

European Commission: Assessment Of The Functioning Of The “Clinical Trials Directive” 2001/20/EC**Response by the Wellcome Trust**

January 2010

Introduction

1. The Wellcome Trust is the largest medical research charity in Europe. It funds innovative biomedical research, in the UK and internationally, spending over €600 million each year to support the brightest scientists with the best ideas. The Wellcome Trust supports public debate about biomedical research and its impact on health and wellbeing.
2. The Trust funds academic-led clinical trials both in the EU and third countries. Timely and robust clinical trials are imperative to ensure advances in biomedical research are translated into safe and effective improvements in healthcare. Such trials require a transparent and consistent governance framework that protects trial participants. We are therefore pleased to have the opportunity to respond to this review on the Clinical Trials Directive (the ‘Directive’) and its implementation.
3. While we support many aspects of the current Directive, a number of elements have had a disproportionately negative impact on academic trials, as evidenced in the Impact on Clinical Research of European Legislation (ICREL) Report¹. Academic institutions are less well resourced and equipped than commercial sponsors to deal with the bureaucratic burden imposed by the Directive. Our response therefore suggests a number of changes to address this problem while maintaining an appropriate regulatory framework:
 - a. Streamlining of assessment processes for multicentre trials to reduce delays**
We would support the streamlining of National Competent Authority (NCA) agreement for multicentre trials, with a single NCA leading the process. We would also support the strengthening of networks of regional Ethics Committees and the reduction of bureaucracy in this process, while retaining input from the Member States involved.
 - b. The introduction of risk-based requirements for trials**
The current ‘one size fits all’ approach to clinical trials is not appropriate since different trials carry a different level of risk and benefit. Changes should be made to ensure that the requirements of the Directive are proportionate to risk, to alleviate the unnecessary burden on specific low risk trials.
 - c. Clarification of key definitions to ensure consistent implementation of the Directive**
A lack of clarity in the definitions for key terms in the Directive has led to inconsistent interpretation of the Directive in Member States. We suggest examples of where clarification would improve the Directive.
4. We would like to see the Directive amended to incorporate these changes. As an interim measure, voluntary guidelines may facilitate the application of the current Directive.

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

5. Throughout the response we have given examples of current concerns where possible. However, in some instances it has been difficult to provide specific details because of issues with confidentiality and intellectual property.
6. In developing this response we have collaborated closely with the UK Academy of Medical Sciences and the Medical Research Council. We are grateful for the input received from Trust funded researchers and Fellows of the Academy of Medical Sciences. The Academy and the Medical Research Council are submitting separate responses, but our key messages are consistent.

Question 1: Examples of improved protection and benefits of the Directive

7. We support the principles underpinning the introduction of the Directive which were to:
 - Protect the health and safety of clinical trial participants;
 - Improve the ethical soundness of clinical trials;
 - Ensure the reliability and robustness of data generated in clinical trials; and
 - Simplify and harmonise the administrative provisions governing clinical trials to allow for cost-efficient clinical research.
8. We welcome the positive impact that the Directive has had in beginning to harmonise clinical trials governance throughout the EU. In particular researchers have noted that the Directive has been particularly valuable in raising Good Clinical Practice (GCP) standards in academic trials, which were previously more variable than in industry. However, the implementation and interpretation of the current Directive has come at a price, increasing time scales and raising the costs involved in conducting trials.

Key Issue 1: Multiple And Divergent Assessments Of Clinical Trials

Question 2: Appraisal of the situation

9. The consultation document accurately sets out the current process for approval in multi-centre trials and the layers of Ethics Committee and National Competent Authority (NCA) approval. We agree with the weaknesses of the system that are highlighted, especially:
 - a. Increased administration costs;
 - b. Resultant delays to trial start dates, due to multiple approval requirements; and
 - c. Inefficient use of resource from each National Competent Authority (NCA).

Question 3: Weaknesses and impacts of divergent assessment

10. The implementation of the Directive has resulted in significant negative impacts. As illustrated by the ICREL report², the increased administrative burden has been a particular problem in academic settings, where many organisations lack resources to handle the requirements. The increased and sometimes disproportionate burden is due to a number of issues, including:
 - a. multiple assessments of clinical trials;
 - b. inconsistent interpretation and implementation of the Directive across Member States; and
 - c. an insufficiently risk-based approach.

