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The Academy of Medical Sciences

Response to the European Commission consultation on the assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC

Summary

The UK Academy of Medical Sciences welcomes the opportunity to respond to this consultation on the impact of the European Clinical Trials Directive 2001/20/EC. We support the original aims of the Directive and the move towards greater harmonisation of the regulation of clinical trials across the EU. However, since its introduction the Directive has dramatically increased the administrative burden and cost of clinical trials, with no evidence of discernible benefits to patient safety or to the ethical soundness of trials. The negative impact of the Directive has been particularly burdensome for academic (non-commercial) clinical trials, while also making Europe a less attractive location for commercial research.

A 'one size fits all' approach to clinical trials is not appropriate and a failure to take into account that individual trials carry different levels of risk and benefit has been raised as a major shortcoming of the Directive and its interpretation. As highlighted in the consultation paper, the Directive is not currently applied in a manner that differentiates risk, leading to excessive bureaucracy and unnecessary delay.

Our response suggests a number of changes to the Directive, including:

- **A full review** to address the Directive's shortcomings and the negative impact it has had on clinical research. The Directive must continue to include both academic and commercial sponsors. However, we would not support extending the scope to cover other aspects of clinical research, such as non-interventional studies.
- **The adoption of a risk-based approach** that allows the regulatory framework to be applied in a manner that reflects practical considerations. The Directive and accompanying guidelines should be revised to ensure consistent implementation and to enable investigators, sponsors and regulators to apply a risk-based approach, with appropriate application of Good Clinical Practice.
- **Streamlining of assessment processes** by National Competent Authorities (NCAs) and Ethics Committees across the EU, but without moving to a fully centralised process. We would like to see Member States work together to reach a 'common agreement' for the regulatory approval of multinational trials, although care must be taken to avoid inadvertently complicating the process for trials undertaken within a single Member State.
- **The strengthening of networks of ethical committees.** This is an important part of harmonisation, which could be further improved by standardising the information submitted to Ethics Committees across Europe. While welcoming the benefits that would come from greater consistency, we do not believe that a single European body for ethics review should be introduced; national views on ethics remain crucial.

Good governance is needed to protect patients but excessive regulation can cause net harm by denying or delaying patients' access to new medicines. Changes to the Directive must be underpinned by a philosophy of assisting the development of new knowledge, innovative medicines and novel approaches to research, in a safe and ethical manner.

Introduction

In developing this response we have collaborated closely with the Wellcome Trust and the Medical Research Council. We are grateful for input received from Fellows of the Academy and Trust funded researchers. The Wellcome Trust and Medical Research Council have submitted separate responses, but our key messages are consistent. The Academy has also contributed to a response from the Federation of the European Academies of Medicine (FEAM).

The Academy of Medical Sciences is the independent body in the UK representing the whole spectrum of medical science. Our mission is to ensure better healthcare through the rapid application of research to the practice of medicine. The expertise and independence of our Fellows allows the Academy to contribute to biomedical and health policy both in the UK and internationally. Our 944 Fellows are the UK's leading medical scientists from hospitals and general practice, academia, industry and the public service.

Throughout the response we have given examples to support our points where possible. However, it has sometimes been difficult to provide extensive detail because of concerns about confidentiality and intellectual property.

Response to consultation questions

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

1. 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.
    - Simplify and harmonise the administrative provisions governing clinical trials to allow for cost-efficient clinical research.

2. 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 cost, resulting in increased time scales and requiring greater investment for trials to take place.

Key Issue 1: Multiple and divergent assessments of clinical trials

Question 2: Appraisal of the situation

3. 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:
    - Increased administration costs.
    - Resultant delays to trial start dates, due to multiple approval requirements.
    - Inefficient use of resource from each NCA.

Question 3: Weaknesses and impacts of divergent assessment

4. The implementation of the Directive has also resulted in significant negative impacts. As illustrated by the *'Impact on Clinical Research of European Legislation'* (ICREL) report, the

increased administrative burden has been a particular problem in academic settings, where many universities, hospitals and research institutions lack the resources to handle the requirements.[1] The increased and sometimes disproportionate burden is due to a number of issues, including:

- multiple assessments of clinical trials;
- inconsistent interpretation and implementation of the Directive across Member States; and
- an insufficiently risk-based approach.

