

Summary

1. The Academy of Medical Sciences urges the European Commission to revise the Directive and develop a harmonised regulatory framework for clinical trials examining the safety and efficacy of medicinal products, that is proportionate to the risk posed to trial participants and which will facilitate the conduct of these studies in Europe. The Academy is pleased to be able to respond to the Commissions concept paper on the revision of the 'Clinical Trials Directive' 2001/20/EC and would urge that the research community is actively consulted as further details on the proposals are considered (for example, on changes to definitions in the Directive and details of the proportionate approach).
2. In developing this response we have worked closely with the Wellcome Trust and our key messages are consistent with their response. The Academy also supports and has contributed to the submission by the Federation of the European Academies of Medicine (FEAM).
3. Our response highlights the following key points:
 - **Clarifying the scope of the Directive:** key definitions and appropriate guidance should be revised to ensure that the Directive is applied only to trials of the safety and efficacy of medicinal products, as originally intended.
 - **Adopting a proportionate approach:** For trials within the scope of the Directive, a regulatory approach is urgently required where approval and ongoing requirements are proportionate to the risks posed and potential benefits. The research community should be given the opportunity to comment on how levels of risk are categorised. The new system should then be piloted, and subsequently implemented across all Member States.
 - **A streamlined process for multinational trials:** We support a system of single submission followed by a coordinated assessment procedure for multinational trials. This would aid harmonisation among Member States and ensure consistent application of a new proportionate approach across the EU.
 - **A consistent approach for academic and commercial trials:** We strongly support the application of a revised Directive to both academic and commercial sponsors. However, we suggest that multi-sponsor trials should be permitted under the Directive, since the flexibility this provides will facilitate international collaboration and promote research translation in a difficult financial climate.
4. It is imperative that the revision of the Directive addresses issues relating to the current lack of proportionality in clinical trial assessment, authorisation and monitoring. For more detailed analysis and case-studies on the impact of the Directive, please refer to Annex A for the relevant chapter of the recent Academy of Medical Sciences report, '*A new pathway for the regulation and governance of health research*'.¹ The UK Government has stated its intention to take forward the recommendations from this report, including increasing the proportionality of the Directive and its application, as part of the 2011 'Plan for Growth'.²

¹ <http://www.acmedsci.ac.uk/index.php?pid=47&prid=88>

² http://cdn.hm-treasury.gov.uk/2011budget_growth.pdf page 51

Clarifying the scope of the Directive (consultation Item 9)

5. The scope of the Directive must be clarified to ensure it is limited to trials examining the safety and efficacy of medicinal products. All other types of trial should remain outside the scope of the Directive and individual Member States should be responsible for overseeing these, as they do for other types of clinical research. In the UK, clinical research is overseen by the robust regulation and governance framework provided by research ethics committees and NHS Trusts.
6. There are significant concerns that experimental medicine is being hindered by being inappropriately classified within the scope of the Directive. Experimental medicine covers a wide range of methods from standard tests to self-reporting of symptoms and questionnaires, through to biomarkers, imaging and biosensors. These studies precede and can inform the development of clinical trials, but are not directly concerned with trials of the safety or efficacy of medical products. Experimental medicine is crucial in improving understanding of human physiology and the pathophysiology of disease, however, researchers undertaking such studies are concerned that the Directive is impeding their work by imposing the same regulatory standards required for trials of the safety or efficacy of medical products.
7. The scope of the Directive must be refined through clarification of key definitions (see Box 1). We disagree with the Commission's proposal that the definition of 'non-interventional trials' should remain unchanged. The definition of non-interventional trials (article 2c) should be clarified, to address the most problematic aspect that has led to the inclusion of studies that involve additional diagnostic and monitoring procedures but which rarely add risk (see Box 2). In addition to clarifying exclusion from the Directive at article 2c, this should be complemented by further clarification of the definition of 'clinical trial' (article 2a).
8. Since Member States have implemented the Directive in different ways, the level to which requirements are standardised will be key to improving the environment for the conduct of clinical trials in the future. However, it should be recognised that this may require rewording and clarification of definitions within the Directive. Current problems with the Directive include:
 - strict interpretation of the definitions in Article 2, particularly of 'non-interventional trials', makes the scope of the Directive very broad (see above);
 - problems created by the broad scope of the Directive are exacerbated by a one-size-fits-all approach, which results in costly delays to trials which pose little risk to participants; and
 - inconsistent interpretation of both the authorisation and ongoing requirements for clinical trials.
9. We would strongly recommend that revision of the Directive must not increase the range of trials which fall within its scope. It is a priority that the scope of the Directive is clarified and a proportionate approach to trials of medicinal products is piloted.
10. We are concerned with the new proposed definition of an Investigational Medicinal Product as a medicinal product 'which is being tested or used as a reference in a clinical trial'. If the product is being used 'as a reference' in the trial it should not be classed as an IMP because it often will follow the current standard of care.