We are not aware of any evidence that shows this increased burden has brought about discernible benefits to patient safety or the ethical soundness of trials.

² http://www.efgcp.be/downloads/icrel_docs/Final_report_ICREL.pdf

11. We agree with the highlighted weaknesses and their impacts. The duplication of work required to submit applications to different NCAs has been raised as an issue; this is exacerbated when NCAs have different requirements, for example in the documentation required for trials of Investigational Medicinal Products (IMP). The failure to take into account the purpose of a study has also been raised as a serious shortcoming. A 'one size fits all' approach to clinical trials is not commensurate with the expected risks which will differ, for example, in a study of a registered drug within its authorised indication versus a phase I-II trial of a novel IMP.
12. In addition to increased bureaucracy and lengthened timescales, the inconsistencies between different NCAs have also had more disruptive effects. For example, different interpretations between the French and UK NCAs meant that a trial that was already running in France, which had not required French NCA approval, could not be extended to an additional site in the UK. UK researchers identified that the trial would require approval by the Medicines and Healthcare Products Regulatory Agency (MHRA), the UK NCA. This difference of opinion between the UK and French NCAs led to negotiations over the trial breaking down³.

Question 4: Streamlining of NCAs

13. The Directive has made some progress in harmonising processes across Member States. However, the lack of clarity around the interpretations of terms leads to potentially different assessments of clinical trials across different Member States' NCAs. In addition to streamlining of NCA assessment, clarification of a number of definitions would assist in the assessment of trials to ensure that Member State NCAs are using the same criteria. This issue is discussed further under Key Issue 2.
14. We would support streamlining of the process and would like to see an option similar to 3.3.2.1 (a) - Common NCA Agreement, adopted, where the relevant NCAs work together to reach agreement. This mechanism would allow Member States to cooperate and to reach a single position. To work successfully, this process must not slow down the approval procedure for multinational trials. We suggest that the NCA from the lead country in a multicentre trial could drive the process, to reduce the potential for conflicting assessment. Definitive guidelines and agreed terminology would be needed to ensure consistent standards and interpretation, regardless of the selected lead NCA. A key issue for researchers would be the ability of NCAs to respond in a timely manner to feed into this process. In some cases collaboration between researchers and the NCAs in multicentre trials is already being used to facilitate the approval process, demonstrating that this streamlining could be effective.
15. As noted in the consultation document the majority of trials take place in a single Member State. It is therefore important that the mechanism for approving these trials is not inadvertently made more complex if NCA approval is streamlined. We suggest that the relevant NCA retains responsibility for approval of these trials, without the need to seek opinion from other NCAs.

Question 5: Streamlining of Ethics Committees

16. We would support streamlining of the function of national Ethics Committees to improve efficiency, while maintaining the ability of regional Ethics Committees to give local and culturally appropriate input into a decision. National views on ethical issues remain crucial, for example countries can vary widely on views regarding embryonic stem cells and embryo research. Thus we would prefer an option similar to 3.4.2 - strengthening networks of national Ethics Committees involved in multinational clinical trials. It would be beneficial to strengthen networks of Ethics Committees so that they can make a more informed contribution to a decision. However, as an extension of 3.4.2 we suggest the same dossier of information should be provided to the network of Ethics Committees while a single Ethics Committee

³ Anecdotal evidence from researcher

should advance the process, to reduce bureaucracy. Any attempts to generate a consensus agreement must however proceed in a timely manner without further delaying the approval process. We agree that it would be important for each Ethics Committee to retain its right to opt-out of the final decision.

17. It would also be of benefit to clarify the scope of NCAs and Ethics Committees as described in 3.4.3, for example in the reporting of suspected unexpected serious adverse reactions (SUSARs) (see paragraph 23 below). It is important that their roles remain separate and duplication of functions should be avoided.
18. We are aware that paragraph 3.4.1, the one-stop shop for submission of assessment dossier, may have been interpreted in some responses as proposing a system for single EU-wide ethical view. For clarity: we would oppose such a system and instead advocate that national Ethics Committees maintain the right to input into a decision as discussed in paragraph 16. However, we acknowledge the benefits of streamlining administration within a Member State. We support mechanisms such as the UK's integrated research application system⁴, which minimises duplication and captures information required by a number of review bodies and ethics committees.

