

House of Commons Science and Technology Committee: Clinical trials and disclosure of data

Response by the Wellcome Trust

February 2013

Key Points

- It is important to open up clinical trials to greater scrutiny to enable the validation of research findings. Trial registration and the publication of summary results are important steps to enable this.
- However, greater transparency of research findings is distinct from the disclosure of the underlying data. While we should all be working towards this, further discussion is needed to address challenges such as infrastructure, resourcing, curation and the protection of confidentiality, in order to improve accessibility in the most effective way.
- We broadly welcome the European Commission's proposals for a Clinical Trials Regulation, but there are a number of elements that would benefit from greater clarification or refinement, including development of the EU Portal, risk proportionality and scope.
- The Health Research Authority has an important role to play in developing common standards for clinical trial transparency, but is just one of a number of players including researchers, funders, publishers, regulators and industry.

INTRODUCTION

1. The Wellcome Trust is pleased to have the opportunity to provide evidence to this important inquiry, and we welcome the fact that the Committee is looking at this topic. We fund clinical trials through both our Science Funding and Technology Transfer schemes, but do not act as a sponsor.
2. We consider that the opening up of clinical trials to greater scrutiny is an important part of the research pathway, as it provides an important means of validating research results. However, it is important to distinguish between enabling access to research findings, and making available the detailed data which underpins those findings, which presents additional issues that we discuss throughout this response.
3. We support the disclosure of findings from research involving clinical trials; the Trust's policy position on clinical trials has just been updated and requires all trials to be registered on our clinical trials register. We also require the researchers we fund to maximise access to research data with as few restrictions as possible, although we recognise there are further discussions to be had with regard to the resourcing, infrastructure and curation necessary to achieve this. We have also signed up to the

AllTrials petition, which calls for the outcomes of all clinical trials to be made publically available¹ (our statement to the petition is included at Annex A).

RESPONSES TO QUESTIONS

Q.1 Do the European Commission's proposed revisions to the Clinical Trials Directive address the main barriers to conducting clinical trials in the UK and EU?

4. It is vital that the proposed Regulation ensures public confidence; to do this it must not only protect participants but also promote the conduct of trials for public benefit. We broadly welcome the Commission's proposal as we consider that it takes significant steps towards delivering these aims. However, there are a number of details that would benefit from clarification or refinement.

Single submission, authorisation and decision processes

5. Current approval processes for multicountry clinical trials result in multiple assessments across Member States with duplication of work and divergent and inconsistent approaches. We therefore 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 common requirements across Member States.
6. We also 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 Medicines and Healthcare products Regulatory Agency (MHRA) and Health Research Authority will be needed to deliver this and we are pleased that these organisations have already had preliminary discussions. 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.
7. The single submission and authorisation process will be based on an IT system that will provide a single entry point for the submission of data relating to clinical trials, called the EU Portal. The smooth development and operation of this EU portal will be critical to the success of the single submission, authorisation and decision processes and to deliver the aim of the Regulation to reduce bureaucracy. 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 the EU portal will be ready by the time the Regulation is implemented and that sustainable resourcing will be provided to support the EU portal. We also suggest that the Commission could gather feedback on and learn from the experience of implementing other EU portals, such as the European Database on Medical Devices.

¹ <http://www.alltrials.net/supporters/wellcome-trust-statement/>

Risk proportionality

8. The current 'one size fits all' approach to clinical trials is not appropriate since different trials carry a different level of risk and benefit. The Regulation must therefore deliver a proportionate regulatory framework that enables regulatory requirements to be adapted according to the risks of the trial. 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.
9. The Regulation proposes a two category approach to risk-adaptation, with further scope for risk adaptation that is independent of these categories. The current MHRA approach to risk adaptation uses a three category approach and also demonstrates how much can be achieved through guidance rather than legislation. We encourage the Government to seek further clarity on the amount of flexibility inherent in the Regulation and to undertake a thorough analysis of the risks and benefits of a two category approach in order to assess whether the level of risk adaptation in the Regulation is sufficient compared to the UK's current three category system.