Box 1: Scope of the Directive - diagnostic and monitoring procedures

The current definition of 'non-interventional trial' means that in many cases the scope of the Directive has been broadly interpreted. The below example shows how the addition of a monitoring procedure can bring a trial within the scope of the Directive according to current definitions. In a study looking at side effects of a vaccine:

- If the vaccine is administered within the terms of its marketing authorisation as part of usual clinical practice, then it would not be subject to the requirements of the Directive.
- However, if researchers want to take cerebrospinal fluid from patients given the vaccine (still within the terms of its marketing authorisation), this intervention means that the study would be now deemed a clinical trial of an investigational medicinal product and subject to the requirements of the Directive.
- In contrast, if cerebrospinal fluid is taken for an unrelated study in which patients are not receiving a medicinal product, this would not be regulated under the Directive. In the UK such a study would be regulated through other mechanisms.

The intended objective of Directive was to provide a harmonised approach for clinical trials of the safety and efficacy of medicinal products. This example illustrates how, in practice, the addition of a diagnostic or monitoring procedure is inappropriately bringing studies within the scope of the Directive. It is the safety or efficacy of a medical product that should be regulated through the Directive, not additional diagnostic intervention.

Box 2: Case study on the impact of the broad scope of the Directive

We understand that some studies in the UK have been seriously impeded because they were considered to be interventional trials. For example, a study that aimed to determine the optimal arterial oxygen saturation in pre-term infants was classed as an interventional clinical trial despite the fact that oxygen is routinely used at the tested concentrations in clinical practice. This study was then required to be GCP and GMP compliant, which are burdensome to implement.

Further examples are provided in the AMS report.³

Adopting a proportionate approach (consultation Item 11).

11. Individual Member States have implemented the Directive in divergent ways which has led to inconsistent and divergent practices in approval and ongoing requirements.⁴ As previously stated, we would strongly support clarifying the scope of the Clinical Trials Directive to ensure that it is limited, as originally intended, to only trials of medicinal products.
12. Within the revised Directive scope, we would strongly support measures to implement a proportionate approach, with clear guidelines and an appropriate assessment system. Trials of medicinal products vary in risk, from minimally interventional studies where the risks are similar to standard care, to much higher risk studies where far less may be known about the investigational medicinal product. It is important that the regulatory requirements are proportionate to risk and this should be set out in the regulations. Such an approach is applied by the Food and Drug Administration (FDA) in the United States.⁵ Categorisation could

³ <http://www.acmedsci.ac.uk/index.php?pid=47&prid=88>

⁴ <http://www.acmedsci.ac.uk/index.php?pid=47&prid=88> page 44

⁵ <http://www.acmedsci.ac.uk/index.php?pid=47&prid=88> page 48

be a practical way to implement a risk-based approach, such as that used in the Medical Devices Directive 2007/47/EC

13. Consideration needs to be given to the specific requirements for trials of differing risk, for example in relation to intensity of auditing, monitoring, safety reporting and insurance. The objective should be to significantly decrease the burden on trials of low risk, particularly for those trials where risk is similar to 'usual care'.⁶ Examples of requirements that need a risk-based approach, greater clarity and guidance are safety reporting and good clinical practice (GCP).
14. The research community should be given the opportunity to comment on how levels of risk are categorised across a proportionate approach to the assessment and monitoring of all trials. A proportionate approach in clinical trial approval and monitoring should take into account:
 - the risk posed to a participant in the study compared to standard care;
 - the risk to the sponsor, institutions, and the health service;
 - the risk to broader public health posed from not conducting the research; and
 - the potential benefits of the trial.