Key Issue 2: Inconsistent Implementation Of The Clinical Trials Directive

Question 6: Appraisal of the situation

19. We agree with the situation outlined: that inconsistent implementation of the Directive leads to extended timelines and is resource intensive. The Directive is not always applied consistently within each Member State, for example, in the UK very similar products are not consistently classified in the same class of interventional or non-interventional medicinal products (see Box 1 for examples of differing classification of medicinal products). There are also concerns that experimental medicine is already being hindered by being inappropriately classified as falling under 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 are crucial in improving understanding of human physiology and the pathophysiology of diseases. However, researchers are concerned that the Directive is impeding this work because it imposes on them the same regulatory standards required to obtain market authorisation.
20. In addition, Ethics Committee approval in a single Member State can be highly variable. Any difficulties resulting from inconsistencies in a single Member State are amplified where more than one Member State is involved.

Box 1: Examples of the classifications of medicinal products

1. For an academic clinical trial in the UK on dichloroacetate, an unlicensed and widely available compound, it was unclear what information was required to support the application to conduct the trial, leading to an extended timescale to gain approval.
2. Urea cream is routinely recommended for diabetics who have dry skin in order to soften the skin and prevent foot ulcers, but there is little scientific evidence to support this. A study to collect data on this was planned, but the cream was not licensed as a medicinal compound and therefore did not meet the terms of Directive, despite being widely used in routine practice. The delay led to the study being abandoned.
3. Research planned to compare liquid nitrogen and 60 per cent salicylic acid as treatments of warts was significantly delayed because the UK MHRA was not clear whether liquid nitrogen

⁴ <https://www.myresearchproject.org.uk/>

was a medicinal product. Consequently, a large amount of time was spent finding out who manufactured the nitrogen and whether the conditions of manufacture met the conditions laid in the Directive. The MHRA subsequently decided that liquid nitrogen was not a medicinal product and fell outside the terms of the Directive. These extended deliberations caused a significant delay in the research project.

21. In addition to the examples provided in the consultation document under section 4.1, there are broader issues with how the Directive has been implemented in different Member States. For example, it is perceived that the approval process is a much greater barrier in some countries (for example, the UK) than for other Member States (for example, the Netherlands)⁵ depending on how the Directive has been interpreted and implemented in national legislation. While clarification of the Directive may be useful to overcome these issues in part, it will also be important that Member States take appropriate action to ensure that their processes are appropriate and consistent. Further details of specific examples of inconsistencies in the application of the Directive are given below.
22. Clarification is required regarding what constitutes a 'substantial amendment' to the terms of the application or trial protocol. The definition itself needs revision to ensure reporting is for the protection of study participants. There is a view that many amendments are reported to avoid non-compliance, rather than because they are 'substantial'.
23. The reporting of SUSARs requires greater clarity and guidance. In the present system, SUSARs are reported to ethics committees, who do not act on this information. This system could be simplified by clarifying that the NCA is the primary stakeholder of this information and providing ethics committees with an annual safety report.
24. In the UK there is a lack of clarity around which staff need GCP training for low risk non-commercial trials. For example, would every member of nursing staff need to be GCP trained if they are administering a low risk intervention to newborn babies? This issue would benefit from clarification and it is important that the resulting requirement is proportionate to the risk involved.
25. UK academics are concerned about the UK interpretation of 'extemporaneous preparation', which currently requires a clinical trials manufacturing licence and Qualified Persons (QP) authorised release of products. It appears that requirements differ for industry verified preparations of this type in other Member States and in the US. Simplified approval requirements might facilitate the acceleration of drug development and we understand this issue has been raised with the EMEA.
26. Harmonisation of insurance requirements across multi-centre trials is also required to bring clarity and reliability to the process. In addressing insurance requirements, consideration should be given as to the best way of enabling effective coverage of paediatric trials on the basis of robust risk evaluation.
27. Given the negative impact of the Directive on academic trials, as described in the ICREL report and consultation document, we do not believe that the solution is to widen the scope of the Directive to include other areas of research. Extending the Directive as it stands to cover, for example, non-interventional trials would have significant negative implications in both cost and time and risk transferring the shortcomings of the Directive to other areas. Rather than extending the Directive, we believe that clearer guidance is needed to ensure that the requirements imposed on a trial should be proportionate to risk. The guidance should also allow for trials that deviate in a clinically insignificant way from provision of standard of care to be quickly reviewed and classified as a non-interventional trial where appropriate.