Scope and definitions

10. We are pleased that the scope of the Regulation has not been increased compared to the Directive. However, the broad scope has created difficulties for some academic trials in the past and we are concerned that this will not be addressed by the Regulation.
11. We note that 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. However, 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.
12. 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, even where the monitoring was a single blood test. 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 Directive² and it is important to consider whether this can be addressed in the Regulation. Studies excluded through an amendment 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.

² Academy of Medical Sciences (2011) *A new pathway for the regulation and governance of health research*

13. A lack of clarity in the definitions for key terms in the current Directive has led to inconsistent interpretation in Member States. 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. However, we consider the introduction of a definition of “clinical studies” to be confusing since this term is often used synonymously with “clinical trials”. It is important that the definition of “clinical study” is amended to reduce the potential for confusion.

Standards and requirements

14. We support the approach taken in the current 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. We are pleased that the Regulation is also flexible with respect to good clinical practice standards since this allows sponsors to determine appropriate requirements for their trial. Any move towards less flexibility is likely to have a detrimental impact on academic clinical trials that are not able to operate to ICH-GCP standards.
15. 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)); the requirement to publish summary results of the trial (Article 34(3)); and to make information in the EU database publicly available (Article 78).
16. Provisions for emergency clinical trials are also welcome but must be reviewed to ensure that they are consistent with the current UK Medicines for Human Use (Clinical Trial) Regulations so as not to undermine the UK’s strong position in this area.

Other barriers

17. Evidence suggests that obtaining R&D permissions at the NHS sites where research is to take place are the greatest regulatory and governance barrier to research studies, including clinical trials of investigational medicinal products.³ These permissions are independent of the regulation of clinical trials, but it is vital that this rate-limiting step is addressed. We therefore warmly welcome the HRA’s pilot project in this area, as noted in paragraph 18.

Q.2 What is the role of the Health Research Authority (HRA) in relation to clinical trials and how effective has it been to date?

18. We have welcomed the establishment of the Health Research Authority, and the provisions in the draft Care and Support Bill to establish it as an independent non-departmental public body. The HRA has a central role to play in the streamlining of research approval processes and promoting common standards for compliance and monitoring. We have been encouraged by the start made by the HRA, particularly the

³ Evidence cited in Academy of Medical Sciences (2011) *A new pathway for the regulation and governance of health research*

establishment of the pilot project for a system of streamlined assessment of research in the NHS. We have also been impressed by the HRA's proactive approach to engage with key stakeholders and other regulators from the outset to discuss and develop its role.

19. The HRA has also showed willingness to engage on the issue of clinical trial transparency and we understand that they are considering this at the moment as part of the organisation's work, particularly with regard to requirements of research ethics committees in the area of transparency and publication, and monitoring of compliance. The joint committee which is currently carrying out pre-legislative scrutiny on the draft Care and Support Bill, which will establish the HRA as a non-departmental public body, is also considering the issue as part of the broader remit and functions of the organisation. We believe that the HRA can play a significant role in promoting and contributing to discussions around these issues, and welcome the fact that the HRA is moving forward with a number of activities including the single assessment pilot mentioned previously and statements in support of research transparency, as well as broader discussions with stakeholders.
20. It is important to note, however, that the HRA is just one of a number of players in this area, and other organisations and stakeholder groups have a similarly important role to play in these discussions in order to embed the principle of transparency throughout the regulatory pathway (see also the discussion of responsibility in paragraph 24, below).

Q.3 What evidence is there that pharmaceutical companies withhold clinical trial data and what impact does this have on public health?

21. Pharmaceutical companies have a major role in global public health, and have a key role to play in discussions around clinical trial transparency. We have welcomed the moves by GlaxoSmithKline to expand access to their clinical trial data, which has helped to move the debate forward, and would hope and expect all pharmaceutical companies to be closely involved in these discussions along with other stakeholders.

Q.4 How could the occurrence and results of clinical trials be made more open to scrutiny? Who should be responsible?

