care needs to be taken to ensure such measures are taken forward in a thoughtful manner that does not inadvertently impede medical research and thus patient benefit.
- Challenges remain around the perception of and terminology used in both the CTR and CTD. Greater efforts are needed to communicate with academics, NHS Trusts, higher education institutions and other stakeholders to avoid confusion and a highly risk adverse approach to clinical research.
- Allowing sponsors to choose the National Competent Authority (NCA) to which they apply may mean stronger NCAs, such as the MHRA, receive more applications than others NCAs. We would like reassurance that this would not have a negative impact on the processing of applications for both national and multi-national trials from the home country of stronger NCAs
- The need to ensure insurance arrangements in the CTR for multi-state trials are not too cumbersome.

The Academy has endorsed a recent joint statement about the CTR led by Cancer Research UK, a copy of which is enclosed. We are looking to continue to work closely with the MHRA with this issue over the coming months. If you have any queries please contact Laurie Smith who is leading for the Academy on this matter (tel.: +44 (0)20 3176 2167, e-mail: laurie.smith@acmedsci.ac.uk).

Yours sincerely,

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Proposal for an EU Regulation on Clinical Trials

A joint statement from non-commercial and commercial organisations

We welcome the proposal for a Clinical Trials Regulation released by the European Commission. The Regulation appears to improve the legislation associated with running clinical trials. This will give clinicians and researchers a better framework for developing and testing treatments, to benefit patients across Europe, while maintaining the high standards of patient safety that currently exist in European clinical research. The harmonisation of clinical trials legislation and the streamlining of the application process for starting trials should particularly benefit the set up and running of multi-national trials in Europe.

This statement outlines the areas of agreement within the health and research communities on where the Regulation will improve the research environment. Aspects of the Regulation that could be improved to further support clinical research are also highlighted. As the exact content and nature of the Regulation continue to be debated, we believe that there is opportunity to push for more effective and proportionate approaches to certain aspects of the legislation.

In summary:

- **Further clarity is needed on the two category risk based approach proposed in the draft Regulation.**
- **We welcome efforts to provide greater clarity around the scope of the Regulation. However, it may be possible to refine these definitions further.**
- **The EU institutions should outline how it would go about creating and implementing the IT systems associated with the Regulation.**
- **Co-sponsorship is important for many academic trials which are conducted through a partnership between universities and hospitals.**
- **We welcome the mechanism for involving patients and their representatives on the panel involved in assessing clinical trials.**
- **Particular aspects of the safety reporting system in the Regulation may require further clarification to give certainty to the staff running trials on what elements they should report on.**
- **Clarification is needed to ensure that it is clear that sponsors continue to be responsible for determining whether modifications to a clinical trial are substantial and that guidance is clear for making these decisions.**
- **We would welcome a more detailed outline of the proposed national indemnity scheme, which is of potential interest to the research community.**
- **Provisions for conducting emergency clinical trials are also welcomed but the requirements for entry into emergency clinical trials should be reviewed to ensure they do not limit patient recruitment.**

What is the Clinical Trials Regulation?

On 16 July 2012, the Commission adopted a proposal for a Clinical Trials Regulation. The proposed Clinical Trials Regulation, once passed, will replace the current Clinical Trials Directive in regulating the clinical trials of medicinal products in patients across Europe. The Regulation came about following calls across the clinical research community that the current Clinical Trials Directive was in need of urgent revision. The Clinical Trials Directive improved the standardisation of the conduct and quality of clinical trials across the clinical research community; this needs to be further developed.

However, key criticisms of the current Directive that still need to be addressed include:

1. Divergent application, largely due to inconsistent interpretation of the Directive across different Member States, has made it increasingly difficult to undertake multi-national clinical trials.
2. The Directive has led to a greater administrative burden (with associated costs and delays) for clinical trials. The assessment undertaken by the Impact on Clinical Research of European Legislation (ICREL)[1] found that non-commercial sponsors required an increase from 1.5 to 2.8 full-time equivalent staff to manage administrative tasks associated with a Clinical Trial Authorisation, and that there was an increase in time between finalisation of protocol and first patient recruited from 144 to 178 days.
3. The 'one size fits all' regulatory requirements mean that low-risk trials on well-understood drugs are regulated in the same way as trials of completely new drugs, where the risks are unknown. This has increased the difficulties in conducting low-risk clinical trials.