⁵ Anecdotal evidence from researcher

Question 7: Weaknesses and impacts of inconsistent implementation

28. We agree with the weaknesses – potential risk to patients and increased administrative costs – outlined in the consultation document. As highlighted in our response to question 6 above, this issue is of particular concern to UK academics.

Question 8: Options to address inconsistent implementation

29. The lack of clarity around some key definitions leads to varying assessments of clinical trials and differences in the way the later stages of trials are handled, for example what constitutes an interventional trial and handling of SUSARs. We would support option 4.3.1 that the Directive be reviewed in order to clarify definitions. However, as noted in response to question 6, it will also be important that Member States take suitable action to address problems specific to their implementation of the Directive.

Key Issue 3: Regulatory Framework Not Always Adapted To The Practical Requirements

Question 9: Examples of insufficient risk differentiation

30. A 'one size fits all' approach to clinical trials is not appropriate since different trials carry a different level of risk and benefit. As highlighted in the consultation paper, the actual risk of a clinical trial for the participant depends on a range of factors, including the: extent of knowledge and prior experience with the IMP; patient population involved; whether or not the IMP is already authorised; and whether the authorised medicine is being used in approved indications or for other therapeutic uses. This is not reflected however, in the current Directive: the requirements of the Directive are not proportionate to the expected risks, and the regulatory framework is not applied in a manner that differentiates risk or reflects practical considerations. It is not necessary or appropriate to have the same requirements for low risk trials as for a high risk trial, such as first-in-man studies of a new agent. For example, low risk trials are currently required to have the same level of auditing as high risk ones, which leads to an excess of bureaucracy and unnecessary delays to low risk trials. Further examples are given in Box 2.
31. In addition to the lack of risk-differentiation, implementation of the Directive is, in some cases, highly process-driven, placing more emphasis on the quality of paperwork than on the quality of the trial itself. We recognise that this is perceived as more of an issue in some Member States than others and therefore there may be scope for improvement through local implementation.
32. We would strongly support a risk-based approach, with clear guidelines and an appropriate system for risk assessment of trials. 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 studies whose risk is similar to 'usual care'. This point is well made in the European Science Foundation Report (see page 9 of the report)⁶.

⁶ http://www.esf.org/fileadmin/links/EMRC/FL_IDCT.pdf

Box 2: Examples of insufficient risk-differentiation

Below are examples of different trials that fall under the Directive. As a result of there being no risk-differentiation built into the Directive, they are all considered to require the same stringency of regulation as, for example, first-in-man studies of a new agent.