The benefit-risk balance will differ significantly between populations. For example, a patient suffering from a life-threatening disease may be prepared to accept greater risk than a healthy volunteer to participate in a trial.

15. How harmonisation of a risk-based approach will be achieved is not outlined or discussed in the concept paper. It is essential that a risk-based approach is piloted and evaluated before its implementation. Although we welcome the use of Annexes to provide more information and guidance, we are concerned that this will be insufficient for true harmonisation. The UK Medicines and Healthcare products Regulatory Agency and Medical Research Council have developed guidelines in the UK that are currently being trialled and could be used to inform methods of a risk-based approach in the EU.⁷
16. The safety reporting requirements for clinical trials, including those for suspected unexpected serious adverse reactions (SUSARs) currently result in unnecessary duplication. For example, currently both NCAs and Ethics Committees receive SUSAR reports, but Ethics Committees do not act on this information. The concept paper does not describe how these reporting requirements will be simplified. We recommend that the revised Directive clarifies that NCAs are the primary stakeholder of information relating to safety reporting and should receive routine reports. Ethics Committees should receive the appropriate summary information needed to fulfil their function.
17. The concept paper draws attention to the International Conference on Harmonisation guidelines on good clinical practice (ICH-GCP) without acknowledging that these guidelines are not appropriate for all types of trials. ICH-GCP was developed in 1996 by the pharmaceutical industry to facilitate multinational trials but these standards are less relevant, and often difficult to apply, to trials in non-commercial settings. This has been acknowledged in the UK where ICH-GCP is not a legal requirement. It is essential that GCP requirements are clear and proportionate to risk.

⁶ <http://www.acmedsci.ac.uk/index.php?pid=47&prid=88> page 51

⁷ <http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesregulatorynews/CON114358>

A streamlined process for multinational trials (consultation Items 1-8)

18. Approximately 75 per cent of clinical trials are based within a single Member State. It is important to ensure that any changes to the process for review of multinational trials do not increase the bureaucratic burden and cost to these trials. Trials in a single Member State should apply, as now, to their National Competent Authority (NCA) for robust national approval.
19. We agree that single submission into an 'EU portal' would simplify the system for multinational trials and ensure consistent information requirements from NCAs. Separate assessment by individual NCAs would not address differences in the interpretation of the Directive or reduce the administrative work of sponsors. Further steps would be required to harmonise these procedures across Member States.
20. This single 'EU portal' should be aligned, where possible, with successful application systems in individual Member States. The UK's Integrated Research Application System (IRAS)⁸ has streamlined the application process for all aspects of health and social care research and provides a good model for a single EU submission for clinical trial authorisation. To promote harmonisation, it is important that the information and documentation required for multinational trials via the 'EU portal' is consistent with that requested by individual Member States for single country trials.
21. The Academy is broadly supportive of the Commission's outlined proposal for a 'co-ordinated assessment procedure' (CAP) for multinational trials, providing this is implemented in such a way as to reduce the time for assessment and facilitates a harmonised and proportionate approach across the EU. It is important that any system enables:
 - Single submission of an application;
 - Single, streamlined assessment and collaborative agreement;
 - Reduced timelines and bureaucracy.

We agree that central assessment by a scientific committee would not be feasible since it is likely that this would delay time to gain authorisation and increase bureaucracy and costs.

22. We would support a proposal for CAP to be taken forward by a single lead 'Reporting Member State', to conduct the assessment based on the technical aspects of clinical trial authorisation. This assessment would then be shared with all relevant Member States and areas of disagreement discussed before reaching the final CAP recommendation. This process should promote harmonisation over time because it would require continuous dialogue between individual NCAs and remove differences in interpretation of the Directive. While we support the CAP procedure in principle, more detail is required on, for example, how the 'Reporting Member State' is selected and how the national and CAP processes will be co-ordinated.
23. CAP must be introduced, for multinational trials within the scope of the Directive, alongside a proportionate approach. The implementation of a single joint assessment via CAP provides a crucial opportunity to implement a proportionate approach that is consistent across Member States.
24. We agree that only aspects of risk-benefit assessment (examples of which are listed under 1.3.1a) should be included within the scope of CAP. Ethical aspects of clinical trial assessment listed under 1.3.1b, such as consent and recruitment, should remain within the remit of Member States. We also support the Commission's appraisal that aspects of clinical trial approvals listed under 1.3.1c, relating to the suitability of the trial sites and the investigator should be carried out by organisations with local expertise. It is vital that there is not duplication in the functions undertaken through CAP and the roles of individual Member States

⁸ <https://www.myresearchproject.org.uk/SignIn.aspx>

NCA or Ethics Committees.

