

Medicines and Healthcare products Regulatory Agency: Consultation on the European Commission's proposal for a Clinical Trials Regulation

Response by the Wellcome Trust

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Key Points

- It is vital that the Regulation ensures public confidence; the protection of participants; and promotes the conduct of trials for public benefit.
- We are pleased that the scope of the Regulation has not been increased compared to the Directive. The scope needs clarifying with respect to products that are available without prescription and a number of the definitions would also benefit from amendment and clarification.
- We welcome steps towards greater risk proportionality in the Regulation compared to the Directive since this will help to reduce the regulatory burden on sponsors and regulators, without compromising the safety of participants or the robustness of trial data. It is vital that the Regulation adopts the most workable model for risk adaptation.
- We support a system of single authorisation and single decision within the UK along with a system of single submission followed by a coordinated authorisation process for multinational trials. This will promote the conduct of trials, particularly across Member States.
- We welcome the flexibility with respect to good clinical practice standards and moves towards further transparency. Provisions for emergency clinical trials are also welcome but must be reviewed to ensure that they do not undermine the UK's strong position in this area.

INTRODUCTION

1. The Wellcome Trust is pleased to have the opportunity to respond to this consultation on the proposals for a Clinical Trials Regulation. We fund clinical trials through both our Science Funding and Technology Transfer schemes, but do not act as a sponsor.
2. It is vital that the Regulation ensures public confidence; the protection of participants; and promotes the conduct of trials for public benefit. In order to achieve this, the Regulation must deliver a proportionate regulatory framework that enables regulatory requirements to be adapted according to the risks of the trial. A proportionate approach will minimise the regulatory burden on sponsors and regulators therefore promoting research, without compromising the safety of participants or the robustness of trial data.

RESPONSES TO QUESTIONS

Q.1 Do you have views on the scope of the Regulation?

3. We are pleased that the scope of the Regulation has not increased compared to the Directive.
4. We note that some trials of some products available without prescription, such as vitamins, minerals and food supplements may be captured in the scope of the Regulation based on the interpretation of “medicinal product” as defined in Directive 2001/83/EC. Robust trials of these products are often conducted in academia and are important to increase our understanding of their safety and efficacy. Trials of these products will not usually fall in the low-intervention category, even though they are widely available without prescription, since they do not have a marketing authorisation. It would be helpful for the Government to seek clarification from the Commission on whether trials of these products are intended to be included in the scope of the Regulation. If the Commission intends to exclude these products, amendments are needed to clarify this. If the Commission intends to include these products, amendments will be needed to ensure these trials are regulated proportionately.

Q.2 Do you agree with the introduction of low-interventional studies?

5. We welcome steps towards greater risk proportionality in the Regulation compared to the Directive and agree with the introduction of low intervention studies.
6. It is vital that the Regulation adopts the most workable model for risk adaptation. The two category approach adopted in the Regulation differs to the three category models currently used by the Medicines and Healthcare products Regulatory Agency (MHRA) and proposed by others, including the Organisation for Economic Cooperation and Development. Superficially it appears that the two category approach only benefits a small subset of trials. However, the Regulation also includes scope for risk adaptation that is independent of the two formal categories, for example around the requirements for authorised products and trial monitoring. The current MHRA approach to risk adaptation also demonstrates how much can be achieved through guidance rather than legislation. Further clarity on the amount of flexibility inherent in the Regulation and a thorough analysis of the risks and benefits of a two category approach will be required to assess whether the level of risk adaptation in the Regulation is sufficient compared to a formal three category system.

Q.3 Do you have views on any of the proposed definitions in Chapter 1 (Article 2) of the proposal?

7. We welcome the approach of describing the scope of the Regulation through the definition of “clinical trial”, rather than relying on the definition of what is excluded (“non-interventional trial”). We think this approach provides greater clarity compared with the approach in the Directive.
8. We consider the introduction of a definition of “clinical studies” to be confusing and in need of amendment. This is potentially confusing for two reasons: First, although the Regulation is internally consistent in the use of its definitions, “clinical trials” and “clinical

studies” are often used interchangeably in other settings, for example, among the academic community and in ICH E6 guidance, which states “the terms clinical trial and clinical study are synonymous”. Second, the definition of “clinical studies” is wider than the scope of the Regulation. We consider it important that the definition of “clinical study” is deleted and the definition of “clinical trial” revised to ensure that any potential for confusion is removed.