- a) *A UK academic trial investigating a peptide hormone that suppresses appetite and thus has potential as an obesity treatment:* Following initial studies in mice and rats, the group wanted to investigate how small changes to the molecule altered its efficacy in humans. The analogues to be tested were naturally-occurring variants of the human hormone, which are less sensitive than the wild-type hormone to degradation by enzyme systems in man; the wild-type hormone cannot be used therapeutically because of its short half-life. However, under the Directive, each molecule must individually go through the full CTA procedure, which is expensive and time consuming. Consequently, the group were only able to test one analogue, and thus may not identify the most effective one.
- b) *A study examining vitamin D, but using a formulation that did not include a calcium supplement:* To obtain the vitamin alone, the group needed to get the vitamin D directly from the manufacturer. Vitamin D is a non-medicinal product, frequently taken by individuals and available over the counter. The regulations set out in the Directive stipulated that the manufacturer was required to have 'good manufacturing practice' (GMP) compliance recognised by its national health authority, a process that delayed the trial by months.
- c) *A study to test the sensitivity of MRI techniques for detecting changes that occur in the brains of patients with liver disease and associated hepatic encephalopathy:* The group planned to investigate whether the psychometric performance of encephalopathic patients can be related to improvements observed on MRI scans. They planned to compare healthy volunteers with patients taking L-ornithine L-aspartate (LOLA) to treat the encephalopathy. LOLA is available over the counter; is licensed as an encephalopathy treatment in Germany; and has also been shown to be of benefit in randomised controlled trials. LOLA was to be used to assess the sensitivity and refine the MRI technique. However, the study was deemed to be a clinical trial and required full approval via the Directive, bringing time and cost implications.
- d) *A study on the ventilation of preterm babies:* An assessment of a clinical care process for preterm babies sought to optimise oxygen saturation limits, within a widely used and acceptable range, with the aim of formalising the clinical care processes used for ventilating preterm babies. However, the assessment was treated as a clinical trial and the systems in place meant that it was as burdensome as a trial of a new agent being used for the first time in a vulnerable group.

Question 10: Appraisal of single sponsor

33. Many trials will involve more than one organisation who will wish to share responsibilities for the trial through sponsorship, and this needs to be recognised by the Directive. At an EFGCP meeting on *Innovative Approaches to Clinical Trial Co-Sponsorship in the EU* in 2009⁷ UK researchers present did not consider sponsorship to be a significant issue, mainly because implementation of the Directive in the UK essentially allows for co-sponsorship of national trials as opposed to a single sponsor. However, this procedure is not recognised in other Member States. Allowing co-sponsorship may facilitate the oversight of trials at sites in other Member

⁷ http://www.efgcp.be/Downloads/confDocuments/Final%20Programme%20Co-Sponsorship%20Workshop_21%20September%202009.pdf

States and reduce the administrative and financial burden and we suggest that the same implementation should be introduced throughout the EU.

Question 11: Revision of implementing guidelines

34. A revision of the guidelines, covering all types of trials already covered by the Directive, would be of benefit if it enabled investigators, sponsors and regulators to apply a risk-based approach, with appropriate application of GCP depending on the risks involved. We would suggest the introduction of different risk categories that take into account the factors that affect the risk of the trial, including: the nature of the intervention; the vulnerability of participants; and complexity and demands of the trial. Clear guidelines with definitions and examples would enable NCAs to assign trials to the correct category more easily, firstly to determine whether the trial is covered by the Directive and secondly to ensure the requirements are proportional to risk. As noted in paragraph 30, it is important that there is a process whereby a trial that deviates in a clinically insignificant way from provision of standard of care can be quickly reviewed and classified as a non-interventional trial.
35. For compounds that are unlicensed but already in use, existing peer-reviewed information could be used to assist in categorising these compounds, for example to determine the level of risk and whether supplementary information should be provided. (See example in Box 1).

Question 12: Would amendment of the Directive be required?

36. The Directive should be reviewed and amended to introduce a risk-based approach to requirements. However, in the interim period, guidelines could be introduced to enable the current Directive to be applied as proportionately as possible.

Question 13: Academic sponsors

37. The Trust strongly urges that the Directive should continue to include both academic and industry sponsors. Not all academic trials are low risk and it is important to provide adequate protection to participants. It is also 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.
38. The ICREL report shows that academic trials have been disproportionately affected by the Directive, largely because academia lacked the resources and infrastructure to manage the changes associated with the Directive. Greater recognition of the difference between trials aimed at developing products versus increasing knowledge about disease models, and the introduction of a more risk-based approach should help to alleviate any unnecessary burden on specific lower risk trials.

Key Issue 4: Adaptation To Peculiarities In Trial Participants And Trial Design

Question 14: Paediatric Medicine

39. It is important that the research environment in the EU promotes high quality paediatric research. However, trials in paediatric medicine have been hindered by the requirements of the Directive, which have created sometimes unnecessary demands on centres undertaking paediatric clinical trials. Researchers have noted that further evidence evaluating the impact of the Directive on paediatric clinical trials is required, for example a report equivalent to the ICREL study, focused on paediatric research would be welcomed.
40. The barriers imposed by the Directive include increased staffing requirements. For example, it was not clear whether a trial involving the administration of a low-risk intervention to new born babies required every nurse involved to be GCP trained or not. Such a requirement might make the trial unfeasible or render it non-compliant.
41. Another example of where clarity is required for paediatric trials is around the necessary approvals for 'step down' units, where babies in trials are moved to hospitals that may not have

the necessary approvals, but are closer to their parents. Requirements which reduce the bureaucratic burden are welcomed here.