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

5. 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 and 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.

6. In addition to increased bureaucracy and 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 down.[2]

Question 4: Streamlining of NCAs

7. The Directive has made some progress in harmonising processes across Member States. However, a lack of clarity around the interpretation of terms leads to potentially different assessments of clinical trials across Member States' NCAs. In addition to streamlining 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.

8. We would support streamlining of the assessment process and would like to see an option similar to 3.3.2.1 (a): Common NCA Agreement, adopted, where the relevant Member State NCAs work together to reach agreement. This mechanism would allow Member States to cooperate and 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

[1] http://www.efgcp.be/downloads/icrel_docs/Final_report_ICREL.pdf
[2] Anecdotal evidence from researcher

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.

9. As noted in the consultation document, the majority of trials take place within a single Member State. It is therefore important that the mechanism for approving these trials is not inadvertently made more complex if inter-country 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

10. We would support streamlining of the function of national Ethics Committees to improve efficiency, while maintaining the ability of individual Ethics Committees to give local and culturally appropriate input into a decision. National views on ethics 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 should advance the process to reduce bureaucracy. Nevertheless, any attempts to generate a consensus agreement must proceed in a timely manner without further delay of 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.

11. 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). It is important that their roles remain separate and duplication of functions should be avoided.

12. 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 10). However, we acknowledge the benefits of streamlining administration within a Member State. We support mechanisms such as the UK's integrated research application system, which minimise duplication and simultaneously capture information required by a number of different review bodies and Ethics Committees.[3]

Key Issue 2: Inconsistent implementation of the Clinical Trials Directive

Question 6: Appraisal of the situation

13. We agree with the outline of the situation: 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

[3] https://www.myresearchproject.org.uk/

consistently classified as either interventional or non-interventional medicinal products (see Box 1 for examples). There are also concerns that experimental medicine is already 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 for market approval. 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 to obtain eventual market authorisation.

14. 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 problems around classification of medicinal products

a) For an academic clinical trial in the UK involving dichloroacetate, an unlicensed and widely available medicinal compound, it was unclear what information was required to support the application to conduct the trial, leading to an extended timescale to gain approval.

b) Urea cream is routinely recommended for diabetics 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.

c) Research designed to compare liquid nitrogen and 60% salicylic acid for the treatment of warts was significantly delayed because the UK MHRA was not clear whether liquid nitrogen 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 out in the Directive. The MHRA subsequently decided that liquid nitrogen was not a medicinal product and fell outside the terms of the Directive, but these deliberations caused a significant delay in the research project.

15. In addition to the examples provided in section 4.1 of the consultation document, there are broader issues with how the Directive has been implemented in different Member States. For example, anecdotal evidence suggests that researchers perceive the approval process to be a much greater barrier in some countries (for example, the UK) than for other Member States (for example, the Netherlands) 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.

16. 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'.

17. The reporting of SUSARs requires greater clarity and guidance. In the present system, SUSARS are reported to Ethics Committees, which do not act on this information. This system could be simplified by clarifying that the NCA is the primary recipient of this information and by providing Ethics Committees with an annual safety report.

18. 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 risks involved.

19. 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 USA. Simplified approval requirements might facilitate the acceleration of drug development and we understand this issue has been raised with the European Medicines Agency (EMEA).

20. 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.

21. 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 risk transferring the shortcomings of the Directive that have already had a negative impact on interventional trials 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 if appropriate.

Question 7: Weaknesses and impacts of inconsistent implementation

22. We agree with the weaknesses – potential risk to patients and increased administrative costs – that are 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

23. The lack of clarity around some key definitions leads to different 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 to clarify definitions. However, as noted in our response to question 6, it will also be important that Member States take suitable action to address problems specific to their national implementation of the Directive.

Key Issue 3: Regulatory framework not always adapted to the practical requirements

Question 9: Examples of insufficient risk-differentiation

24. A 'one size fits all' approach to clinical trials is not appropriate since different trials carry different levels 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; the 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. However, this is not reflected in the current Directive, i.e. 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 high risk studies, which currently leads to excessive bureaucracy and unnecessary delay to low risk trials. Further examples are given in Box 2.