22. There are several methods by which clinical trials can be made more open to scrutiny. The most important of these is trial registration, which is a crucial first step in opening up clinical trials for examination. Information about clinical trials should be placed in an appropriate accredited registry, including details of the interventions and outcomes being measured. This should also include a lay summary of the trial, including aims, interventions, methods and outcomes, in a form which can be easily understood by a non-specialist or lay reader.
23. We also support efforts to publish summary results of clinical trials available, and welcome the requirement for this in the Clinical Trials Regulation (see paragraph 15). We recognise that it may be more difficult to publish negative findings in peer reviewed journals, but do not think this should be a long-term barrier to making all results and outputs available. We consider that, where appropriate, a range of approaches to

making research findings available should be considered, such as websites, data repositories and trial registries.

24. Full disclosure of the data underlying research outcomes represents a larger challenge, as data must be made available in a form that is both accessible and useful, while protecting the confidentiality of research participants. This in turn presents challenges around putting in place the appropriate infrastructure and curation to facilitate this while protecting individual identifiable data, and there are also issues of resourcing and cost. Researchers and research sponsors will need to consider whether appropriate facilities are in place to manage, store and provide access to large volumes of data, whether sufficient expertise is contained within the research team, and whether additional tools or facilities will be required to enable access. There may also be cases in which it is useful to have more tightly controlled access to fuller datasets, for example to protect intellectual property or data exclusivity, or to safeguard research participants. None of these challenges are inherently insurmountable, but they require careful consideration.
25. Responsibility for ensuring that clinical trials are made more open to scrutiny lies with a number of stakeholders, including researchers, research sponsors, funders, publishers, regulators and industry. All stakeholders have a responsibility to explore methods of increasing transparency of clinical trials and to work together to promote common standards and mechanisms. It is important also to consider the role of research ethics committees here and how their role in scrutinising research proposals relates to the monitoring of research transparency. Although the HRA is not itself a regulator, there may be a role for it as it develops in the promotion of common standards around research transparency. There is also a role for the MHRA where the release of clinical trial results and data has a direct bearing on safety assessments for medicines and devices.

Q. 5 Can lessons about transparency and disclosure of clinical data be learned from other countries?

26. Clinical trials are an increasingly global activity, and so it is important to consider trial transparency in this context and to take a global approach. This does, however, bring its own challenges around resourcing and infrastructure, discussed above. It also raises the question of where responsibility should lie, for example in the country or countries where the trial takes place, or in the country where the sponsor is located, should this be different.
27. The UK saw its global share of patients recruited to clinical trials fall from six to two to three per cent between 2000 and 2006.⁴ Steps are being taken to address this decline and ensure that the UK creates and maintains competitive environment for clinical trials for the benefit of patients and the economy. The proposal for a Clinical Trials Regulation will also improve the regulatory environment in the EU. It is important that measures to promote transparency and sharing of clinical data are considered within this wider context. Seeking global, rather than country-specific, solutions to transparency will maximise the benefits to society and while ensuring that the UK maintains its competitive advantage.

⁴ www.ukcrc.org/index.aspx?o=2874

Annex A – Wellcome Trust statement to the AllTrials petition on clinical trial transparency

The Wellcome Trust is pleased to sign this petition. We support full and unrestricted access to the outputs of research, including clinical trials, and consider this to be a key component of the research pathway and of our vision to achieve extraordinary achievements in human and animal health.

We consider that all trials should be registered in an appropriate accredited register, with information on the trial protocol and sponsor. The Trust's own [clinical trials policy](#) sets out our requirement for all trials to be registered on our clinical trial register, which is a subset of the larger International Standard Randomised Controlled Trial Number (ISRCTN) Register. We expect all current and future trials funded by the Trust to be registered in this way. We also encourage the development of more accessible lay summaries to ensure public engagement.

We also support efforts to ensure full reporting of trial methods and results. We expect our researchers to maximise the opportunities to make their results and outputs freely available, as set out in our open access policy and in our policy on data management and sharing. We recognise that it may be more difficult to publish negative findings in peer reviewed journals, but do not think this should be a long-term barrier to making all results and outputs available. We consider that, where appropriate, a range of approaches to making research findings available should be considered, such as websites, data repositories and trial registries.

We recognise that there is also ongoing discussion about the importance of greater transparency for all data underlying clinical trials. We began a review of our own clinical trials policy in early 2012, and expect to publish our updated policy soon. We expect our researchers to work towards the full disclosure of research data, although we recognise that there are a number of issues that must be addressed in order to facilitate the most effective sharing of clinical trial data.