42. The introduction of a genuinely risk-based approach and guidance on how the principles of GCP can be applied to trials with differing levels of risk should help to overcome these barriers, since not all paediatric trials are high risk. The vulnerability of participants is only one factor of the overall risk, as noted in response to question 11.

Question 15: Emergency Clinical Trials

43. In England and Wales, the Mental Capacity Act (2005) clearly sets out the conditions under which emergency medical research can be carried out and has succeeded in resolving the difficult balance between ensuring an individual's safety and maintaining a facilitative environment for research. It should be noted that different legislation applies in Scotland and it is our understanding that this alternative approach has not inhibited emergency research in Scotland. Good practice should be shared throughout the EU and we would encourage the adoption of the relevant parts of the Mental Capacity Act (2005) into the Directive.

Key Issue 5: Ensuring Compliance With Good Clinical Practices (“GCP”) In Clinical Trials Performed In Third Countries

Question 16: Comments on third country trials

44. The Trust funds clinical trials in developing countries and therefore our response concerns only developing countries, which are particularly resource-limited settings. We agree with the situation set out in the document and while it is important that internationally accepted norms of GCP are applied in third countries, the large number of guidelines is confusing. We would therefore advise against the creation of further guidelines. We do not consider it to be appropriate for the EU to regulate beyond Member States, but would emphasise the importance of supporting capacity building in developing countries to enable the application of similar standards and principles as set out in EU legislation.
45. Ensuring the requirements for GCP are proportionate and risk-based, as discussed earlier, should alleviate the burden on specific developing country trials where appropriate. It is particularly important to ensure that unnecessary bureaucracy, time and costs are avoided in these countries, which lack the resources to deal with them but are particularly in need of research that improves healthcare.

Question 17: Options for ensuring GCP in third countries

46. It is important to avoid two tiers of standards in Europe and developing countries. Compliance with GCP should be a valuable capacity building exercise, therefore we would encourage adoption of the options that support capacity building (7.3.1); strengthening of international cooperation (7.3.3); and transparency (7.3.5). The US Food and Drug Administration (FDA) provides optional assessment (7.3.4) and this can also contribute positively to capacity building processes, although it requires sufficient support from the sponsor, which may not always be available.
47. We would discourage an increase in EU scrutiny (7.3.6) in developing countries since the development of local scrutiny is of greater benefit in promoting capacity building. This will ensure that trials conforming to GCP are performed and regulated locally in the longer term, avoiding the need for unsustainable regulation from the EU.

Question 18: Other aspects

48. We would encourage the Commission to work with the US, industry and academia to reach agreement on how processes can be aligned between the regions to maximise the opportunity

for collaboration. Initiatives such as the Sensible Guidelines for the Conduct of Clinical Trials⁸, which provide a forum for international agencies to discuss the issues, may already be contributing to this.

49. To ensure a supportive and facilitative environment that allows clinical research in the EU to flourish, it is vital to maintain both EU and national level funding for clinical research and its infrastructure, and to promote education and training. For example, the Wellcome Trust and its partners in the UK Clinical Research Collaboration (UKCRC) provided €94.2 million in 2006 to develop and strengthen clinical research facilities across the UK. Continued funding and a supportive regulatory environment are vital in maintaining UK and European excellence in this field.
50. We urge the Commission to use this opportunity to make revisions that will alleviate some of the bureaucratic, cost and time burdens of the current Directive, while maintaining an appropriate regulatory framework that protects trial participants. The Directive impacts on both academia and the pharmaceutical industry, and it is crucial to achieve the right balance in the amendments for the benefit of the EU clinical research environment.

⁸ <http://www.ctsu.ox.ac.uk/projects/sg>