9. Article 2(2)e states that a study is deemed a clinical trial when a clinical study “involves diagnostic or monitoring procedures in addition to normal clinical practice”. This has the potential to draw many studies involving the monitoring of standard treatments into the scope of the Regulation, and the requirements of the Regulation would act as a barrier and disincentive to the conduct of these important studies. This has been a concern under the current Directive¹ and it is important for the Government to consider addressing this in the Regulation. For example, replacing the text in Article 2(2)e with the text of Article 2(3)c – “additional monitoring or diagnostic procedures do not pose more than minimal additional risk or burden to the safety of the subject...” – would reduce the number of studies captured by the definition of “clinical trial” in this way. Excluded studies would still be covered by the scope of NHS Research Ethics Committees and therefore patient safety would not be compromised, while this approach has potential to foster more research into standard treatments.
10. Under the Directive there have been trials where medicinal products have been inconsistently classified as either investigational medicinal products (IMPs) or non-investigational medicinal products (NIMPs) by different Member States. The Regulation replaces the concept of NIMPs with auxiliary medicinal products (AMPs). However, we consider that the definitions of IMPs and AMPs should be developed to ensure that there is a clear distinction between them. We are also concerned about the breadth of the definition of IMP. There would be value in amending the definitions to ensure that reference products that are routinely used in standard clinical practice are not classified as IMPs.

Q.4 Do you agree that a single authorisation and a single decision (for both regulatory and ethics approval) through an EU portal will be of benefit to researchers? If so, how will this benefit you?

11. We support a system of single authorisation and single decision within the UK. This is a natural progression from the current move towards greater streamlining. A strong relationship between the MHRA and Health Research Authority will be needed to deliver this and we are pleased that these organisations have already had preliminary discussions on this.
12. Clarity is needed on which elements of the regulatory and governance system would come under this single authorisation and decision, particularly whether this extends to NHS R&D permissions. In order for the UK to provide a competitive environment for the conduct of clinical trials, it is vital that further regulation and governance checks at the local level do not significantly extend authorisation and decision timelines.

¹ Academy of Medical Sciences (2011) *A new pathway for the regulation and governance of health research*

13. Smooth development and operation of the EU portal will be critical to the success of the single authorisation and decision approach and to deliver the aim of the Regulation to reduce bureaucracy. This is particularly important for UK stakeholders as there is a risk associated with moving away from the successful Integrated Research Application System to a new system. Sufficient and sustained funding will be needed to develop and deliver the EU portal. We recommend that the Government should seek assurances from the Commission that sustainable resourcing will be provided to support the EU portal.

Q. 5 Do you agree that the proposed multi-state application and authorisation process reduces the burden on researchers? If so, how and would you be able to quantify this reduction?

14. We support a system of single submission followed by a coordinated authorisation process for multinational trials. This should reduce the burden on researchers both directly – by removing duplication between multiple submissions – and indirectly by ensuring greater harmonisation in decision making and the application of requirements across Member States. We consider it is important that Member States will only be able to opt-out of the joint decision in a limited set of circumstances as proposed, since a wider opt out would undermine the value of the coordinated approach.

Q.6 Keeping in mind that the proposal introduces a single decision (including regulatory and ethics approval) - would an extension of the timelines beyond the Commission's proposal (maximum 65 days) impact significantly on the conduct of clinical trials? And what timeline would be acceptable for this single decision?

15. It is important that the Regulation takes all possible steps to ensure that the EU provides a competitive environment for clinical trials. We therefore consider that the timelines set out in the proposal should be maintained wherever possible.

16. The authorisation procedure must allow for proper consideration of the issues by the Member States concerned and the reporting Member State. Where the processes need to be adjusted to take this into account, this should be done without increasing the overall timelines.

Q.7 What opportunities do you see to introduce more risk-adapted elements?

17. If products available without prescription are included in the scope of the Regulation, further risk-adaptation will be needed to ensure that trials of these products are regulated proportionately and do not have to comply with the full requirements of the legislation (see question 1).

Q. 8 Have you ever experienced difficulties obtaining insurance for a clinical trial? and

Q. 9 Do you recognise the Commission's suggested rise in costs of insurance?

18. The Trust does not sponsor clinical trials therefore we have limited experience around obtaining insurance. We do not directly cover indemnity costs so cannot provide evidence about increases in the costs of insurance. Our discussions with the academic research community suggest that there do not appear to be serious difficulties in obtaining insurance for trials in the UK. However, academics note there are difficulties and high costs associated in obtaining insurance for conducting trials at sites in other Member States.

Q. 10 Do you see benefits in a Government run scheme? If so, please explain what you think the benefits would be?

19. The proposed National Indemnity Scheme could benefit academic clinical trials as it would be provided free of charge where the trial is not intended to produce data for a marketing authorisation. This would be particularly valuable to alleviate the difficulties and high costs associated with conducting trials at sites in other Member States. However, further details on the system, including the cost of implementing this in UK, are needed from the Commission and MHRA to develop a better understanding of the potential costs and benefits. For example currently academic sponsors – often funded by the public sector – spend significant amounts on insurance, which could be diverted to delivering research under this system, but this benefit may be negated if the system is costly for the Government to implement.

Q.11 Do you think that there are opportunities to include more specific requirements for GCP, or is the regulation specific enough?

20. We support the approach taken in the UK Medicines for Human Use (Clinical Trial) Regulations that the International Conference on Harmonisation guidelines on Good Clinical Practice (ICH-GCP) should not be a legal requirement and that instead appropriate GCP standards should be written into the protocol. The Regulation applies a similar approach, saying that studies “shall take account of” the detailed quality standards set out in ICH-GCP (Article 44), with key features codified explicitly in the Regulation. ICH-GCP is based on industry standards and some aspects of this are not practical for academic trials. We are very concerned that specifying further GCP requirements within the Regulation will result in a loss of flexibility for sponsors to determine appropriate requirements for their trial. Such a change is likely to have a detrimental impact on academic clinical trials that are not able to operate to ICH-GCP standards.

21. We are concerned about a lack of consistency in the wording between Recital 29 and Article 44. Recital 29 says “the ICH guidelines on good clinical practice should be used as guidance for the application of rules set out in this Regulation” whereas Article 44 says “the sponsor and the investigator ... shall take due account of” these guidelines. In order to ensure consistency and flexibility we would like to see Recital 29 amended in line with Article 44.

22. We would appreciate greater clarity on the requirement for non-clinical data to be submitted in the application dossier to “be based on studies complying with Union legislation on the principles of good laboratory practice” (GLP; Article 25(3)). For example, is this intended to mean that data must be generated in a GLP-certified laboratory or a laboratory operating to the principles of GLP? In general, academic laboratories are not GLP certified. While contract research organisations may be used to produce the necessary data, there may be cases where some data are produced in an academic lab. Restrictive interpretation of this clause may therefore present issues for trials based on data from academic laboratories.

Q. 12 Have you identified any potential risks or improvements to the quality of clinical trials based on the proposed Regulation?

23. We welcome the Regulation's moves towards greater transparency around clinical trials, for example on the requirement for registration of trials where information is submitted in the application dossier (Article 25(6)) and to make information in the EU database publicly available (Article 78). Issues that need to be taken into account in developing measures to promote transparency include:

- patient consent and confidentiality;
- the risks of access and analysis by third parties with vested interests which could produce information that undermines public understanding of a treatment or research finding;
- maximising usefulness and minimising risks by balancing the level of detail in the data (e.g. aggregated findings versus patient level data) with how widely these data are shared (e.g. publicly available versus controlled access); and
- the need to ensure the environment incentivises the funding and delivery of clinical trials, for example by granting researchers a period of exclusivity for the use of their data.

24. We also welcome the streamlining of safety reporting requirements which is an improvement on the Directive. This streamlining includes reduced annual reporting requirements for IMPs used within the terms of their marketing authorisation and the potential to exclude certain adverse events from reporting in the protocol. This proportionate approach will enable sponsors and investigators to concentrate on other important issues, without compromising patient safety. We note that there may be further opportunities for safety reporting requirements to be simplified, which has the potential to bring further benefits.

Q.13 Are there any features that you think should be included in the proposal that would make the EU a more attractive place for the conduct of clinical trials?

25. The Regulation would legislate to allow emergency clinical trials under certain conditions, in line with international guidelines. In order to benefit from the exemptions in this section, a clinical trial must only pose "minimal risk" to the subject (Article 32(e)). However, minimal risk is not defined and no such "minimal risk" clause exists in the current UK Medicines for Human Use (Clinical Trials) Regulation Amendment 2006 that relates to this. The introduction of this clause risks undermining the progress that the UK has made in the regulation of emergency clinical trials. Many emergency conditions require development of new treatments. However, the risks associated with new treatments are often unknown in the early stages of development. Imposing a restriction of "minimal risk" trials will therefore compromise the testing and development of new treatments for emergency conditions with high mortality rates.

Q.14 Are there any other elements of the proposal that you would like to comment on?

26. 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 to support these decisions.

27. We welcome the inclusion of co-sponsorship in the Regulation. This should facilitate the sharing of responsibilities across organisations, where one organisation is not able to take these on in their entirety. This is particularly important in academic trials, for example to allow joint sponsorship by a hospital and university. The recognition of co-sponsorship in the Regulation also has the potential to facilitate academic collaborations across the EU.

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