25. National views on ethical issues remain crucial, for example countries can vary widely on views regarding embryonic stem cells and embryo research. Alongside Member States continuing to carry out independent ethical review, we would encourage interactions between Member State ethics committees to share best practice and improve efficiency.
26. We would not support the idea of deferring CAP disagreements to the Commission or Agency for a central decision that would be enforced at the EU level, as this would increase bureaucracy and disrupt dialogue between Member States that is important for harmonisation. We propose that the Member States involved in the trial should reach a consensus recommendation, in a similar process to that currently used in the Voluntary Harmonisation Procedure (VHP).
27. CAP should not be mandatory for all clinical trials. This would unnecessarily burden the majority of clinical trials which occur in only one Member State by introducing new processes and delays. If CAP is shown to reduce timelines and streamline approvals the desirable long-term goal would be that all multinational trials within the scope of a revised Directive would submit clinical trial assessments via this route.
28. There should not be any extension to the statutory timescales prescribed by the current Directive. Any increase in authorisation timelines through using the CAP process could decrease Europe's competitiveness in the medical research sector. However, we consider that individual NCAs should remain at liberty to set more ambitious targets for the authorisation of single-country trials.
29. We support the idea of pre-assessment to identify low-risk trials so that the timelines for approval can be reduced for these studies. The revised Directive will need to ensure that a pre-assessment procedure does not increase bureaucracy and further clarification will be required around who is responsible for assessing whether a trial fits into this category. We suggest that the trial sponsor should be responsible for determining if a trial is low risk, and appropriate support from relevant NCAs will be required to facilitate this process. It is important that a suitable definition of 'type-A' trial is established. The research community should be given the opportunity to comment on this and how levels of risk are categorised across a proportionate approach to the assessment and monitoring of all trials.

A consistent approach for academic and commercial trials (consultation Item 10)

30. We agree with the appraisal that academic sponsors should not be excluded from the scope of a revised Directive, which should continue to apply to both academic/non-commercial and commercial sponsors. Not all academic trials are low risk and it is important to provide adequate protection to participants. This is also fundamental to facilitating collaborations between academia and industry throughout Europe, a key priority in the EU green paper on the common strategic framework for EU research and innovation.⁹ It is essential for the health of the EU biosciences sector that collaboration between academia and industry is promoted and therefore consistency in approach and promotion of best practice should be supported.
31. The Impact on Clinical Research of European Legislation (ICREL) project report shows that academic trials have been disproportionately affected by the Directive, largely because academic sponsors have less resource and infrastructure to navigate the bureaucratic

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<http://europa.eu/rapid/pressReleasesAction.do?reference=MEMO/11/76&format=HTML&aged=0&language=EN&guiLanguage=en>

challenge associated with the Directive.¹⁰

Other issues

Insurance/indemnisation (consultation Item 14)

32. This section of the consultation paper is unclear on the problems that the proposed options are trying to address and more information and clarity is needed on the options outlined. The Commission should outline whether Member State indemnification for clinical trials would be obligatory or optional, whether Member State indemnification would also apply to commercially sponsored trials, and how this would be funded.

Single sponsor (consultation Item 15)

33. We are pleased that the Commission recognises the distinction between liability and responsibility. However we do not support the concept that single sponsorship should be maintained in its current form. Harmonisation is important and is not hindered by multi-sponsorship.

34. Trials may involve more than one organisation who will wish to share responsibilities for the trial through sponsorship and this possibility needs to be accommodated within the Directive. Under the current system the concept of a single sponsor has prevented the conduct of clinical trials between EU Member States because the sponsorship from one Member State has not been accepted by other Member States. A system of multi-sponsorship has been used successfully within the UK and could be used as a framework for implementation within and between other Member States. Furthermore, multiple sponsors should facilitate collaboration with non-EU countries since, for example, European Member States cannot act as sponsors for trials in the US.

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¹⁰ http://www.efgcp.be/downloads/icrel_docs/Final_report_ICREL.pdf