25. In addition to the lack of risk-differentiation, in some cases implementation of the Directive is highly process-driven, with researchers perceiving that regulators can place 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.

26. We would strongly support a risk-based approach, with clear guidelines and an appropriate system for risk assessment of trials. Consideration should 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 low risk trials, particularly for studies where the risk involved is similar to that of 'usual care'. This point is well made in the European Science Foundation Report (see page 9 of the report).[4]

Question 10: Appraisal of single sponsor

27. Many trials will involve more than one organisation who will wish to share sponsorship responsibilities for the trial, and this needs to be recognised by the Directive. At a European Forum for Good Clinical Practice meeting on '*Innovative Approaches to Clinical Trial Co-Sponsorship in the EU'* in 2009, UK researchers did not consider sponsorship to be a significant issue, mainly because the implementation of the Directive in the UK essentially allows for co-sponsorship of national trials.[5] However, this procedure is not recognised in other Member States. Allowing co-sponsorship may facilitate the oversight of trials at sites in other Member States and reduce the administrative and financial burden; we suggest that the same implementation should be introduced throughout the EU.

Question 11: Revision of implementing guidelines

28. A revision of the guidelines, covering all trials within the Directive, would be of benefit if it enabled investigators, sponsors and regulators to apply a risk-based approach with

[4] http://www.esf.org/fileadmin/links/EMRC/FL_IDCT.pdf
[5] http://www.efgcp.be/Downloads/confDocuments/Final%20Programme%20Co-Sponsorship%20Workshop_21%20September%202009.pdf

appropriate application of GCP depending on the risks involved. We 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 the 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. Revision of the guidelines should not replace a full review of the Directive (see question 12).

Box 2: Examples of insufficient risk-differentiation

Below are examples of different trials that fall under the Directive. The lack of risk-differentiation built into the Directive means that 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, researchers 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 clinical trial authorisation procedure, which is expensive and time consuming. Consequently, the group were only able to test one analogue, and thus may not have identified 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 obtain 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 to patients taking L-ornithine L-aspartate (LOLA) to treat the encephalopathy. LOLA is available over the counter and is licensed as an encephalopathy treatment in Germany, and has also been shown to be of benefit in randomised controlled trials. LOLA was used to assess the sensitivity and to 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.

29. 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?

30. 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 (see question 11).

Question 13: Academic sponsors

31. The Academy strongly recommends that the Directive continues 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 across the commercial and non-commercial sectors should be supported.

32. 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

33. 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 application of the requirements under 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, and a report equivalent to the ICREL study, focused on paediatric research, would be particularly welcomed.

34. 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 newborn babies required every nurse involved to be GCP trained or not. Such a requirement might make the trial unfeasible or render it non-compliant.

35. 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 would be welcomed here.

36. 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

37. It is important the researchers are able to carry out emergency clinical trials in specific circumstances. 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 good environment for research. Good practice such as this 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

38. 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.

39. Ensuring that 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, due to the lack of resources and the particular need for research that improves healthcare.

Question 17: Options for ensuring GCP in third countries

40. 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 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.

41. 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

42. One additional concern raised by researchers relates to the identity of the trial Chief Investigator (CI). Since the introduction of the Directive, the identity of a CI appears to be limited to a smaller group of professionals, including only doctors, nurses, dentists and pharmacists. Several successful trials could not now be re-run with the same CI as previously. This has implications for continuity but, more importantly, can restrict an individual with the most expertise in a given area from leading on a trial.

43. 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 Trials[6], which provide a forum for international agencies to discuss the issues, are already contributing to this.

44. 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. Continued funding and a supportive regulatory environment are vital in maintaining UK and European excellence in this field.

45. We urge the Commission to use this opportunity to make revisions that will alleviate the bureaucratic, cost and time burdens of the current Directive, while maintaining an appropriate regulatory framework. It is important to achieve the right balance in the amendments for the benefit of the EU clinical research environment, which impacts on both academia and the pharmaceutical industry alike.

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Contributions were provided purely in an advisory capacity and this response may not reflect the views of all the individuals listed above.

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[6] http://www.ctsu.ox.ac.uk/projects/sg