The Regulation addresses key criticisms of the Directive, along with other problems raised by the community including requests for more detailed guidance, simplified monitoring requirements and clarity on sponsorship issues. As a Regulation that will apply directly in Member States, it will harmonise the legislation for conducting clinical trials across Europe. This will resolve a central issue with the existing Clinical Trials Directive that has led to divergent systems for regulating clinical research across Europe, making running trials across Member States problematic. It is important that the Regulation is accurately translated into the languages of Member States to ensure that harmonisation is achieved and the legislation is not misinterpreted.

Scope of the Regulation

Introducing the concept of a low-interventional trial is an important step to adopting a risk based approach in clinical trials legislation. Clinical trials can use a wide range of medicines from those that are being tested in people for the first time to those which have already been used in established clinical practice for many years. A risk proportionate approach would recognise that the requirements associated with the application and monitoring processes of a trial can be reduced for medicines with well-known safety profiles without compromising the safety of participants.

The Regulation also introduces proportionate approaches to trial management into legislation, for example the frequency of on-site monitoring and the level of independent monitoring of data and safety. These measures should enable sponsors to adapt their risk management plans for clinical trials.

Uncertainty remains over the extent to which the proposed Regulation will adapt the requirements for trials of marketed products used for a new purpose, which are not included in the low-interventional trial category. **Further clarity is needed on the two category risk based approach proposed in the draft Regulation.** It also needs to be established whether there is sufficient flexibility to apply greater risk differentiation in within the Regulation.

We welcome efforts to provide greater clarity around the scope of the Regulation. However**, it may be possible to refine these definitions further**, for example to avoid confusion around the new concept of 'clinical studies' so that the scope of the Regulation is clear.

Application procedure for conducting clinical trials

The Regulation's introduction of a single application portal with a single application dossier is particularly attractive to streamlining and harmonising the application process for clinical trials.

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

Measures proposed in the Regulation should reduce the time it takes for multiple Member States to approve multinational clinical trials. Efficient operation of the IT systems associated with a single European portal will be crucial to the success of all of the measures set out in the Regulation. **The EU institutions should outline to the community how it will go about creating and implementing the IT systems associated with the Regulation.**

Ambitious timelines have been set by the proposed Regulation for both Member States to gain ethical and regulatory approval and also for Sponsors to respond to regulatory queries. We welcome the efforts to speed up the assessment process although certain sponsors may not be able to meet them due to lack of resources**.**

The health and research community welcomes the formal introduction of the concept of co-sponsorship for clinical trials. Co-sponsorship is important to non-commercial organisations across Europe as it allows sponsors who could not otherwise run clinical trials to share responsibilities associated with trials. **Co-sponsorship is important for many academic trials which are conducted through a partnership between universities and hospitals.**

The Regulation provides a mechanism for involving patients and their representatives in the panel involved in the assessment of clinical trials. **This is welcomed as an advance in the way that patients and the public are involved in clinical research activities.**

Operation of clinical trials

The Regulation has sought to address several issues associated with the conduct and operation of clinical trials. We welcome the consolidation of safety reporting legislation and the reduction in reporting for products that are used in their licensed use. There may be scope to go further to reduce the amount of reporting associated with trials which use medicines with established safety profiles. **Particular aspects of the safety reporting system in the Regulation may require further clarification to give certainty to the staff running trials on what elements they should report on.**

It is important that requirements for notifying the regulator of changes to a trial through substantial modifications are proportionate. The proposals for substantial modifications are not clear about the balance of responsibility between sponsors and regulators in determining whether a modification is 'substantial'. **Clarification is needed to ensure that it is clear that sponsors continue to be responsible for determining whether modifications to a clinical trial are substantial and that guidance is clear for guiding these decisions.**

The introduction of a national indemnity scheme is of potential interest. **We would welcome a more detailed outline of this proposal.**

Provisions for conducting clinical trials in emergency situations are also welcomed as an improvement on some of the key concerns with the previous Directive. However, the requirements in the proposals that clinical trials in emergency situations should not impose more than minimal additional risks or burdens on patients are potentially too broad. **The requirements for entry into clinical trials in emergency situations should be reviewed to ensure they do not inadvertently limit the intention of the provision.**

A commitment to transparency through the registration of clinical trials is welcomed along with requirements to report when trials reach certain milestones.

For further information, please contact Daniel Bridge (daniel.bridge@cancer.org.uk, 0203 469 8153).

Supporter organisations: