



House of Commons
Science and technology
Committee

Clinical trials

Written evidence

6 March 2013

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Written evidence submitted by the Department of Health (CT00)

INTRODUCTION

1. The Government ensures the safety of patients in clinical trials via the regulator – the Medicines and Healthcare products Regulatory Agency (MHRA) – and Health Research Authority (HRA) while providing national infrastructure through the NHS to encourage clinical trials to be conducted in the UK.
2. Clinical trials required to test new medicines are regulated by MHRA. Regulation is governed by the EU Clinical Trial Directive which has been transposed into UK law.
3. The following evidence addresses the matters set out in the inquiry's terms of reference.

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. In recent years we have seen a decline in clinical trial activity in the EU. The number of clinical trials conducted in the EU fell by 25 percent between 2007 and 2011. In the UK, the number of trials fell by 22 percent over the same period. This decline cannot solely be attributed to the Clinical Trials Directive¹: an independent review by the Academy of Medical Sciences of the regulation and governance of health research found that 'the governance arrangements within NHS Trusts are the single greatest barrier to health research'², which the Government is addressing through initiatives of its National Institute for Health Research (NIHR)³. However, the current legislation has had an effect on the cost and feasibility of conducting clinical trials and the complexity of the regulatory framework has been cited as a barrier.

5. The European Commission's proposal for a Clinical Trials Regulation was adopted on 17 July 2012. The Commission's stated aim in publishing the proposal was to boost clinical research in Europe by simplifying the rules for conducting clinical trials.

6. The Government welcomes much of what is included in the European Commission's proposal for a Clinical Trials Regulation. We consider that the proposal has the potential to create a more favourable environment for the conduct of clinical trials in the EU, by making it easier to conduct trials in multiple Member States and introducing a proportionate and risk-adapted approach to clinical trials.

7. There are several elements that the Government is particularly pleased to see included in the proposal, including:

- the introduction of risk-adapted regulation of clinical trials, including the introduction of the concept of low-intervention studies, the streamlining and simplifying of the safety reporting requirements and the adoption of a proportionate monitoring approach;

¹ Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use"

² Academy of Medical Sciences. *A new pathway for the regulation and governance of health research*. Jan 2011. <http://www.acmedsci.ac.uk/p47prid88.html>

³ National Institute for Health Research. *Faster, easier clinical research*. http://www.nihr.ac.uk/systems/Pages/faster_easier_clinical_research.aspx

- the introduction of one application for multi-state clinical trials replacing individual applications in different Member States which we believe has the potential to decrease the burden on researchers and promote the conduct of clinical trials in the EU (although we will be looking to improve the efficiency of the process); and
- the concept of one single submission and one single decision replacing the current separate regulatory approval and approval by Ethics Committees. This concept is introduced for both single and multi state trials.

8. There are, however, aspects of the proposal that the Government has concerns over. For example, we will be examining in more detail the proposal to oblige Member States to set up a national indemnification mechanism that, on a not-for-profit basis, provides insurance cover for all clinical trials conducted in the UK, giving sponsors the choice between private insurance and a Government scheme.

9. As regards disclosure of clinical trials data, the Government fully supports the Commission's ambition to increase transparency and views positively the elements of the proposal designed to do this, including through ensuring that the EU database should be publicly accessible and that there should be a presumption that the summary of the results of clinical trials be made available to the public through this database. The Government is considering whether further measures could be included in the Regulation to increase transparency.

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

10. The Health Research Authority (HRA) was established on 1 December 2011 as a Special Health Authority. The overarching purpose of the HRA is to protect and promote the interests of patients and the public in health research. The HRA protects patients from unethical research while enabling patients to benefit from research by simplifying processes for ethical research.

11. Through the National Research Ethics Service (NRES), the HRA provides for the ethical review of health research proposals including clinical trials, to protect the rights, safety, dignity and wellbeing of research participants and potential participants. The HRA also acts as a member of the UK Ethics Committee Authority (UKECA) by agreement with the four nations. UKECA has responsibilities for establishing, recognising and monitoring ethics committees that give an opinion on the ethics of research under the Medicines for Human Use (Clinical Trials) Regulations 2004.

12. The HRA is simplifying processes for research through cooperation with other bodies such as the MHRA to create a unified approval process for research approvals and to promote consistent and proportionate standards for compliance and inspection.

13. From 1 April 2013, the HRA will be taking on further functions relating to approving the processing of confidential patient information. The Government intends to legislate to establish the HRA as a non-departmental public body when parliamentary time allows, and clauses in the draft Care and Support Bill for this purpose have been published for pre-legislative scrutiny.

14. The Government is committed to transparency and the publication of research findings is a high priority area for the HRA. Ethics committee review already asks whether research will be registered on a public database, and how researchers intend to report and disseminate the results of that research. The decision by an ethics committee to give a favourable opinion includes consideration of these plans.

15. A summary of the final report on the research should be submitted to the main research ethics committee within one year of the conclusion of the research. The HRA also publishes research summaries of approved studies on its website to promote transparency in research, to encourage registration and publication and to provide a simple website publication of research approved by NRES in the UK.

16. The HRA intends to follow up on applicant-declared intentions to register and publish trial results. It intends to monitor compliance, to identify researchers, funders and institutions that are not registering or publishing approved research. The HRA is currently exploring how best to implement these improvements and safeguards, and expects to establish a new system in 2013.

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

17. Clinical trials required to test new medicines are regulated in this country by the MHRA. The current legal requirements placed on companies carrying out clinical trials relate largely to ensuring that the rights, safety and well-being of clinical trial subjects are protected, and that the data generated is robust. Companies are required by law to report serious, unexpected adverse reactions experienced by trial subjects which are thought to be related to the medicine under test. They are also required to report the outcome of such trials, including negative outcomes, to the regulator.

18. All clinical trials relevant to evaluation of the product concerned are required to be included in submissions for marketing authorisations for new medicines, whether the results are favourable or unfavourable to the product. This includes details of abandoned or incomplete studies and trials concerning therapeutic indications not covered by the particular application. This is a requirement in legislation.

19. Following marketing of a drug, the legislation provides clear requirements that any request from the regulatory authorities to the marketing authorisation holders (MAHs) for the provision of additional information, including data from clinical trials, necessary for the evaluation of the benefits and the risks afforded by a medicinal product is answered fully and promptly. There is also a legal requirement that new information, including data from clinical trials, that may necessitate changes to a medicine's product licence are provided to the MHRA.

20. Recent changes to legislation have provided further clarity that the requirements for provision of data relate to both positive and negative clinical trials and data relevant to use in all indications and populations and includes data from trials when the product has been used outside of the terms of the marketing authorisation (off-label use).

21. The system of regulation of medicine is predicated on the provision of all relevant information to regulators in order to conduct their assessment of the safety, quality and efficacy of the application. The marketing authorisation holder is responsible in legislation for submission of all information relevant to the evaluation of the medicinal product included in the dossier submitted in support of their application. Each application is accompanied by a signed declaration confirming inclusion of all relevant information. The MHRA does not have evidence that there is systematic or large scale withholding of data, but has investigated cases in the past where clinical trials and safety data were not properly reported.

22. For example, the MHRA carried out an investigation into GSK's compliance with legal obligations to report key safety information and on promotion of unlicensed uses of Paroxetine (Seroxat). The investigation concluded that GSK could and should have communicated safety information sooner than they did but that the law was not sufficiently clear to support legal action. In response, the UK legislation on reporting requirements was

strengthened in 2008. European law has now also been strengthened, the latest changes coming into force in August 2012.

23. More recently, the European Medicines Agency (EMA) issued infringement proceedings against Roche in October 2012, following an inspection carried out by the MHRA earlier in the year, which found amongst other things that a significant amount of safety data from clinical trials had not been reported. The EMA's Pharmacovigilance Risk Assessment Committee is currently reviewing data provided by Roche and whether there will be a change to the balance of risks and benefits of any of the medicines involved. The review will reach its conclusion in March 2013.

24. Regulated clinical trials also require a favourable opinion from an ethics committee. Research ethics committees (RECs) within NRES ask their applicants about the intentions to register, publish and disseminate the findings of the research; to make data and tissue available; and to tell participants about the outcomes of the research. Now that NRES is part of the HRA, the HRA plans to look at compliance against those stated intentions.

25. HRA is exploring with RECs the issues they consider when they ask about these intentions and the extent to which they consider them as part of their opinion. From April 2013, it will start a simple check through the final report RECs receive to see whether or not people have published and made the data and the tissue available as they said they would to the REC.

26. HRA recognises that there are a range of issues: a deliberate act to not publish or not make data available when it has been agreed is misconduct, if wilful; studies that would be only of an educational value and unsuitable to be published and interpreted; barriers to publishing where people report that it is much more difficult to get some types of studies, and potentially negative results, published. HRA is in dialogue with key stakeholders to tease out the issues and is planning an event in April 2013 to debate them, following which it will publish a position statement.

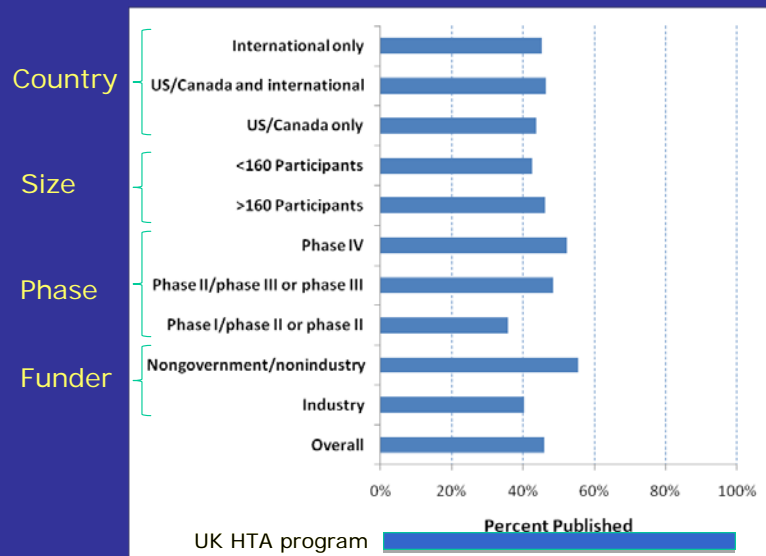
27. In evidence on 31 January 2013⁴ to the Joint Committee scrutinising the draft Care and Support Bill that would establish HRA as an executive non-Departmental public body, the HRA chief executive, Dr Janet Wisely, said HRA would, with a view to building confidence in research, support having a role for the HRA in promoting transparency in research mentioned on the face of the Bill. The Government awaits the Joint Committee's report and recommendations with interest and will give them careful consideration.

28. At an HRA event on 7 February, Sir Iain Chalmers, co-ordinator of the James Lind Initiative, presented evidence suggesting that:

- around half the trials registered by 1999 had been published by 2007, irrespective of country, size, trial phase, or funder (i.e. non-publication is not peculiar to the pharmaceutical industry), though UK Government-funded research compared favourably, with the NIHR Health Technology Assessment Programme publishing nearly 100 per cent;

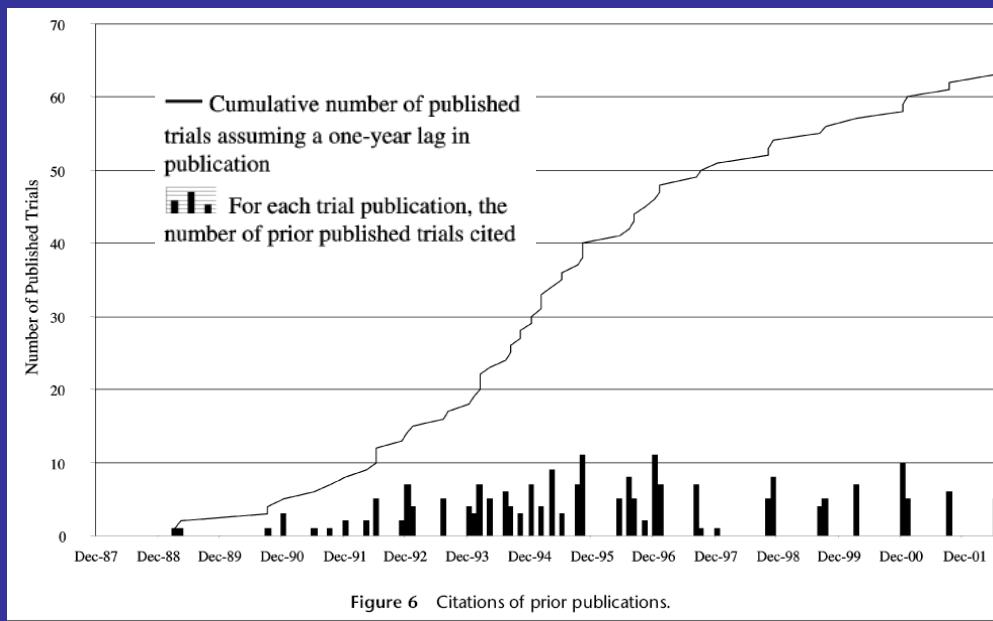
⁴ <http://www.parliament.uk/business/committees/committees-a-z/joint-select/draft-care-and-support-bill/publications/>

Proportion (%) of clinical trials registered by 1999 and published by 2007 (from Ross JS, Mulvey GK, Hines EM, Nissen SE, Krumholz HM (2009) Trial Publication after Registration in ClinicalTrials.Gov: A Cross-Sectional Analysis. PLoS Med 6(9): e1000144).



- trials are being unnecessarily repeated because researchers are not cumulating all the evidence before designing and embarking on further trials (i.e. increasing the publication of trials can help make available more of the evidence researchers need to take into account in carrying out effective systematic literature reviews that inform future research).

New trials of aprotinin ignored previous trials



29. On 8 February, the HRA board agreed to sign the AllTrials.net petition⁵, which calls for all trials past and present to be registered, and the full methods and the results reported.

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

30. The Government is fully supportive of transparency in the publication of clinical trial results including the proposal being considered by the HRA set out in paragraph 27. Academic trials for which funders or sponsors are responsible should ensure transparency in the publication of results for the trials they fund, as at present a significant proportion are not published. The Government also believes that an increase in voluntary action on the industry's part will build public trust. The Government is therefore encouraged by voluntary schemes which individual companies are developing themselves. The Government is in discussions with all stakeholders, including industry, to see how publication of clinical trial data can be further encouraged, whilst being mindful of the need for a proper balance between data transparency and the legitimate concerns of industry.

31. Since July 2012, the MHRA has begun publication of all UK approved SPCs (Summaries of Product Characteristics) and PILs (Patient Information Leaflets) on its website⁶. The MHRA is publishing this information in stages. This first wave is for products that have been checked and are up to date with the licensing history. Information on further products will be added over the coming months.

Since October 2005, MHRA has published public assessment reports following approval of new medicines, providing details of the information on which its decision to approve a marketing authorisation was based⁷. The EMA publishes similar public assessment reports for all new medicines approved by the European Commission⁸. Public assessment reports have been published in the EU since the adoption of the European Community Code for medicinal products⁹).

32. At European level, the EMA established the EudraCT clinical trial database in May 2004. Details of trials of investigational medicinal products are placed on EudraCT as part of the clinical trial authorisation process. Data extracted directly from EudraCT were made available to the public in March 2011 as the fully searchable EU Clinical Trials Register.

33. This Register gives public access to information¹⁰ on interventional clinical trials of medicines authorised in the 27 EU Member States and Iceland, Liechtenstein and Norway since May 2004. The database also allows the public to search for information on all clinical trials of investigational medicinal products authorised to be carried out outside the EU if these trials are part of a paediatric investigation plan. The Register does not, however, currently include the results from these clinical trials.

⁵ <http://www.alltrials.net/>

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<http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm>

⁷ <http://www.mhra.gov.uk/Publications/PublicAssessmentReports/index.htm>

⁸ http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

⁹ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

¹⁰ The details in the clinical trial descriptions available in the EU Clinical Trials Register include: the design of the trial; the sponsor; the investigational medicine (trade name or active substance identification); the therapeutic areas; the status (authorised, ongoing, complete).

34. Through the NIHR, the Department of Health part funds the UK Clinical Trials Gateway, which enables patients and clinicians to search a number of different international trial registries including the US ClinicalTrials.gov registry.

35. As stated earlier, the Government is fully engaged in the negotiations on the new EU Clinical Trials Regulation and agrees with the Commission's proposals to increase transparency. The Government is considering whether further measures could be included in the Regulation to increase transparency.

36. AT EU level, the EMA has been taking forward work to increase the amount of the information made publicly available. As a result, from late 2013 it is planned that EU Clinical Trials Register will also provide public access to summary trial results for all trials of investigational medicinal products on the Register (once these have been included in EudraCT).

37. In addition, the EMA has committed to the proactive publication of the data from future clinical trials supporting the authorisation of medicines. To address the practical and policy issues that will arise, including exactly which data fields will be published, the EMA is developing a policy on proactive publication of clinical-trial data. This is expected to come into force on 1 January 2014. The Government fully supports the work that is being done by the EMA.

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

38. Looking further afield than the UK and the EU, the Government is following developments in other countries. While registries of clinical trials have been set up in some countries (US, Australia and New Zealand), the issue of disclosure of results does not appear to have been fully resolved anywhere.

39. The US trials registry ClinicalTrials.gov created a results database in September 2008 to implement Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA 801), which requires the submission of "basic results" for certain clinical trials, generally not later than one year after the Completion Date. A BMJ paper (BMJ 2012;344:d7373) however found that only 22 percent adhered to the mandatory reporting rules.

40. We continue to monitor these developments as input into our own considerations on the issues.

February 2013

Written evidence submitted by Michael Power (CT01)

I am responding only to the fourth question “*How could the occurrence and results of clinical trials be made more open to scrutiny? Who should be responsible?*”

1. Clinical trials could be made more open to scrutiny by including a statement in the consent form that de-identified data would be made publically available.
2. The National Research Ethics Service (NRES) of the NHS Health Research Office have a template for informed consent on their website. This template should be updated to include a statement about making trial data freely available — even if this is not specifically required by the ICH guidelines on Good Clinical Practice (discussed in paragraph 4) or by the forthcoming European Union Regulation on Clinical Trials. The statement should include:
 - a. A commitment to make all the data from the trials, suitably anonymized, publically and freely available on the internet without unreasonable delay. Data should be in a form suitable for statistical analysis. The Committee may want to clarify what delay would be reasonable. Because the end of a trial and the publication of a research report can be manipulated, their dates should not be used to define “reasonable delay”.
 - i. Peter C Gøtzsche, director of the Nordic Cochrane Centre, makes similar recommendations for improvements to the new European Union Regulation on Clinical Trials— see Gøtzsche PC. Deficiencies in proposed new EU regulation of clinical trials. *BMJ* 2012;345:e8522 doi: 10.1136/bmj.e8522.¹
 - ii. The European Medicines Agency intends to require trial data to be made available in form suitable for statistical analysis — see European Medicines Agency. *Access to clinical-trial data and transparency*. Workshop report. 2012.²
 - b. An explanation of how data will be anonymized, how it will made available, and when it will be published (for example within 2 years of the planned termination date, or within 2 years of the actual termination date if this is earlier.)
 - c. Assurance that the results of this research will be made available to other researchers in complete detail, subject only to full protection of identity, and cannot be withheld by the organisation conducting the trial
 - d. Assurance that the ethics committee will ensure that these commitments are upheld, and that any investigators who do not comply would be subject to professional discipline and would not be allowed to conduct human research in the future.
3. The International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) brings together the regulatory authorities and pharmaceutical industry of Europe, Japan, and the US. The ICH develops and publishes a number of guidelines that aim to ensure that “safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner”. A certificate of training

¹ Published online 20 December 2012 at www.bmj.com/content/345/bmj.e8522.

² www.ema.europa.eu/docs/en_GB/document_library/Report/2012/12/WC500135841.pdf.)

in the ICH guidelines on Good Clinical Practice (GCP) is required for the principal investigator of clinical trials conducted in NHS facilities. The ICH should update its GCP to include the same statement suggested in paragraph 3 for the NRES template.

4. All UK universities and NHS Trusts require the protocols of clinical trials to be approved by their Research Ethics Committees. These committees should ensure that clinical trial protocols and consent form are made public, and that the consent form adheres to the standards set by the NRES template for informed consent.
5. The Research Councils UK (RCUK) — the strategic partnership of the UK's seven Research Councils — should remove the hedging from the part of their definition of unacceptable research conduct that refers to failure to “make relevant primary data and research evidence accessible to others for reasonable periods after the completion of the research”. The statement should be reworded along the lines of “make all primary data accessible within a reasonable period after the start of the research”.
6. The RCUK, the Medical Research Council and other research funders, the UK University Research Ethics Committees Forum, and the Association of Research Ethics Committees should use their influence to ensure that researchers and their employers are aware of the need to include a statement about availability of data in the informed consent forms for clinical trials.
7. Guidelines on how clinical trials are reported³ should be updated to include an appropriate statement of data availability in the study consent form.
8. Journals should require authors of clinical trial reports to follow guidelines such as CONSORT.
9. Guidelines on assessing the quality of evidence (such as the GRADE system) and manuals for developers of evidence-based guidance (such as the NICE “Guidelines manual”) should include in their criteria for assessing the risk of bias in a research report the presence of a statement explaining how and when primary data will be publically available.
10. Declaration of interests. I have no potential or actual financial interests that would be affected by the Committee’s recommendations. However, as a clinical researcher, a tax-payer willingly funding the NHS (which funds both healthcare and research), a patient, the Evidence-Based Practice Lead in my NHS Trust, and someone whose request for de-identified data from a clinical trial has been refused, I have multiple interests in the Committee’s recommendations.

January 2013

³ Such as the CONSORT statement — www.consort-statement.org/

Appendix. Evidence summary on what UK-relevant policies/guidelines there are on making clinical trial data available

Institution Policy/guidance	Statement that data must be made available	Statement that informed consent should include making data available
<p>Medical Research Council</p> <p>Good research practice: Principles and guidelines August 2012</p> <p>www.mrc.ac.uk/consumption/idcplg?IdcService=GET_FILE&dID=36739&dDocName=MRC002415&allowInterrupt=1</p>	<p>Weak</p> <p>“Extending access, through initiatives such as data sharing, promotes the efficient use of resources for new research, assures the quality of research outputs and helps to maximise the impact of outputs on health”</p>	<p>Nil</p> <p>“For all research involving people as participants, their tissues or data, the relevant principles of Good Clinical Practice (GCP), an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects, should be followed (13). Where practicable, consent that is freely given and informed should be sought from all competent participants. Guidance on writing participant information is available from the National Research Ethics Service (NRES)(14); this includes guidance for research that involves adults who lack capacity to give consent or children (15).”</p>
<p>International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.</p> <p>Good Clinical Practice: ichgcp.net</p>	<p>Nil</p>	<p>Nil</p> <p>“2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.”</p> <p>3.1.2 The IRB/IEC should obtain the following documents:</p> <p>trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g. advertisements), written information to be provided to subjects,</p>

Institution Policy/guidance	Statement that data must be made available	Statement that informed consent should include making data available
		Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities.
<p>NHS Health Research Office National Research Ethics Service (NRES) www.nres.nhs.uk/applications/guidance/consent-guidance-and-forms/ Medicines for Human Use (Clinical Trials Regulations) 2004. Informed consent in clinical trials www.nres.nhs.uk/applications/guidance/consent-guidance-and-forms/?entryid62=66934</p>	Nil	<p>Nil</p> <p>“25. The ethics committee that reviews a clinical trial (referred to in this note as “the main REC”) must consider various matters before giving its opinion. These include:</p> <ul style="list-style-type: none"> • The adequacy and completeness of the written information to be given, and the procedures to be followed, for the purpose of obtaining informed consent to the subjects’ participation in the trial.”
<p>NHS Health Research Office National Research Ethics Service (NRES) Consent form template www.nres.nhs.uk/EasysiteWeb/getresource.axd?AssetID=143371&type=full&servicetype=Attachment</p>	Nil	<p>Nil</p> <p>“I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from [COMPANY NAME], from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.”</p>
University of Newcastle	Nil	Nil

Institution Policy/guidance	Statement that data must be made available	Statement that informed consent should include making data available
Research and Enterprise Services Consent Form www.ncl.ac.uk/res/research/ethics_governance/ethics/toolkit/consent/consent_form.htm		“The use of the data in research, publications, sharing and archiving has been explained to me.”
Research Councils UK (RCUK) — the strategic partnership of the UK's seven Research Councils. Policy and Code of Conduct on the Governance of Good Research Conduct October 2011 www.rcuk.ac.uk/Publications/researchers/Pages/grc.aspx	Weak UNACCEPTABLE RESEARCH CONDUCT Mismanagement or inadequate preservation of data and/or primary materials, including failure to: ... <ul style="list-style-type: none"> • make relevant primary data and research evidence accessible to others for reasonable periods after the completion of the research: 	NIL “Appropriate procedures to obtain clearly informed consent from research participants - should be in place”
UK University Research Ethics Committees Forum An informal forum for those involved in research ethics review in UK Universities	N/A	N/A
Association of Research Ethics Committees www.arec.org.uk/	N/A	N/A
Universities UK Our five current strategic priorities are: 5. research funding and governance www.universitiesuk.ac.uk/PolicyAndResearch/Pag	Weak “Transparency and open communication in ... in making research findings widely available, which includes sharing negative results as appropriate... ”	Nil

Institution Policy/guidance	Statement that data must be made available	Statement that informed consent should include making data available
es/default.aspx The concordat to support research activity www.universitiesuk.ac.uk/Publications/Pages/concordattosupportresearchintegrity.aspx		
Government Office for Science (www.bis.gov.uk/go-science) <i>Rigour, Respect, Responsibility: a Universal Ethical Code for Scientists</i> www.bis.gov.uk/assets/goscience/docs/u/universal-ethical-code-scientists.pdf		
European Union Regulation on Clinical Trials Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. European Commission. 2012 ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf	Weak 3.6 Directive 2001/20/EC contains relatively few rules on the actual conduct of trials. These rules are partly contained in Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products ¹² , and partly contained in Commission guidance documents. The proposed Regulation brings together these rules. 3.13. In particular, the protocol shall include: ... a description of the publication policy	NIL

Institution Policy/guidance	Statement that data must be made available	Statement that informed consent should include making data available
	... duly substantiated reasons for submission of the summary of the results of the clinical trials after more than one year	

Written evidence submitted by the Global Alliance of Publication Professionals (CT02)

Introduction

1. We are the Global Alliance of Publication Professionals (www.gappteam.org). We are a global organisation set up to highlight the work of professional medical writers. As such, the question of publication of clinical trials falls firmly within our area of interest and expertise.
2. We note that the scope of the inquiry is wider than just publication of clinical trials, and also refers to the conduct of clinical trials, which is less within our core area of interest. We will therefore not be submitting evidence in relation to questions 1 and 2 of the committee's terms of reference, but will concentrate instead on questions 3–5.

Question 3: “What evidence is there that pharmaceutical companies withhold clinical trial data and what impact does this have on public health?”

3. Turning first to the question of the evidence that pharmaceutical companies withhold clinical trial data, we are concerned about how the debate is framed by use of the word “withhold”. This implies an active process of trying to hide data. In reality, data may remain unpublished for a variety of reasons, such as lack of the resources needed to ensure that data are written up for publication and submitted to journals, or rejection of papers by journals.
4. We are not aware of any evidence at all that pharmaceutical companies specifically “withhold” data (as distinct from not publishing data for other reasons), and in the absence of such evidence it would be wrong to claim that data are withheld.
5. In contrast, there is considerable evidence about the extent to which clinical trials remain unpublished, albeit that that evidence seldom if ever examines the reasons for non-publication. However, much of that evidence is severely limited by being out of date.
6. The relevance of the date of research on non-publication of clinical trial results should not be underestimated. In recent years, publication practices have changed dramatically within the pharmaceutical industry. Data on publication rates from 10 years ago are likely to have little relevance to today's situation.
7. Guidelines on Good Publication Practice (GPP) for Pharmaceutical Companies were first published in 2003 [1]. These guidelines recommended that pharmaceutical companies should publish the results of all their clinical trials. To our knowledge, this was the first serious attempt within the pharmaceutical industry to ensure completeness of publication. Public backing by pharmaceutical companies was initially slow. However, an updated version of the guidelines (known as GPP2) was published in 2009 [2], which gave the guidelines new impetus.
8. During the same period of time, the FDA Amendments Act (FDAAA) of 2007 came into force in the USA. This required pharmaceutical companies to make the results of their clinical trials publicly available on the clinicaltrials.gov website, which further increased the impetus for transparency of clinical trials results.
9. In light of these moves towards greater openness, many pharmaceutical companies now have policies which commit to publishing the results of all their clinical trials, irrespective of outcome. An example of such a policy is the one by GlaxoSmithKline [3]. Such policies were rare 10 years ago. The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) published a position statement in 2010 encouraging pharmaceutical sponsors to publish all their clinical trial results in the peer-reviewed literature [4].

10. It is therefore important that data on completeness of publication be up-to-date. One widely quoted statistic is that 50% of clinical trial data remain unpublished. This comes from a systematic review which was published in 2010 [5], but which included results of older studies, many of which dated from the 1990s. It is therefore unlikely to be relevant.
11. We are not aware of any systematic reviews looking only at recent data. However, we are aware of two reasonably recent good quality studies looking at completeness of publication of clinical trial data.
12. Bourgeois et al investigated publication of drug trials registered on clinicaltrials.gov and reported their results in 2010 [6]. They found that overall, 362/546 studies (66%) were published in peer-reviewed journals and a further 75 had results disclosed on a website, giving a total of 437 studies (80%) with disclosed results.
13. Ross et al also examined clinical trials registered on clinicaltrials.gov, although limited their research to studies funded by the US National Institutes of Health. They published their results in 2012 [7]. Their results were remarkably similar to those of Bourgeois et al, finding that 432/635 trials (68%) were published in peer-reviewed journals. They did not report whether any studies were made available on websites.
14. Both studies found that publication was often slow, taking longer than 2 years after study completion in many cases. This is not entirely surprising, as writing up results for publication can be a time-consuming process, and it may be many months from completion of a paper to publication, as many journals have long lead times. If a paper is rejected from one journal and has to be submitted elsewhere, then delays will increase. It is therefore possible that final disclosure rates would have been higher in both studies, had follow up been longer.
15. Contrary to the popular myth that non-publication of data is a problem mainly of the pharmaceutical industry, Bourgeois et al found that total rate of disclosure of clinical trial results (ie publications in peer reviewed journals plus postings of results on websites) was higher in industry-sponsored studies than in independent studies. 305/346 industry sponsored studies (88%) had disclosed results, compared with 41/74 government sponsored studies (55%) and 50/65 non-profit studies (77%). This seems to be consistent with other evidence: a systematic review published in 2010 found 5 studies that compared industry-sponsored studies with independent studies, 3 of which found a higher probability of publication in the industry studies, one of which found no difference, and only one of which found higher publication rates in non-industry studies [8].
16. Bourgeois et al also found that, despite the higher eventual publication rate of industry sponsored studies, they were initially slower to be published than independent studies. However, industry-sponsored studies were larger and more often multicentre studies, and it is reasonable to hypothesise that the greater delay before publication was a consequence of the greater complexity of the studies.
17. We are not aware of any direct evidence that non-publication of clinical trial data harms public health. However, it seems reasonable to assume that it would have this potential. Public health is continually improved by the application of new research findings, and if trial results remain unpublished, then they cannot benefit public health. Further, non-publication of clinical trial data breaks the “ethical contract” researchers make with clinical trial participants to share clinical trial data to advance medical knowledge and potentially benefit others.

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

18. There are many creative ways in which clinical trials could be made more transparent, some of which would involve a complete overhaul of the way in which drugs are licensed. However, we are taking a pragmatic and realistic view, and assume that there is little

chance that that will ever happen, and that the suggestions we make need to be compatible with the current system for licensing drugs or minor modifications thereof.

19. We would like to stress the importance of ensuring that specific resources are available for publication of research results. Publications do not write themselves. It is likely that many studies remain unpublished simply because the researchers simply lack the resources to write up their results for publication.
20. Although lack of resources is less often a problem in the pharmaceutical industry, we suspect it is a very common problem in non-industry research, and may contribute to the lower publication results seen in research that is not sponsored by the pharmaceutical industry, as we noted in paragraph 15 above. We suggest that when grants are awarded for clinical research, it should become standard practice to ring-fence an element of the grant for publication, as we have argued in more detail in a recent published article [9]. This is a no-cost solution that could be readily implemented
21. We believe that non-publication of clinical trial results is an ethical issue, and so should be a legitimate concern of research ethics committees. There is a good argument for a commitment to publication of results being a condition of ethical approval to conduct trials. We understand that the National Research Ethics Service is sympathetic to this point of view, but currently lacks any robust means of following up such commitments to ensure that they are met. One of us (AJ) is a member of an NHS Research Ethics Committee and has written about some of the challenges of this in more detail [10].
22. Ensuring that research ethics committees monitor completeness of publication would be a highly achievable and practicable step. Although there are some barriers to doing this, we believe that those problems are solvable, and we urge Parliament to give whatever support it can to the National Research Ethics Service to help it to implement a suitable system.
23. Grant giving bodies, such as the MRC, could also play a useful role in this context. It should be a condition of any grant for clinical research that the results of the research be published. Again, enforcement mechanisms would need to be in place if this were to be meaningful.
24. Much clinical research in the UK takes place within the NHS and/or academic institutions: these are organisations over which the government has at least some influence. It should be possible to ensure via researchers' contracts of employment that they are obliged to ensure that any clinical trials in which they are involved are published.
25. Considering the pharmaceutical industry, the industry itself has already taken great strides to improve the completeness of publication in recent years. However, we believe that further steps could and should be taken, and one possible such step would be for regulatory bodies such as the MHRA and the EMA to adopt a more open culture. Currently, clinical study reports submitted to those bodies remain confidential. There could be greater on-line disclosure of CSR content.
26. We understand that there might be commercial implications to full CSR disclosure; however, this might be mitigated if all sponsor companies are required to provide the same degree of disclosure.
27. It is worth noting that making clinical study reports available would do considerably more for transparency than any attempt to increase rates of publication in peer-reviewed journals. The level of detail available in clinical study reports submitted for regulatory purposes far exceeds that in publications in journals.
28. Nonetheless, concerns have been expressed that making reports widely available could lead to inappropriate secondary analyses by those with an axe to grind, and if picked up by the press could potentially do harm.

29. We suggest that a possible way forward would be to make some study reports available as part of a pilot project. This could, for example, be done for phase III studies in specific therapy areas. The costs, benefits, and harms of making the reports available could then be evaluated before any decisions were made about rolling out the initiative more widely.

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

30. Turning to your final question about what evidence can be learned from other countries, the USA has passed laws that mandate the disclosure of clinical trial results for licensed drugs. The FDA Amendments Act of 2007 (FDAAA) requires, among other things, that results of clinical trials be posted on the clinicaltrials.gov website within 1 year of study completion.
31. In addition to the benefits of posting results, posting details of the design of studies on the clinicaltrials.gov website helps eliminate redundancy and inefficiency in the design of clinical trials. This allows competitive Pharma/independent researchers to follow a sanctioned lead in design of their trials. This is particularly useful in the establishment of acceptable trial design, such as choice of comparators, sample size, treatment and sample collection schedules, and outcome measures.
32. Although there was apprehension from industry about the FDAAA requirements, extensive efforts and resources have been made to develop and implement results disclosure policies (eg, entire departments have been created within industry to cope with results disclosure requirements). Recent evidence indicates that industry compliance with FDAAA is significantly higher than non-industry compliance [11]. Notably, the time required for results disclosure was greatly under-estimated by the US government and updated estimates had to be issued [9]. Researchers and sponsors should be provided with realistic estimates if governments expect compliance with their legislative initiatives.

Conclusions

33. We must stress the importance of ensuring that sufficient resources are available for publication of results. Publications do not write themselves. Good researchers are not always efficient writers of scientific papers, and it is important that assistance from professional medical writers be made available to those who need it.
34. It is important to realise that non-publication of clinical trial results is not primarily a problem of the pharmaceutical industry: recent evidence shows that, although non-publication remains a problem in all sectors, it is closer to being solved in the pharmaceutical industry than elsewhere.
35. While much public discourse has focussed on demonising the pharmaceutical industry, this is not only unsupported by evidence, but is also unhelpful. There are those who make money by selling ineffective “alternative therapies” who use public distrust of the pharmaceutical industry as one of their main marketing strategies. Painting the pharmaceutical industry as being evil helps these quacks and charlatans considerably when they employ that strategy, which can result in real harm to patients.
36. We would therefore urge the committee to focus on practical solutions to the problem of inadequate disclosure of clinical trials rather than on apportioning blame. We believe that the three most effective practical solutions would be to ensure that researchers are properly funded to disclose their results, embedding monitoring of results disclosure firmly within the National Research Ethics Service, and evaluating the possibility of opening up data submitted to drug regulators to public scrutiny.

Submitted by the Global Alliance of Publication Professionals: Dr Adam Jacobs, Mr Art Gertel, Dr Cindy Hamilton, Mr Gene Synder, and Professor Karen Woolley

Conflict of interest statement

All GAPP members have held, or do hold, leadership roles at associations representing professional medical writers (eg, AMWA, EMWA, DIA, ISMPP, ARCS), but do not speak on behalf of those organizations. GAPP members have, or do provide professional medical writing services to not-for-profit and for-profit clients.

January 2013

References

1. Wager E, Field EA, Grossman L. Good publication practice for pharmaceutical companies. *Curr Med Res Opin* 2003;19:149-54
2. Graf C, Battisti WP, Bridges D et al. Good publication practice for communicating company sponsored medical research: the GPP2 guidelines. *BMJ* 2009;339:b4330 (doi: 10.1136/bmj.b4330)
3. <http://www.gsk.com/content/dam/gsk/globals/documents/pdf/GSK-on-disclosure-of-clinical-trial-information.pdf>
4. International Federation of Pharmaceutical Manufacturers & Associations. Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. http://clinicaltrials.ifpma.org/clinicaltrials/fileadmin/files/pdfs/20100610_Joint_Position_Publication_10Jun2010.pdf
5. Song F, Parekh S, Hooper L, et al. Dissemination and publication of research findings: an updated review of related biases. *Health Technol Assess* 2010;14(8) (doi: 10.3310/hta14080)
6. Bourgeois FT, Murthy S, Mandl KD. Outcome reporting among drug trials registered in ClinicalTrials.gov. *Ann Intern Med* 2010;153:158-66
7. Ross JS, Tse T, Zarin DA et al. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis *BMJ* 2012;344:d7292 (doi: 10.1136/bmj.d7292)
8. Schott G, Pachl H, Limbach U, et al. The financing of drug trials by pharmaceutical companies and its consequences. Part 2: a qualitative, systematic review of the literature on possible influences on authorship, access to trial data, and trial registration and publication. *Dtsch Arztebl Int* 2010;107:295-301
9. Woolley KL, Gertel A, Hamilton C et al. Poor compliance with reporting research results – we know it’s a problem...how do we fix it? *Curr Med Res Opin* 2012;28:1857-1860 (doi:10.1185/03007995.2012.739152)
10. <http://dianthus.co.uk/can-ethics-committees-help-tackle-publication-bias>
11. Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. *BMJ* 2012;344:d7373 (doi: 10.1136/bmj.d7373)

Written evidence submitted by the Cochrane NI Review Group (CT03)

We are responding to the third and fourth questions.

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

1. We started working on a Cochrane review of neuraminidase inhibitors in 1998. Cochrane reviews are studies summing up what is known of the effects of an intervention in healthcare. In this case the “intervention” was the class of drugs called neuraminidase inhibitors or NIs. NIs are supposed to alleviate influenza, either by shortening duration of illness and diminishing dangerous complications such as pneumonia or by acting prophylactically (prevention) in contacts of people with influenza or on whole populations exposed to the threat. At the time NIs comprised two anti-influenza compounds: *zanamivir* (Relenza, GW now GSK) and *oseltamivir* (Tamiflu, Roche)^{1 2}.

2. The Cochrane Collaboration (CC) is an international network of volunteer scientists who carry out reviews of evidence on interventions in health care according to highly structured and reproducible methods. Cochrane reviews are considered as the gold standard in evidence-based decision making for interventions (www.cochrane.org).

3. Cochrane reviews are widely cited by governments and health departments worldwide. The CC receives considerable funding from the UK Department of Health, and is completely independent from pharmaceutical companies or other potentially conflicting influences. The Cochrane group conducting the review of NIs consists of researchers at the University of Oxford, University of Queensland, Bond University, Johns Hopkins University, and independent scientists in Osaka and Rome. Comments by any reader can be posted on the Cochrane protocol or the full review at any time. The comments are taken seriously, as this account shows.

4. In 2009, our review was in its third update³, the world was in the middle of an influenza pandemic (or so WHO was telling us) and we received a letter from a Japanese paediatrician, Dr Keiji Hayashi. Dr Hayashi wanted to know how it was possible that in our 2005 update we had included 8 unpublished Tamiflu trials contained in extreme summary form within another review funded by Roche and carried out by Roche staff and consultants. How could we possibly have done that as we had not seen the original studies? We asked the two Roche consultants for the data. They told us to go and ask Roche. We did. Roche asked us to sign a confidentiality agreement with a secrecy clause. We declined. We cannot publish a Cochrane review subjected to secret and restrictive clauses. This would compromise independence, transparency and reproducibility of the review⁴.

Once the British Medical Journal (BMJ) got involved with Channel 4 News^{5 6 7} and brought media pressure to bear, Roche publicly promised full study reports⁸. However Roche gave us only the first of the 4-5 parts of the 10 trials. They told us that was all we needed for our review. We now know that this is not the case. By reading the Roche material and some NICE documents leaked to the BMJ, we discovered that the reports that a pharmaceutical company produces for each drug trial that it conducts (called clinical study reports) are massively complex documents, containing hundreds or thousands of pages of information with minute details about trials, their planning and execution. This represents a major shift in the level of detail that Cochrane reviewers such as ourselves have been used to, since in the past we have relied on journal articles that are typically only a few pages in length.⁹

5. We discovered many more Tamiflu trials. The list has grown from the 26 we had originally identified to 123 – the vast majority Roche sponsored. We asked for all the Roche completed clinical study reports so we could assess them for our review. In the 3 years since this request, we have had a lengthy negotiation with Roche regarding the release of these trial details, documented publically in <http://bit.ly/HIbwqO> and <http://www.bmj.com/tamiflu/roche>. To date we have had no success in obtaining the trial data from Roche. Without these trial data it is not possible to conduct a review of the evidence for this drug.

6. At the end of 2010 the European Regulator EMA accepted a ruling by the European Ombudsman that trial data for drugs on which a regulatory decision had been made should be accessible. They opened their archives. We received incomplete reports for 16 Tamiflu trials, all they had. Because of timing constraints, our 2012 update of our Cochrane review is based on over half of the evidence provided by EMA and approximately 2000 pages of FDA comments on Tamiflu¹⁰. We are in the process of reviewing the other half of the Roche Tamiflu trial data.

7. One consequence of our access to this bonanza of regulatory material has been a comparison between the details and broad message of the few published trials and their regulatory much more detailed reports. There are discrepancies in reporting harms and some important aspects of study design between publications and regulatory reports. We also think that the drug interferes with natural antibody production¹⁰. If confirmed, this finding would suggest that use of Tamiflu weakens natural host defences and may weaken response to any antigen stimulating interventions such as vaccines.

8. On the basis of regulatory evidence released from EMA and FDA we have also found that the positive effects of the drug are not as marked as those claimed by the manufacturer and its consultants in industry-sponsored publications. Like FDA, we found the effect of Tamiflu on influenza complications (e.g. pneumonia) and person-to-person transmission unproven¹⁰.

9. As these effects were at the basis of the scientific rationale for stockpiling Tamiflu, we wonder whether access to all trial data would have avoided stockpiling at huge public expense. But we do not know for sure because we do not have all the data.

10. The practical result of all this is our refusal to consider published trials (either on their own or as part of reviews) for inclusion in our Cochrane reviews. There is growing international concern regarding the limitations of relying solely on the very short versions of drug trials^{11 12 13}. So now we have asked EMA to do a more thorough job by requesting the remainder of the missing sections of the trials they originally looked at and all the other missing trials. The idea is that EMA asks Roche for the data and then has to release it following its new policy. This is documented at <http://www.bmj.com/tamiflu/ema>.

11. Meanwhile what started as a comment from a Japanese colleague has turned into a global campaign for access to data on trials^{12 13 14}. You can read about that here <http://www.bmj.com/content/345/bmj.e7304>. The BMJ set up a Tamiflu micro site on BMJ.com with our correspondence with Roche, WHO and CDC <http://www.bmj.com/tamiflu>. The latter two continue to recommend the use of Tamiflu, seemingly disregarding the lack of evidence for their effects that we and others have documented. They also refuse to answer our questions (see <http://www.bmj.com/tamiflu/who> and <http://www.bmj.com/tamiflu/cdc>).

12. As independent medical scientists we are deeply disturbed that despite serious concerns by ourselves and many other independent scientists in this field regarding the effectiveness of Tamiflu and the secrecy surrounding its trials, it appears that recommendations for the use of this drug continue to be at odds with what trial evidence shows. The financial consequences of these recommendations are ongoing, notwithstanding the costs of stockpiling this drug during the swine flu outbreak in 2009, are considerable for the NHS at a time of tight financial constraints. Most of all, no one seems to know exactly how much has been spent on a drug for which no one (apart possibly the manufacturer) has seen and analysed the full data set. We can say this, as we have analysed documents, reviews and Health Technology Assessment reports produced by WHO, CDC and NICE. These are based on journal articles reports of published trials and in some cases on additional data furnished by the manufacturer on an *ad hoc* basis. We assume these data were subject to the same controls Roche tried to impose on us.

13. We have also engaged GSK, asking them for clinical study reports and individual participant level data for their drug Relenza. Some of the press coverage recently suggested that GSK after its record fine in the US courts of justice for fraud (<http://www.dailymail.co.uk/news/article-2167742/GlaxoSmithKline-pay-3b-fine-pleading-guilty-healthcare-fraud.html>) would open its archives to researchers. GSK has told the world that requests for data would be handled with the intermediary of an independent committee scrutinizing the worthiness of the analysis plans in the

application. Despite the plaudits, our group is yet to receive any data from GSK and we remain unconvinced, as we want reproducibility of our Cochrane analyses. We recognize that we do not hold a monopoly on truth.

14. Obstacles and conditions (such as exclusivity, secrecy or contractual bans on sharing) attached to data release make reproducibility of results harder or impossible because they constrain our ability to share the data underlying our analysis with third parties seeking to reproduce or verify our analysis.

15. We are disappointed that the DH has not intervened to require Roche to make the missing trial data publicly available after the amount of tax payers' money that was spent on it. We also find it hard to comprehend how the CMO and NICE have not been held accountable for their decisions.

16. Our attempts to independently assess the evidence for the effectiveness of the NI drugs highlights 3 major problems that we believe are generalisable to other drugs.

17. First, there is clear evidence that full reports of trials are not available for public scrutiny, even by well known researchers such as our Cochrane group. This means that vital evidence for the safety and effectiveness of Tamiflu is simply not available. This does not allow individual clinicians to make rational decisions for their patients. The second problem is that our reading of EMA, Japan's PMDA and the US FDA's reports (see our Cochrane review) suggests that their scrutiny does not encompass the full dataset but a pre-agreed selected subset of toxicology and pharmacodynamics studies plus a few (usually two) trials per indication. In the United States, these trials are dubbed "pivotal". Although the US FDA appeared to have done a much more thorough job than EMA with data re-analysis and trial site visits, the regulatory perspective is different from ours. Our job as Cochrane researchers is to look at all the relevant evidence, not judge whether a product is worthy of a market authorization or license on the basis of a pre-arranged set of studies.

18. The third problem is decision-makers who make policy on the basis of short journal publications and expert advice and are unwilling to revise their policies when new evidence emerges that journal publications and expert advice have mislead. In the case of Tamiflu this may have had damaging effects to public and clinician confidence in the rigour of how medications are assessed in the UK for safety and effectiveness, and risk that NHS funds have not been used for interventions which offer the best value for money. The individuals responsible for making these decisions do not appear to be accountable, even when evidence shows that their decisions may not stand up to scrutiny

This is how three front-line public health physicians in the Midlands see the effect of current anti-viral policies on their role:

"Many of us in PCTs considered our role to have been transformed from front line public health to that of an NHS delivery system for the pharmaceutical industry."

(<http://www.bmj.com/content/345/bmj.e7305/rr/620772>)

19. Trials are experiments conducted on human beings. Full reporting of their results (anonymized to prevent individuals being identified) should be a right, not a gift. It is ethically wrong not to make their results public. Your doctor should be in possession of all the facts or be able to access a source that does. Think about that next time he prescribes something for you.

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

1. All past, current and future trials should be registered in one of the trial registers as soon as their protocol is finalized. For old trials retrospective registration should be allowed. Registration provides consumers and/or taxpayers with a complete overview of what is going on. On its own however, registration is not enough because there is evidence of reporting bias of register entries, including failure to update them.

2. Clinical study reports should be made available with minimal redactions in PDF format in a central website. This should be run by a publicly funded body and governed autonomously. Only this type of availability should be considered “publication” i.e. *making public*.
3. The Committee should not consider “publication” to mean either journal articles of a few pages’ length, or similar-length summaries posted on sponsors’ websites. In both cases the potential for introducing reporting biases and consequent distortions of the evidence has been shown to be very high.
4. Sponsors’ failure to publish and maintain the trials entries should be considered unethical. The medical director of the sponsor and principal investigators should be routinely reported to the GMC.
5. The relevant individual participant level data should be made available in anonymized form from the central resource. The body should require a reason for the request and apply a level of scrutiny to requests which deters frivolous requests.
6. The costs of regulating the new system would be offset by preventing the use of drugs for which there is no or little evidence of effectiveness or that cause harm.

Cochrane Neuraminidase Review Group

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Disclosure Statement

All authors have applied for and received competitive research grants. All authors are co-recipients of a UK National Institute for Health Research grant to carry out a Cochrane review of neuraminidase inhibitors (<http://www.hta.ac.uk/2352>) which used as its basis more than 25,000 pages of Clinical Study Reports for oseltamivir

In addition:

Tom Jefferson was an ad hoc consultant for F. Hoffman-La Roche Ltd in 1998-1999. He receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore (Italy), none of which are on Clinical Study Reports. He is occasionally interviewed by market research companies for anonymous interviews about Phase 1 or 2 products. In 2011-12 Tom acted as an expert witness in a US litigation case related to Tamiflu.

Peter Doshi received €1500 from the European Respiratory Society in support of his travel to the society’s September 2012 annual congress where he gave an invited talk on Tamiflu. He is funded by an institutional training grant from the Agency for Healthcare Research and Quality (AHRQ)

#T32HS019488. AHRQ had no role in study design, data collection and analysis, decision to publish, or preparation of the submission.

Matthew Thompson received payment for running educational courses at the University of Oxford and University of Oxford ISIS consulting services for external teaching and training.

Mark Jones has no conflicts of interest to declare.

Rokuro Hama has written the following books:

Published in January 2008: “Tamiflu: harmful as feared” (Kin-yobi Publishing Co). Royalties were split between his institution and the Tamiflu sufferers group 7%-1%.

Published in November 2008: “In order to escape from drug-induced encephalopathy”. NPOJIP(Kusuri-no-Check). Royalties to his institution.

Dr Hama provided scientific opinions and expert testimony on:

11 adverse reaction cases related to oseltamivir where applications were made by their families for adverse reaction relief by PMDA (Pharmaceuticals and Medical Devices Agency). This is reported in: IJRS 2008;20:5-36. Two cases were paid in May 2005 and others were not.

A law suit on the fatal adverse reactions to gefitinib against AstraZeneca and the Japanese Minister of Health Labor and Welfare. Dr Hama argued that gefitinib's fatal toxicity was known before approval in Japan as shown in “Gefitinib story”: <http://npojip.org/english/The-gefitinib-story.pdf> and in other articles: <http://npojip.org/>. Paid by the plaintiff's lawyers.

Chris Del Mar provided expert advice to GlaxoSmithKline about vaccination against acute otitis media in 2008-2009. He receives royalties from books published through Blackwell BMJ Books and Elsevier.

Chris Del Mar and **Tom Jefferson** have recently updated their Cochrane review on physical interventions to prevent the spread of acute respiratory infections with World Health Organization (WHO) funds.

January 2013

Main related publications (items marked * are attached):

1. Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006;367:303-13*
2. Jefferson T, Demicheli V, Di Pietrantonj C, Jones M, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database of Systematic Reviews 2006;(3):CD001265
3. Jefferson T, Jones M, Doshi P, Del Mar C. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. BMJ 2009;339:b5106*
4. Doshi P. Neuraminidase inhibitors: the story behind the Cochrane review. BMJ 2009;339:b5164*
5. Cohen D. Complications: tracking down the data on oseltamivir. BMJ 2009;339:b5387

6. Godlee F, Clarke M. Why don't we have all the evidence on oseltamivir? *BMJ* 2009;339:b5351
7. Editor's Choice: We want raw data, now. *BMJ* 2009; 339 doi: 10.1136/bmj.b5405
8. Smith J, on behalf of Roche. Point-by-point response from Roche to BMJ questions. *BMJ* 2009;339:b5374*
9. Doshi P, Jones MA, Jefferson T. Rethinking credible evidence synthesis. *BMJ* 2012;344:d7898 doi: 10.1136/bmj.d7898*
10. Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, Thompson MJ. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database of Systematic Reviews* 2012, Issue 1. Art. No.: CD008965. DOI: 10.1002/14651858.CD008965.pub3*
11. Drug Data Shouldn't Be Secret by Peter Doshi and Tom Jefferson *The New York Times*, April 10, 2012. URL: <http://www.nytimes.com/2012/04/11/opinion/drug-data-shouldnt-be-secret.html> Shortened URL: <http://nyti.ms/lvgh9c>
12. Doshi P, Jefferson T, Del Mar C (2012) The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience. *PLoS Med* 9(4): e1001201. doi:10.1371/journal.pmed.1001201
Short URL: <http://bit.ly/HIbwqO>. PDF for printing: <http://bit.ly/HFBYTV>
13. Godlee F. Clinical trial data for all drugs in current use. *BMJ* 2012;345:e7304 doi: 10.1136/bmj.e7304 (Published 29 October 2012)
14. Payne D. Tamiflu: the battle for secret drug data. *BMJ* 2012;345:e7303 doi: 10.1136/bmj.e7303 (Published 29 October 2012)
15. Godlee F. Open letter to Roche about oseltamivir trial data. *BMJ* 2012;345:e7305 doi: 10.1136/bmj.e7305 (Published 29 October 2012). <http://www.bmj.com/content/345/bmj.e7305>

Written evidence submitted by Margaret McCartney (CT04)

1. I am Margaret McCartney, a general practitioner in Glasgow. I have been writing about medicine in society over the last decade for the British Medical Journal, the lay press, Radio 4's Inside Health and I am the author of The Patient Paradox – why sexed up medicine is bad for your health. I have won national and international prizes for my writing about evidence based medicine including the Healthwatch Award. I am a member of the Royal College of General Practitioners. The non publication of clinical trials is of major concern to me and I have written about this over the last decade.
2. I have no conflicts of interest, except that as a GP and a patient myself, my patients and I suffer directly when there are unpublished clinical trials into healthcare interventions I prescribe or take.
3. The problems generated by the non publication of clinical trials are
 - a) I can have no faith that patients taking part in clinical trials are not doing themselves harm. This is because previous trials may have been done showing that the intervention is dangerous but have gone unpublished. This means that I cannot be sure that the intervention is reasonable to test. This means that I cannot trust the clinical trials recruitment process, and useful developments are less likely to occur.
 - b) I can have no trust that the healthcare interventions I prescribe or suggest do more good than harm. This means that I give patients less good information than they should have about the risks and benefits of an intervention. This means that I may be doing more harm than good, but I do not know this is the case. This causes unnecessary risk to patients.
 - c) The scientific process is the best way we have of sorting out which healthcare interventions are best for people. However this noble process has been subverted because of the desire to profit. The profit motive – which I believe has caused many of the problems of no-publication of research – has meant a lack of trust in the medical research process. This means that many people may be unwilling to be entered into a clinical trial, and it also means that many people may turn to alternative medicine. This in turn also causes harm, including financial.
 - d) I was approached by a drug company 2 years ago seeking to perform a clinical trial in my practice. I asked what would happen if they did not publish the trial results, and I did. The bottom line was that they would sue me. Of course I did not get involved in the trial. This is evidence that doctors who believe in data being published can have no guarantee that the trials they are involved with will reach the light of day. This means that I in turn, as a GP, can not trust the drug companies.
 - e) As quoted in my book, The Patient Paradox, GPs have been accused by head of the British Pharmaceutical Industry as being 'luddites' for not prescribing new drugs quickly. Because doctors are afraid of the data they don't know about, they are rightly often sanguine when it comes to new drugs on the market. But healthcare charities often receive money from the pharmaceutical industry. It is often charities, rather than the pharmaceutical industry directly, who make plays for new drugs to be prescribed. Yet the same charities are offering 'educational' material to doctors, as well as urging NICE to recommend new treatments. I believe that this financial bind causes many charities not to question the non publication of clinical trial results and the harms that the non publication of clinical trials can cause.

2. The non publication of clinical trials would be easy to rectify. A law could ensure that all clinical trial data was published online by 12 months after close of trial. We protect citizens through law in all sorts of other ways – why not this also?

I really don't see why this would be difficult to do.

February 2013

**Joint written evidence submitted Andrew Russell and John Hughes,
Patient & Public Member, UKCRC Board (CT05)**

Introductory Comment

We are the two Patient & Public Board members of the UK Clinical Research Collaboration, a partnership chaired by the Chief Medical Officer for England, which aims to improve the clinical research environment. The views expressed here are personal and are not necessarily shared by fellow Board members of the UKCRC. You will be aware that the Collaboration includes representatives from government, principal research and academic bodies, regulatory organizations, key charities and from industry, including the pharmaceutical industry.

The Scope of our Comments

We focus on the need for robust and independent regulation of the development process for new pharmaceutical products, currently by the Medicines & Health Products Regulatory Agency (MHRA), which is consulting on its draft Corporate Plan 2013-18.

The tone of the MHRA Corporate Plan is very much one of co-operation and compromise with the pharma industry. It places emphasis on the economic benefits of encouraging the industry to maintain a strong base in the UK and to carry out clinical trials here. Whilst we acknowledge the importance of this industry to the UK economy, we think there should be greater emphasis on regulation for the safety and benefit of the public, patient and taxpayer, in this Corporate Plan.

The Need for Full Publication of Clinical Trial Results

The recent publication “Bad Pharma” by Dr Ben Goldacre makes a strong case that companies have failed routinely to publish trial results that have proved unfavourable to their products in development. This distorts meta-analyses in favour of the product, minimising evidence of side-effects and exaggerating health benefits. This serious charge signals a need for a strong and proactive regulator with an independent mind-set. Whilst the Medicines For Human Use (Clinical Trials) Regulations 2004 make registration and reporting mandatory, we question whether this requirement is always met by companies, and whether the MHRA sees it as its key role to enforce this aspect of the law.

The Case for Robust Regulation

Recent experience has shown that it is not in the best interests of an industry, nor of the public, for a regulator to be too close to that industry. The failure of the Financial Services Authority to guard against banks’ malpractices has proved disastrous for the whole UK population and to banks themselves. We believe that there is a lesson to be learnt in relation to pharmaceuticals, particularly in the light of the current lack of transparency in research findings, and the huge cost to the taxpayer of prescription drugs. We think that the MHRA, if it is to remain the principal regulator, should be less shy of asserting the need for strong regulation in its Plan.

The Clinical Practice Research Database (CPRD)

The CPRD, whilst a very valuable additional means of enhancing the safety and effectiveness of drugs in use, should not be relied upon as the primary protection for patients. Clinical trials, fully registered and reported, should remain the principal tool in the MHRA’s vital gatekeeper role.

Customers, Stakeholders and Conflicting Aims

Inevitably there is a potential degree of conflict between the stated function of the MHRA to promote and support innovation beneficial to prosperity by creating conditions favourable to the pharma industry, and its role as the key regulator of the industry's products.

Whilst the term "customer" is not defined in the MHRA's draft Plan, it appears to refer to bodies such as companies applying for products to be licensed. Satisfying them through a "faster, more efficient service" (p18) is desirable, and ensuring the MHRA's financial viability through charges is important, but the requirements of the public, the most important stakeholder, should constitute the core aim of the agency.

The Plan's approach to this is "proportionate regulation". This phrase lacks clarity, and in view of the objective to reduce regulation (p17), we question whether this is a sufficiently transparent approach bearing in mind the high level of accountability essential for patient safety and proper use of taxpayers' money. We would welcome more transparent criteria indicating the kind of risks which will merit regulatory attention.

Reference (p16) to reducing work which is not financially profitable to the agency, and to the increased pursuit of commercial opportunities, cause us concern. This indicates that the MHRA will see itself primarily as a business, rather than as a regulator acting for the public. At the extreme, a regulatory agency which prioritizes its own financial survival and success is unlikely to remain fit for purpose. Pharmaceuticals in development, under registered clinical trials, should be monitored to ensure that all trial results are made public in summary form.

The risks of "regulatory capture" and "revolving door"

Whilst it is important for the regulatory authority to maintain clear communication with commercial companies and their representative bodies, we believe they should be wary of assuming that all the authority's interests are held in common with companies.

In order to discourage personal conflicts of interest we suggest that contractual measures, if not already in place, be introduced to prevent senior MHRA staff accepting paid positions within the pharma or medical devices industries for a period of 3 years after the end of their employment in the MHRA.

Concluding Comment

We welcome the opportunity to make comment on this inquiry and hope that these views will be taken into consideration by the Commons Science & Technology Committee in determining its conclusions and advice.

February 2013

Written evidence submitted by the London School of Hygiene & Tropical Medicine (CT06)

Thank you for the opportunity to submit written evidence to the Select Committee on Clinical Trials.

This submission responds to the question: “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?”

My concern relates to the conduct of clinical trials in emergency situations. Such clinical trials are essential in improving the safety and effectiveness of emergency care. For example, few of the treatments currently used in the emergency management of patients with head injuries have ever been shown to be safe and effective. Indeed, corticosteroids were widely used to treat head injury until a large clinical trial (the CRASH-1 trial) showed that they increased, rather than decreased, the risk of death.¹

There are many treatments in daily use for which there is uncertainty about their effectiveness and safety.

When evidence is uncertain and the decision to give treatment A or treatment B does not have a sound scientific basis: some patients will get treatment A and some will get treatment B as part of their normal medical care. For example, before the CRASH-1 trial, just over half of doctors used corticosteroids and the rest did not. In the CRASH-1 trial, patients were randomly allocated to corticosteroids or placebo, so that we could find out whether or not corticosteroids were helpful. Because the allocation was made in a truly random way, we had two comparable groups of patients, half of whom received corticosteroids and half of whom did not. By comparing the outcomes in the two groups, we discovered that the doctors who used corticosteroids were wrong. The treatment did not work – it was harmful – thanks to the trial the doctors who used corticosteroids could stop doing so. This important information could not have obtained without a proper trial. However, there are many more uncertainties that need to be resolved.

Patients in emergency care trials are often in life threatening situations where urgent treatment is necessary. Because of the urgency of the situation and the patients’ clinical condition they are usually unable to give written informed consent to trial participation. These situations are a wholly appropriate exception to the general rule of written informed consent.

In this respect, Article 32 of the proposed Regulation, on clinical trials in emergency situations states the conditions for waiving “consent at the time”.

Informed consent may be obtained after the start of the clinical trial to continue the clinical trial and information on the clinical trial may be given after the start of the clinical trial provided that all of the following conditions are fulfilled:

- a) *due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, it is impossible to obtain prior informed consent from the subject and it is impossible to supply prior information to the subject;*
- b) *no legal representative is available;*
- c) *the subject has not previously expressed objections known to the investigator;*
- d) *the research relates directly to a medical condition which causes the impossibility to obtain prior informed consent and to supply prior information*
- e) *the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject.*

¹ The CRASH Trial Collaborators: Effect of intravenous corticosteroids on death within 14 days in 10,008 adults with clinically significant head injury (MRC CRASH Trial): a randomised placebo-controlled trial. *Lancet* 2004;364:1321-28.

It is my view that the wording of the new Clinical Trial Regulation could undermine the progress we've made in the UK to date on this important issue. There are particular difficulties with (b) and (e).

(b) It is likely that in many situations a relative or other legal representative may indeed be "available". However, no consideration is given to the ability of a relative to give consent in such an emergency situation. In cardiac arrest, severe trauma or major bleeding, it is unlikely that a relative or other legal representative would have the time or mental capacity to make an informed decision. The distress experienced by a relative when their loved one is at high risk of death must not be underestimated. Secondly, in some situations obtaining consent from a legal representative whether a relative or other, delays the administration of potentially life-saving interventions. For example, we have shown that in the CRASH-2 clinical trial of tranexamic acid in life threatening bleeding, the delay incurred by seeking consent from a relative, prevented many patients from receiving the early treatment benefits and that some patients died as a result of this needless "consent ritual".^{2 3}

(e) Many emergency conditions require the testing of new treatments. For example, in the case of traumatic brain injury, a condition with a high case-fatality rate, few proven treatments have ever been proved to be effective. New treatments are urgently needed. The risk associated with new treatments might not be known in the early stages of development. If only trials with minimal risk are permitted, new treatments for many emergency conditions with high death rates will never be developed. Treatments which are specific for patients with a particular condition need to be tested in the relevant population. If only minimal risk trials are allowed, this will undermine development of new treatments.

The Clinical Trials Directive 2001/20/EC presented a major threat to emergency care research and it required a statutory instrument (Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006), 5 years later to correct this and allow clinical trials in emergency care to be conducted.

We must be careful not to cause more problems with the new proposals.

February 2013

² The CRASH-2 collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *The Lancet* 2011;377:1096-101.

³ Roberts, I., Prieto-Merino, D., Shakur, H., Chalmers, I., Nicholl, J. Effect of consent rituals on mortality in emergency care research (2011) *The Lancet*, 377 (9771), pp. 1071-1072

Declaration of interest

1. I consult regularly for the pharmaceutical industry. I maintain a full declaration here http://www.senns.demon.co.uk/Declaration_Interest.htm. The views expressed here are my own and should not be ascribed to any organisations with whom I am associated.

Statement of experience

2. I am an experienced medical statistician who has worked for the National Health Service, the Swiss pharmaceutical industry and has held two chairs at British universities, including one in Pharmaceutical and Health Statistics at University College London (1995-2003).¹ Submission

Background

3. I have long maintained that data from clinical trials sponsored by the pharmaceutical industry should be available not only to regulatory agencies but also to patients and prescribers. For example, in an article entitled *Statistical Quality in Analysing Clinical Trials* published in 2000 I wrote,

‘The results that were needed to convince a regulator are precisely those that in an ideal society we would expect subscribers and reimbursers to want also. No sponsor who refuses to provide end-users with trial data deserves to sell drugs’[1] (p26).

4. Nevertheless I am dismayed that in inviting comment on this important issue the Science and Technology Committee (STC) has been prepared to become part of the publicity machine of *Bad Pharma*[2], a badly researched and highly biased, if well-written, book by Dr Ben Goldacre that is misleading in many respects, in particular in its discussion of drug regulation. For example a paper[3] that Goldacre cites as proving bias of FDA panellists in favour of applications in which they have an interest shows the opposite of what he claims[2] (p126). If the way in which STC understands scientific issues with important policy implications is through reading misleading and inaccurate polemics, this is a sad reflection on the place of science in British public life.
5. The book is quite wrong to imply that the regulators do not do a good job. They do a much better job than the medical press and it is necessary for the Select Committee to appreciate this in order for it to understand that the *medical press cannot be any part of an effective solution to the problem of missing data*. Despite Goldacre’s assertions to the contrary (see his claim on p34), the medical press *is* biased against negative studies. (See my recent papers[4, 5]) on the subject to understand how Goldacre has misunderstood the relevant literature.) The medical press is also very slow to retract incorrect and misleading articles, including those containing false data, as the recent scandal involving Duke University clearly illustrates. (See Baggerly and Coombes for a full exposé of this story[6].) Furthermore published articles rarely provide the data that enable a thorough check of their claims. Even reviewers are not provided these data, as I know having reviewed for such journals for many years. Thus any solution to the problem of missing clinical trials data should *not* involve the medical press.

¹ Details of my qualifications and experience are available at <http://www.senns.demon.co.uk/Consult.htm>

6. Furthermore, responsibility for publishing results is divided between authors and editors. Although it is a necessary condition for a trial to be published for authors to prepare a paper and submit it, it is not sufficient, since any given journal may refuse it. A system is necessary in which those who apply for permission to run a clinical trial are the publishers. In this way they can be made entirely responsible for the successful conclusion of their publishing obligation.
7. Thus, rather than relying on journals, I propose that a web-based system of publishing trial results should be used. In fact we should move towards a system where the results of clinical trials are always made available on the internet and this becomes the primary means of communication, with medical journals limited to publishing commentaries. Many of the leading medical journals have high rejection rates and also embargo presentation of results of a trial accepted for publication by them until the journal publishes them. The combination of these two features adds delay and uncertainty to the business of publishing.

Specific recommendations.

8. For regulatory trials as part of the drug regulatory process sponsors should be required to provide a *publishing plan* as to how the data will be made available on the internet to all interested parties. This should be part of the dossier submitted to the regulator. Many research councils make similar requirements that a dissemination plan be part of any grant application.
9. It should be part of the drug regulatory process to make sure that this plan is considered adequate. In other words in addition to the Quality, Safety, and Efficacy requirements there should be a Dissemination requirement.
10. Marketing approval for a drug should not be granted until the sponsor has demonstrated that the *publishing plan* has been fulfilled.
11. Mere publishing of an article in the medical press should not be considered an adequate alternative to fulfilment of a *publishing plan* by publication on the internet.
12. For non-regulatory trials. As part of any submission to an ethical committee for clinical trial approval any submitting party should be required to provide:
 - a. A *publishing plan* with an undertaking to make the results available on the internet.
 - b. A statement of all previous applications that have ever been made to any ethical committee with an explanation as if and how any previous obligations have been met.
13. On no account should the medical press be regarded as part of the solution to the problem of missing data. A system needs to be developed that is completely independent of medical journals.

February 2013

References

1. Senn, S.J., *Statistical quality in analysing clinical trials*. Good Clinical Practice Journal, 2000. **7**(6): p. 22-26.
2. Goldacre, B., *Bad Pharma: How Drug Companies Mislead Doctors and Harm Patients* 2012, London: Fourth Estate. 430.
3. Lurie, P., et al., *Financial conflict of interest disclosure and voting patterns at Food and Drug Administration Drug Advisory Committee meetings*. JAMA : the journal of the American Medical Association, 2006. **295**(16): p. 1921-8.
4. Senn, S.J., *Misunderstanding publication bias: editors are not blameless after all* F1000Research, 2012. **1**(59). <http://f1000research.com/articles/1-59/v1>
5. Senn, S.J., *Authors are also reviewers: problems in assigning cause for missing negative studies*. F1000Research, 2013. **2**(17). <http://f1000research.com/articles/2-17/v1>
6. Baggerly, K. and K. Coombes, *Deriving chemosensitivity from cell lines: Forensic bioinformatics and reproducible research in high-throughput biology*. The Annals of Applied Statistics, 2009. **3**(4): p. 1309-1344.

Written evidence submitted by Christopher Lawrence Roy-Toole (CT08)

About the Respondent

I am a Barrister with an interest in NHS information governance and the regulation of clinical research. I have a visiting scholarship to the Sheffield Law School, now nearing its end, and which has been used to examine the regulatory landscape for medical devices. I have also been involved with the research ethics committee system since 2007. Until I became fed up with the workings of the National Research Ethics Service, and took a leave of absence in January 2013 to regain my composure, I was a volunteer member of the NNT1 Research Ethics Committee in Newcastle upon Tyne ['NNT1 REC']. It is one of the research ethics committees overseen by the National Research Ethics Service. NNT1 REC handles a wide range of research applications, including those to commence clinical trials of investigational medicinal products at Phases II to IV.

The Select Committee wishes to receive evidence on the functioning of the new Health Research Authority in relation to clinical trials. I can give evidence about that based upon what I have seen as a REC member.

Here are some relevant facts;

- In January 2009, I argued that the research ethics committees in the United Kingdom were unfit for purpose and should be replaced with an independent regulatory authority for bio-medical research.
- In December 2009, I submitted proposals to the European Commission as part of its public consultation on the functioning of the Clinical Trials Directive. In this, I contended that the roles of the ethics committee and the national competent authority should be merged to create a composite single regulator for clinical drug trial research. This new regulator for clinical drug trials would be better able to disseminate regulatory information to where it was needed and could be 'tuned' to apply targeted enforcement action to where it was most required.
- I sent a copy of these proposals to the UK Department of Health in January 2010. I did not get a response.

- In July 2010, by a happy coincidence, the Secretary of State for Health announced that there would be a review of arms' length bodies in the health sector with a view to establishing a "single research regulator" for UK bio-medical research.
- A collaborator and I then devised further guidance and submitted those proposals to the Academy of Medical Sciences which was, by that time, inviting submissions as to what a single research regulator should look like.
- I sent a copy of those proposals to the Department of Health in October 2010. I did not get a response.
- So I am unsure about the collective mental process that prompted the Department to announce a 'single research regulator', to set it up as it has been set up, and to style it as the Health Research Authority. But I do know that it does not look anything like the model that I put forward.
- Apart from these, I have no competing interests to declare.

Preamble

I shall restrict my responses to only two of the questions posed by the Select Committee:

1. WHAT IS THE ROLE OF THE HEALTH RESEARCH AUTHORITY (HRA) IN RELATION TO CLINICAL TRIALS AND HOW EFFECTIVE HAS IT BEEN TO DATE?
2. HOW COULD THE OCCURRENCE AND RESULTS OF CLINICAL TRIALS BE MADE MORE OPEN TO SCRUTINY? WHO SHOULD BE RESPONSIBLE?

Because of the restriction imposed on the length of written submissions, I must adopt an abbreviated approach. The Clerk to the Committee has allowed me a modest extension in length.

This memorandum is therefore intended to direct the Select Committee to relevant matters for further investigation, rather than to provide a comprehensive statement of all matters of fact or law.

If further clarification is required on any matter of law, fact or procedure, then the Select Committee should not hesitate to contact me for further information.

I am willing to give oral evidence to the Select Committee if I am required to do so.

Executive Summary

The “Bonfire of the Quangos” is a grossly wasted opportunity for reform of NHS research regulation and governance. The HRA reflects this fact.

The HRA does not unify the regulatory landscape for research. It fragments it. The UK now has the same problem in NHS clinical research that the Francis Report identified in NHS hospital care: overlapping regulators and a lack of demarcation in function. Patients in research could be put at risk by the continued separation between the MHRA and the REC system.

The HRA has not yet delivered tangible benefits for clinical trials in the UK. Nor will it if the health research Quangos retain their current form.

The solution is to align the MHRA and the REC system closer together so that it can act as one, as if it were a real single regulator. REC members will have to be organised differently and work differently. New opportunities can be grasped if MHRA and REC work together. The cost effectiveness of drug research could be decided at an earlier stage if there were to be real joined-up regulation with NICE.

There are no statutory powers for any UK Quango to compel publication of results from clinical trials or other research. A possible solution is to follow the lead of the Americans and enact legislation to compel publication of clinical trial results. This requires the political will to punish defaulters and the resources to police them. The MHRA is probably the ‘best of the bunch’ to carry out this function.

Regulators and public bodies hold information that is useful to researchers who could use it to examine the safety of existing medicines. There is a case for a new “European Freedom of Information Regulation” to harmonise the rules for access to information held by the EMA and national competent authorities. The way to deal with confidential information is to provide a judicial decision in a speedy and accessible way. There should be a fast-track system established at the Office of the Information Commissioner to enable researchers to apply for information access. The Information Commissioner, not the HRA, should be at the centre of this. Skilled specialist staff and more resources are needed for that.

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Evidence

QUESTION 1: THE ROLE OF THE HRA IN CLINICAL TRIALS

1. The Government hailed the Health Research Authority ['HRA'] as “the single regulator” for health research. But the best way to sum up the HRA is to remember what Voltaire said about the Holy Roman Empire ['HRE'].
2. The HRA was established under statutory instrument and is subject to Directions from the Secretary of State. If the statutory aims of the HRA appear too general, vague, or even conflicting, it is because the Department of Health is still working out what to do with it.
3. It is hard to point to any part of the current functions of the HRA and describe them as ‘regulatory’. To be a regulator one must have powers of investigation, inspection and prosecution under legal powers. But most of what the HRA is expected to do is of an advisory nature. If the HRA encounters sub-standard research, it is expected to notify other agencies that do have the power to take enforcement action. Outside the REC system, the HRA has no investigative or enforcement powers at all. So one has to ask: *what is the HRA there for then and do we really need it?*
4. The HRA is not ‘single’ because remains it separate in function and organisation to the Medicines and Healthcare products Regulatory Agency ['MHRA'] and so does the REC. The twin roles of national competent authority and ethics committee were not merged as logic would demand from a “single regulator” for clinical drug trials under the EU Clinical Trials Directive. Compare the working of the Dutch METC and the Hungarian ETT TUKEB.
5. The HRA will also remain separate from the Human Fertilisation and Embryology Authority ['HFEA'] and the Human Tissue Authority ['HTAuth']. Or at least for now. It very much depends. This is because the Department is still ‘blowing in the wind’ as to what is to be done with these two Quangos. The Department will hold another review of regulation in their sector even though a consultation on their merger has recently been concluded.
6. The Government latched onto the idea of a single regulator to add weight to its claim that something would be done to meet the demands of Industry and Academics to cut ‘red tape’. But the Government failed to consult widely on what needed to be done. It relied too much on the Academy of Medical Sciences to produce the miracle solution. The Academy failed

to deliver it. So the Department sidelined the Academy in this. And rightly so. But the Department also shied clear of more radical and ‘disruptive’ proposals that might threaten civil service posts. The Department showed no clear strategy. So it simply put a new label on what it had already. The Department liked NRES because NRES unswervingly did what it was told to do. So NRES became the “HRA core”. Now the HRA is responsible for appointing and overseeing research ethics committees, a job that others used to do, but not much else.

7. To speak bluntly of the HRA: *“the Department has put lipstick on a pig”*.
8. The danger now is that the HRA will feel impelled to devise new functions for itself, not because they are needed, *but because its existence must be justified*. Thus, on 19th September 2011, I witnessed the HRA Chief Executive state that NRES must “bid” for new functions or others would bid against them.
9. *Consider the wisdom of having multiple and overlapping regulators in the NHS research sector in the light of the Francis Report’s conclusions on “NHS Mid Staffs”*.
10. The functional separation between competent authority and ethics committee creates a danger for patients involved in clinical drug trials. It prevents easy collaboration between a research ethic committee and the MHRA for information sharing or joint decision making. The REC needs access to the scientific expertise that the MHRA can provide. This is because experts acknowledge that scientific review cannot be separated from ethical review. The risks, burdens and benefits of research can only be assessed with access to topical advice on the safety profile of the drugs under test.
11. The Department of Health obfuscated the issue in its guidance to the REC. The REC has a maximum of 60 days to arrive at a decision and this longstop was set at the insistence of Industry lobbyists. In reality, a REC cannot be expected to make a detailed scientific review in the 10 days or so that they are given to read the papers. So the Departmental guidance does not require them to do so. But it is unreasonable to expect the REC to decline to review the science and to rely solely on “credible assurances” that someone else has examined the science for them. Yet the guidance encourages them to do just that. What is a ‘credible assurance’ and is it more ‘credible’ if it is made by a researcher who comes often before the same committee? So ethics committees very often require their own assessment of the

science, despite the state of the guidance. But there is a risk of fish slipping through a ragged net.

12. Patients can be killed just as easily by increased dosages of licensed drugs in Phase II and Phase III of clinical trials as they can by novel molecular entities in Phase I. Yet anecdotal evidence suggests that the research ethics committees that are provided with the scientific opinion of the MHRA at the time of their ethical review can presently be numbered in low single figure percentages. *So why are steps not being taken to promote easy access by the REC to MHRA scientific advice in all types of clinical drug trials by changing the way that these bodies are organised or else by merging them ?*
13. NRES, MHRA, and the Human Tissue Authority made commitments on paper to share information between each other. Research ethics committees can also have access to specialist scientific advice in high-risk studies as a result of reforms introduced after the so-called 'Northwick Park Disaster'. But I do not know of any study that shows how well all this works. And some say that Phase I trials are still the one area of research in which research ethics committees have the least rules to work by. *So, despite these changes, where is the evidence that the REC is better equipped now than it was in 2006 when the Brent Medical Ethics Committee approved the TGN1412 protocol?*
14. The Department of Health and NRES never published a full report of the facts of 'Northwick Park' dealing with the decision of the Brent MEC or the quality of the rules that the Brent MEC was required to follow, especially in the matter of insurance. The Duff Report called for something like that to be made available as a matter of urgency. I did the same in a Departmental journal in 2009. Professor Adam Hedgecoe made his own commentary on 'Northwick Park'. He cited institutional habituation and a lack of timely access to independent scientific opinion as causal factors in the sequence of events that lead to the study being approved by the ethics committee. *Where is that report?*
15. An end must be put to the questionable practice of allowing applicants to cherry-pick a "REC-u-Like". Some applicants avoid a 'hard' REC.
16. *The HRA has not yet delivered any additional and conclusive benefits to the regulatory process for clinical drug trials.* The HRA claimed that it would deliver a 'one-stop' platform for researchers making applications for research approval to both the MHRA and the ethics committee. This was to be done through the optimisation of its existing IRAS online portal. IRAS cannot deliver this joined-up working in its present state and the project

has been put on hold. So what will replace IRAS, if anything, and will it also have the ability to deliver joined up working between MHRA and HRA?

17. The decision to keep the HTAuth and HFEA separate from the HRA also compounds an existing problem about how to deliver joined-up regulation and oversight for clinical trials involving Advanced Therapy Medicinal Products. How will the HRA now deliver a 'one-stop' submissions platform for Advanced Therapy trials that require approval from HFEA or HTAuth?
18. The need for joined-up working between MHRA and ethic committee will become more acute after the introduction of the European Clinical Trials Regulation. This is because there will be a central portal for clinical trial authorisations at European level and national competent authorities and national ethics committees will be expected to make their own arrangements in order to work with it. The most efficient 'national team' will win business from the rest. At present, the United Kingdom is not 'match fit'.
19. So why is the HRA currently fixating on ways to ease the burden on the NHS R&D Departments that oversee the governance of research on individual NHS sites? The Select Committee might like to ask what the *NIHR HRA Feasibility Study and Pilot* hopes to accomplish and whether the money should be better spent on improving common working at the 'sharp end' of regulation, in the approvals system between the REC and the MHRA.
20. NHS R&D Departments need more radical solutions than a pilot study to save them from inefficient working. Moving research functions out of NHS Trusts and into state sponsored corporate enterprises with single-point management responsibility might be one way forward. But that idea is outside the scope of the current Inquiry.
21. The REC is made up of volunteers. This puts the entire edifice of HRA/NRES on an increasingly shaky foundation. Committee meetings have risen from one per month to three. There are frequent begging emails asking for volunteers to make up the numbers. Perversely, the volunteer must now expend added effort to fast-track the 'small stuff' in research that cannot be classified as a clinical drug trial. NRES calls it called "Proportionate Review". But it is unpopular with volunteers because it places a disproportionate burden on them. It would have been more sensible to fast-track the 'Big Stuff' instead. The workload should be spread across smaller ethics review teams. Lay volunteers should be spared the

mounds of scientific paperwork that they cannot decipher unaided and be allowed to focus on the patient's standpoint in research.

22. The solution now is to collapse the research ethics committees into regional centres to pool manpower resources. In these regional centres, the HRA and MHRA must work together in a synchronised manner to handle clinical trials of drugs and devices. But they must also share their information for a range of regulatory purposes, of which some are necessary now and others in the near future. Consider the cost savings that might result if MHRA and ethics committee could in future work together with NICE to deliver a "hybrid assessment" *from the outset*. This means that clinical drugs trials would be assessed not just for safety and efficacy, as they are now, but also for cost-saving effectiveness and the impact on patients' quality of life.
23. This requires RECs to be overhauled by: (1) making the transition to full time operation using a skilled cadre of *independent-minded* ethical reviewers under proper contracts for services and; (2) providing support functions that really matter to protect the patient, not the civil servants, or for that matter, the vested interest groups in research.

QUESTION 2: HOW TO MAKE CLINICAL TRIALS MORE TRANSPARENT AND WHO MUST DO IT?

'A statutory duty to publish results'

24. The Select Committee should consider the case for new law comparable to the US Food and Drugs Administration Amendments Act 2007 to mandate the publication of results by all researchers in UK clinical trials. It must enable substantial financial penalties to be levied on defaulters and perhaps other economic penalties besides.
25. Would an EU-wide Regulation for research publication be the best answer to allow for a solution across the entire Northern Hemisphere?
26. Evidence from the United States shows that statutory rules for the publication of clinical trial results are not enough. Voluntary codes of publication linked to 'soft' penalties such as funding restriction or editorial bars are too much in their infancy to form a view about their effectiveness. Using penal sanctions to encourage publication and punish non-compliance might work better.

27. What is the experience in the United States in the interplay between US FDAAA 2007 and the US Freedom of Information Act? Where are the 'pinch points' for them and for us? UK FOIA allows information to be withheld before publication. The Scots FOI law has a specific research exemption. So would a statutory duty to publish conflict with relevant exemptions under FOI laws? How to resolve it?
28. The REC cannot monitor publication of results from clinical trials because the publication duty usually arises after the research has been completed. The role of the REC ends with the conclusion of the research study. Therefore it is not an effective tool to police publication of research. The HRA Chief Executive was wrong to suggest otherwise in a recent letter to the BMJ.
29. The HRA may soon instruct the REC to take a bad publication history into account in deciding whether to give a favourable opinion to a new research application submitted by the same sponsor. The REC has no legal powers to compel publication of results. So this might expose the REC to complaints that it had acted *ultra vires* and so to judicial review.
30. The HRA wants to set up a system to monitor whether researchers who apply through IRAS are living up to any commitment to publish results. It has not said how. The MHRA controls the portal to the Clinical Practice Research Datalink. The NIHR controls its own database of portfolio studies. The HRA only controls a database with summaries of research projects that began with approval from a UK REC. The HRA has no special legal power to access other people's databases. *There is no joined-up governance of NHS research databases to show who is publishing what in UK research.*
31. So no Quango in the United Kingdom is best placed to monitor compliance with a legal duty to publish research. Without comprehensive monitoring of compliance under a real single regulator with powers of information access, enforcement in the UK will remain patchy at best.
32. Because the MHRA has inspection and enforcement capabilities, there is no option but to entrust it with the task of investigating and punishing breach of any special laws that require publication of research data from clinical trials of drugs and devices. The FDA now does it in the USA. But it comes down to resources.

Public Access and the Public Interest

33. This is the problem in access to research data: *there is a tension between the public right to access information that is held by the State and the right to expect that legitimate private interests will be protected whenever the State acts in a regulatory capacity.* The tension can only be resolved by deciding what is justified in the public interest. This can only be decided by someone with judicial powers.
34. *If decisions about the release of confidential information could be speeded up, then clinical trials might become more transparent.*
35. Protecting commercial interests and regulatory activities are the main grounds on which a regulator must treat information as confidential. But an EU Regulation and the UK Freedom of Information Act 2000 both allow confidentiality to be overridden if the public interest justifies disclosure of information about marketed drugs and clinical drug trials. The proposed Clinical Trials Regulation does not alter this. Contrast the position for medical devices, where outdated EU laws prevent disclosure.
36. The proposed European Clinical Trials Regulation will establish a central database of information received through an EU portal for applications for clinical trials authorisation and for the submission of safety data about tested drugs. The public will have access to this central database unless confidentiality claims can be “justified”. It is likely that the European Medicines Agency will manage the database.
37. But how will the proposed Clinical Trial Regulation affect :
 - The citizen who seeks information that is held by the EMA but which is not otherwise featured on the database?
 - The citizen who reads information from the central database that leads him to request other information that is held only by the national competent authority in his own member state?
 - The citizen of one member state who requires access to information held by a different competent authority in another member state?
 - Multiple applicants from multiple countries who want access to the same data originating from the same clinical trial or the same marketed drug and all at the same time?

- Who decides whether the citizen can have access to data: the EMA or national competent authority?
 - Who must the citizen appeal to when access is denied: the Ombudsman or the national tribunal that adjudicates on access to public information?
38. At present, a citizen must complain to the European Ombudsman to compel the European Medicines Agency to give access to its information. The Ombudsman's powers appear to be persuasive and advisory. The citizen would be better off if he had access to a regulatory body that could compel access to data held by the EMA and the national competent authorities. There would be certainty. The European citizen would benefit even more if he could appeal to a regulatory body in his own country that could grant access to information held on the EU database or by a competent authority in another member state. It would be faster and cheaper.
39. Look at what the European Union is now doing to overhaul national laws on the processing and free movement of Personal Data in the European Union. We can extract from that to develop a better approach to public access to information about medicinal drugs. So:
- a) We need a "European Freedom of Information Regulation" to harmonise national laws providing for public access to government information.
 - b) Every member state must have a supervisory body for Freedom of Information just as they must for Data Protection. These must have the power to compel disclosure, as the UK Information Commissioner does.
 - c) Each national supervisory board must be sufficiently similar to allow for joint operations and joined-up thinking.
 - d) There must be a 'consistency mechanism' to enable decisions on data access to be taken by one supervisory board and applied across borders of member states. In that way, clinical data could be accessed no matter where it is deposited across the EU regulatory apparatus. Fragmentation of the clinical data landscape is a major problem and this could help fix it.
 - e) Consistent rule making can be assisted by the formation of a European Freedom of Information Advisory Board, similar to that proposed for Data Protection.

40. The national competent authority should decide whether to allow access to information held within the EU database, not the EMA. To avoid ‘black holes’ in data access, the competent authority should be deemed to have total access to all data held by EMA on or off the database.
41. The national competent authority should be answerable to a Freedom of Information supervisory authority in every member state. This would allow the citizen to seek access to data through his own national institutions.
42. There would be no need for a European super-regulator and the Ombudsman might be permitted a lesser role in handling the disputed disclosure of clinical data from research.
43. In the United Kingdom, the Office of the Information Commissioner should be given funding for a specialist department acting under new enabling powers. Its purpose would be to make enforceable decisions on the disclosure of confidential information held by regulators and other public authorities, including Universities, concerning clinical trials and marketed drugs. The powers would engage in those cases where information access is required for the purposes of secondary research. The new powers would focus on commercially sensitive information and regulatory information.
44. The Information Commissioner’s special department would need the resources to assess the scientific merit of the application for data release. We must not encourage a ‘free for all’ amongst those academics who only wish to make a name for themselves by nit-picking over someone else’s data.
45. It would be a fast-track decision process to handle information access requests in those cases where fast-tracking is thought necessary. Fast-tracking should be reserved for those cases in which the requested data is to be used for secondary research. This can be justified on two grounds: (1) secondary research analysis of existing clinical data can yield public benefits and (2) researchers could be made to operate under special terms of professional confidentiality that could not be placed on a member of the public.
46. The Information Commissioner is the correct candidate for these new powers, not the HRA. The HRA has no powers to order information release under FOI laws.
47. Section 251 National Health Service Act 2006 provides a template for the sort of powers that the Information Commissioner’s team would need. Section 251 allows the release of

identifiable and confidential patient information without consent. Data security measures can be required as a condition of access.

48. One must therefore question the wisdom of transferring the section 251 advisory group out of the National Information Governance Board and into the HRA. It should have been aligned with the Information Commissioner to give independent and specialist assessment of information handling in the NHS.
49. The MHRA and the other regulatory agencies will have to engage in joined-up working with the Information Commissioner under new powers if they are serious about giving effect to data transparency in clinical research. They must also share information to allow agreed standards to be drawn up. But some of the Information Commissioner's staff will need to be re-educated as to what is expected of them. One policy worker indicated to me that ICO would not submit evidence to this Inquiry because it was all to do with drug companies and so had nothing to do with them. Worrying, is it not?

February 2013

Written evidence submitted by Dr Elizabeth Wager (CT10)

Statement of competing interests

I am a freelance writer, editor, trainer and publications consultant. I work with pharmaceutical companies, publishers, academic institutions and individual researchers. In 2012 about 40% of my income came from pharmaceutical companies. I am a former employee of the pharmaceutical industry (I was UK Medical Writer for Janssen Cilag 2002-9 and UK Head, International Medical Publications, Glaxo Wellcome / GlaxoSmithKline 2009-11) and will be eligible for some pension from each of these companies. I am a member of the European Medical Writers Association (EMWA) and the International Society for Medical Publications Professionals. I have received travel expenses and run workshops for both these organizations. I am the author of various guidelines related to this topic, including Good Publication Practice for Pharmaceutical Companies and the EMWA guidelines on the role of medical writers in developing peer-reviewed publications.

Scope of submission

I wish to comment on two questions:

(Q3) What evidence is there that pharmaceutical companies withhold clinical trial data and what impact does this have on public health?

(Q4) How could the occurrence and results of clinical trials be made more open to scrutiny? Who should be responsible?

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

3.1 There is considerable evidence that pharmaceutical companies withhold clinical trial data. This may take the form of failing to publish all results from studies (ie selectively publishing only some of the findings) or failing to publish entire trials.

3.2 Recent evidence of the possible effects of incomplete reporting comes from Egan et al (*Can J Hosp Pharm* 2012;**65**:387-93). They examined different meta-analyses (which combine data from several trials) about drugs commonly used to treat high blood pressure. Some of these meta-analyses suggested the drugs were associated with an increase in the incidence of cancer, while others did not. Egan et al concluded that the reason the studies reached different conclusions was outcome reporting bias (i.e. selective reporting of study findings). An earlier study of anti-depressants comparing information submitted to regulatory authorities with results published in journals also provided clear evidence of publication bias by drug manufacturers (Melander et al *BMJ* 2003;**326**:1171-3). The effect of this bias (in which positive studies were published more than once and studies with negative findings were not published) was to make the drugs appear more effective than they really were.

3.3 More evidence of reporting bias comes from a study published in the *BMJ* last year (2012;**344**:d7202). Hart et al took 42 meta-analyses of 9 drugs approved by the FDA (the US regulator) in 2001-2. They re-analysed the published meta-analyses (which had included only published studies) and included unpublished data obtained from the FDA (ie supplied by the manufacturers to the US regulator but never published). Including the unpublished data caused the drug to appear less effective in 46% of cases and more effective in 46%.

3.4 From my personal experience of working within the pharmaceutical industry (2002-2011) I was aware of under-reporting. This had a variety of causes, the most common being:

- transfer of resources from drugs that were no longer being developed
- lack of interest of clinical investigators (who did not perceive findings to be particularly interesting or did not have time to write up the results of their research)
- journal space constraints (especially before the availability of electronic supplementary files)

- rejection by journals (especially before the creation of less selective journals, such as *PLoS One*, and journals specifically focused on negative findings)
- omission of unfavourable or inexplicable outcomes.

In my experience, these reasons were much more common than deliberate policies to suppress findings or studies, although I am aware that there is evidence that companies have engaged in such behaviour.

3.5 While this enquiry may focus on problems with pharmaceutical companies, it is important to note that non-publication and selective reporting are also well documented among academic research. For example, Chan et al examined studies funded by the Canadian Institutes of Health Research and found that 59% of outcomes related to treatment adverse effects were incompletely reported (Chan et al *Canadian Medical Association Journal* 2004;171:735-40).

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

4.1 The most obvious way to ensure that the occurrence of trials is transparent is to require that all trials must be registered on a public register such as the ISRCTN or ClinicalTrials.gov. Registration of study design details before the study begins can also help to reduce, or at least identify, the selective reporting of outcomes, or changes in study design occurring between initiation and publication. Since 2005, many of the major general medical journals (including *The Lancet* and *BMJ*) have refused to publish trials unless they have been registered. This policy led to a sharp increase in trial registrations. US legislation (specifically the FDA Amendments Act of 2007/8) strengthened this trend by making registration compulsory for many trials of new medicines. Most pharmaceutical companies therefore comply with this legislation and the journal editors' requirements and register all Phase II to IV studies of new drugs.

4.2 The FDAAA also required the posting of summary tables of study findings on ClinicalTrials.gov within 12 months of the end of most studies of new drugs. Although studies have revealed shortcomings in these postings, and the occurrence of late or incomplete disclosure, this legislation has greatly increased the availability of summary trial findings.

4.3 However, while the summary results tables on ClinicalTrials.gov are useful, they are not easy to understand without some knowledge of trial design. Therefore clinicians and patients continue to rely on other sources of information that present results in context and provide more explanation and interpretation. The conventional method of communicating study results to doctors is via articles in peer-reviewed medical journals and this continues to be regarded as the best method of publication although it is by no means perfect (see Wager *PLoS Clinical Trials* 2006;1(6):e31).

4.4 Given the reliance of doctors on journal articles and the benefits that this type of publication carries (such as permanence, the possibility for corrections or retractions, some measure of quality control via peer review, the opportunity for post-publication commentary and discussion) companies should be encouraged to submit reports for publication. One mechanism would be to require companies (and associations such as the ABPI) to endorse Good Publication Practice guidelines (see Graf et al *BMJ* 2009;339:b4330) which call on companies to endeavour to publish all results of clinical trials on marketed products.

4.5 Preparing articles for medical journals requires time and expertise. In my experience of working for pharmaceutical companies, external investigators are not always equipped or prepared to do such work, especially for studies they consider routine or relatively uninteresting. Most journal editors therefore recognise that professional writers can have a legitimate role in helping to develop such publications, so long as their involvement and financing are fully disclosed. Professional writers should only be regarded as 'ghost writers' if their contribution or link to the funder is not properly acknowledged. There are several guidelines on the role of medical writers in peer-reviewed publications, such as those from the European Medical Writers Association (Jacobs & Wager, *Current*

Medical Research & Opinion 2005;**21**:317-21). The case for greater involvement of professional writers has recently been put forward by Woolley et al (*Current Medical Research & Opinion* 2012;**28**:1857-60). They conclude that ‘professional medical writers .. could help ensure results are reported in a complete, timely, and ethical manner’.

4.6 While journal articles will continue to be widely used by doctors and patients, alternative methods for disseminating research results should be investigated. Structured summaries or tabular formats (such as those on ClinicalTrials.gov) should be developed. Regulatory authorities (such as the EMA) require companies to produce detailed clinical trial reports but these remain confidential after submission to the authorities. Greater transparency could be achieved if regulators opened up their archives to the public or if companies posted clinical trial reports (or their summaries) on their corporate websites.

4.7 One barrier currently preventing companies from making trial reports available is that medical journals will only consider findings that have not been published elsewhere. Therefore if a company wishes to publish an article in a medical journal it will be deterred from posting a study report or extended summary on a website. The journal editors do allow the very short summary postings required by FDAAA, but should be encouraged to relax their requirements about prior publication to encourage the wider dissemination of full clinical trial reports or extended summaries (see Wager & Abbasi, *Journal of the Royal Society of Medicine* 2009;**101**:1-2). Regulators (such as the EMA) should also become more transparent and disclose the information submitted to them that forms the basis of product licensing. The EMA has recently indicated that it is considering greater transparency and this is to be welcomed, but it is not yet clear either when this will happen or how.

February 2013

Written evidence submitted by Sir Iain Chalmers (CT11)

“HOW COULD THE OCCURRENCE AND RESULTS OF CLINICAL TRIALS BE MADE MORE OPEN TO SCRUTINY?”

1 HOW COULD THE OCCURRENCE OF CLINICAL TRIALS BE MADE MORE OPEN TO SCRUTINY?

1.1 Government regulation should be introduced requiring all clinical trials, together with their protocols, to be registered publicly at inception (Chalmers 2004a).

1.2 Patient-friendly information should be available for all trials open to recruitment, as it is already for all cancer trials (Godlee and Chalmers 2010).

2 HOW COULD THE RESULTS OF CLINICAL TRIALS BE MADE MORE OPEN TO SCRUTINY?

2.1 People being invited to participate in controlled trials should require written assurance that the full study results will be published, and that these will be sent to all participants who indicate that they wish to receive them (Evans et al. 2011; www.testingtreatments.org).

2.2 Regulation is needed to ensure that all clinical trials are published (Chalmers 2004a; www.alltrials.net), and that information identifying sponsors, institutions and individuals who have failed to publish registered trials is also published, with either acceptable explanations or resultant sanctions.

2.3 All clinical trials should be published, regardless of the type of intervention(s) evaluated, and whether they are commercially sponsored or non-commercially sponsored (Chalmers et al. 2012). A focus on regulation of the pharmaceutical industry cannot be expected to have any impact on non-publication of trials of interventions other than medicines.

2.4 The academic journal system cannot be relied upon to deal with the problem of under-reporting of research (Smith 2006). Trial registration provides the most appropriate alternative framework for publishing the results of clinical trials.

3 Personal background: three decades of failure to promote real change

3.1 I am a clinically qualified health services researcher, currently responsible for coordinating the work of the James Lind Initiative (JLI). The JLI has been funded by the National Institute for Health Research to promote acknowledgement of uncertainties about the effects of treatments and research to address them.

3.2 Biased under-reporting of research results in avoidable suffering and deaths of patients and waste of resources in health care and health research (Chalmers and Glasziou 2009). I have been concerned about the scientific and ethical consequences of biased under-reporting of research since the early 1980s (Grant and Chalmers 1981). In a letter published in the BMJ in 1985 I proposed that the term ‘negative trial’ should be outlawed, because “All trials that have been well conceived and well conducted – whatever their results – represent positive contributions to knowledge” (Chalmers 1985).

3.3 Since the early 1990s, I have emphasised that “failure to provide adequate, publically available reports of the results of clinical trials does an injustice to the patients who have participated in them, as well as to others who have collaborated with the investigators and those who have provided funds or other resources” (Chalmers 1990). From the mid-1990s onwards I have challenged research ethics committees to use their regulatory influence to reduce this problem (Savulescu et al. 1996; Pearn and

Chalmers 1996; Chalmers 1997; Roberts et al. 1998; Chalmers 2002; Antes and Chalmers 2003; Smith and Chalmers 2007; Garattini and Chalmers 2009). I have also challenged professional organisations – the Academy of Medical Sciences and the Royal College of Physicians of London in particular - to follow the lead of the Faculty of Pharmaceutical Medicine in deeming it unethical to acquiesce in under-reporting of research. There is little evidence that the issue has been taken seriously by research ethics committees or professional organisations.

3.4 The inquiry by the House of Commons Health Committee into the Influence of the Pharmaceutical Industry in 2004 provided an opportunity to draw the problem to the attention of parliamentarians and I submitted written evidence and gave oral evidence to the Committee (Chalmers 2005). I have subsequently raised the problem of biased under-reporting of research with parliamentarians through an article in *Science in Parliament* (Chalmers 2007) and evidence submitted to the Health Committee's inquiry into 'Aspects of the work of the National Institute of Health and Clinical Excellence' (Evans et al. 2007), and through the Science and Technology Committee's inquiry into 'Peer review in scientific publications' (Chalmers 2011).

3.5 My attempts over 30 years to persuade researchers, research funders, professional organisations, research ethics committees, parliamentarians and governments to take this issue seriously have not been successful, however. A few years ago I wrote an article entitled 'From optimism to disillusion about commitment to transparency in the medico-industrial complex' (Chalmers 2006a). In it, I drew attention to efforts made by some individuals and organisations during the 1990s to address the problem of biased under-reporting, but I also referred to the emergence of increasing evidence that fundamental problems remained and that the situation might actually be getting worse. I ended the article by expressing my hope that I might be able to write another essay in five years entitled 'From disillusion to optimism in about the scientific integrity of the pharmaceutical industry and the people collaborating with it'.

3.6 My approach since then has been to try to increase public awareness of how the public is being 'sold short' just as long as half the studies to which they have contributed are not being reported (Chalmers 2004a; 2006b). In 2006, colleagues and I published a book for the public to increase general knowledge about why it is important to test treatments rigorously, and how to recognise inadequate evidence, including incomplete evidence (Evans et al. 2006). The book was translated into six other languages, a second edition was published in 2011 (Evans et al. 2011), and it is now the foundation of a website called Testing Treatments *interactive* which makes available video and audio material and other resources helping to illustrate the concepts covered in the book (www.testingtreatments.org). Both editions of the book (and the website) have a suggested Action Plan for its readers. Among other things, this suggests that they should:

Encourage and work with health professionals, researchers, research funders, and others who are trying to promote research addressing inadequately answered questions about the effects of treatment which you regard as important.

Agree to participate in a clinical trial only on condition (i) that the study protocol has been registered and made publicly available (ii) that the protocol refers to systematic reviews of existing evidence showing that the trial is justified; and (iii) that you receive a written assurance that the full study results will be published, and sent to all participants who indicate that they wish to receive them.

3.7 I am hopeful that making the public more aware of the scandal of under-reporting of research will help to bring about the changes needed, despite the very powerful forces that will continue to defend the *status quo*.

3.8 Jeremy Paxman summed up the current situation in a word. On Wednesday 27 July 2011 there was a discussion on Newsnight about the Bateson review of research using non-human primates. Susan Watts' introductory package noted that the review made clear that "those using primates should

publish any negative results, to prevent work being repeated unnecessarily.” Paxman’s interviewees were Paul Matthews, a member of the Bateson Review Group, and Tipo Aziz, Professor of Neurosurgery at Oxford University.

Matthews: “There is one other point that is important to bear in mind. Negative results are not results of no value.”

Paxman: But they’re results of no value if noone knows about them.

Matthews: ... This is what the committee felt very strongly needed to be part of the change that we help to drive forward from now on.

Paxman: So what you’re saying is, that if you don’t get the result you’re looking for, or a result you consider to be of any use, you should nonetheless publish it so that others know.

Matthews: Absolutely. If you ask a good question, a positive result is of value and a negative result is of value.

Paxman: Why doesn’t that happen already?

Aziz: For several reasons. If one achieves a negative result very few journals will publish it.

Paxman: Surely, on the web anyone can publish anything.

Aziz: Yes, but perhaps not in the most respected journals, one that would bring impact or cite your work. The other thing is, publishing negative work also detracts from your chances of getting further research funding.

Paxman: What? If you admit that it didn’t work out you might not get paid to do it again?

Aziz: Not the same experiment again, but to do further research along those lines.

Paxman: That’s nuts isn’t it?

3.9 I hope that the Science and Technology Committee will agree with Jeremy Paxman that the current situation is indeed ‘nuts’ - unethical, unscientific and uneconomic nuts.

3.10 My efforts to prompt improvement in clinical trial transparency over most of the past 30 years have manifestly failed. However, it is becoming clear that Sense about Science’s recently launched public campaign (www.alltrials.net) and Ben Goldacre’s bestselling book *Bad Pharma* may be ‘game changers’. For the first time in over 30 years I feel that there is reason to hope for substantive progress. I think that those who continue not to take under-reporting of research seriously will find themselves on the wrong side of history. I hope that the Committee will see to it that, after decades of inadequate action, something substantial will be done to deal with the current, indefensible situation.

February 2013

References

Antes G, Chalmers I (2003). Under-reporting of clinical trials is unethical. *Lancet* 2003;361:978-979.

Chalmers I (1985). Proposal to outlaw the term 'negative trial'. *BMJ* 290:1002.

Chalmers I (1990). Under-reporting research is scientific misconduct. *JAMA* 1990;263:1405-1408.

Chalmers I (1997). Fraud and misconduct in medical research. *Journal of the Royal College of Physicians of London* 1997;31:216-217 (book review).

Chalmers I (2002). All unbiased comparative studies should be published. *BMJ* 324:483.

Chalmers I (2004a). Government regulation is needed to prevent biased under-reporting of clinical trials. *BMJ* 329:462.

Chalmers I (2004b). In the dark. Drug companies should be forced to publish all the results of clinical trials. How else can we know the truth about their products. *New Scientist* 2004, 6 March:19.

Chalmers I (2005). Written and oral evidence. In: House of Commons Health Committee. The Influence of the Pharmaceutical Industry. Fourth Report of the Session 2004-2005, Vol. II. London: Stationery Office, Ev 194-208.

Chalmers I (2006a). From optimism to disillusion about commitment to transparency in the medico-industrial complex. *Journal of the Royal Society of Medicine* 2006;99:337-341.

Chalmers I (2006b). Biomedical research: are we getting value for money? *Significance* 2006;3:172-75.

Chalmers I (2007). When does clinical science cease to exist? *Science in Parliament* 2007;64: 19-20.

Chalmers I (2011). Written evidence to Science and Technology Committee (PR47) – Eighth Report. Peer review in scientific publications. Ordered by the House of Commons to be printed 18 July 2011.

Chalmers I, Glasziou P (2009). Avoidable waste in the production and reporting of research evidence. *Lancet* 374:86-89.

Chalmers I, Glasziou P, Godlee (2012). All trials must be registered and the results published: academics and non-commercial funders are just as guilty as industry. *BMJ* 346:f105.

Evans I, Thornton H, Chalmers I (2006). *Testing Treatments*. London: British Library.

Evans I, Thornton H, Chalmers I (2007). Submission to the House of Commons Health Committee inquiry into aspects of the work of the National Institute of Health and Clinical Excellence (NICE).

Evans I, Thornton H, Chalmers I, Glasziou P (2011). *Testing Treatments*. London: Pinter and Martin. Downloadable for free at www.testingtreatments.org.

Garattini S, Chalmers I (2009). Patients and the public deserve big changes in evaluation of drugs. *BMJ* 338:804-806.

Godlee F, Chalmers I (2010). Information about ongoing clinical trials for patients. *BMJ* 2010;340:456-57.

Grant A, Chalmers I (1981). Register of controlled trials in perinatal medicine. *Lancet* 1981;1:100.

Pearn J, Chalmers I (1996). Is selective reporting of well-designed clinical research unethical as well as unscientific? *Nederlands Tijdschrift voor Geneeskunde* 140:220-221.

Roberts I, Li Wan Po A, Chalmers I (1998). Intellectual property, drug licensing, freedom of information, and public health. *Lancet* 1998;352:726-729.

Savulescu J, Chalmers I, Blunt J (1996). Are research ethics committees behaving unethically? Some suggestions for improving performance and accountability. *BMJ* 1996;313:1390-1393.

Smith R (2006). *The trouble with medical journals*. London: RSM Press.

Smith R, Chalmers I (2007). Ethics and medical publishing. In: Ashcroft R, Dawson A, Draper H, McMillan J, eds. *Principles of Health Care Ethics*. Chichester: John Wiley, 2007: 751-758.

Written evidence submitted by Sir Alasdair Breckenridge (CT12)

I write this submission in my personal capacity and as a former chairman of the Medicines and Healthcare products Regulatory Agency (MHRA).

In order to better understand my responses to the questions posed, I provide a short background to the present Clinical Trials Directive (CTD) and the proposed Clinical Trials Regulations (CTR)

BACKGROUND.

1. Clinical trials in the UK are currently regulated under the European Clinical Trials Directive (CTD) (2001). The aims of the CTD are to afford greater protection to subjects in clinical trials, to ensure the quality of clinical trials and to harmonise regulation and conduct of trials throughout Europe.

The CTD, being a Directive, had to be transposed into UK law and this was carried out in 2004, one of the earliest transpositions of this Directive in European member states.

2. Under the CTD,

- ethics committees were established on a legal basis,
- each clinical trial had to have a sponsor,
- for the first time phase I studies in healthy volunteers had to be authorised by a National Competent Authority (NCA)
- NCAs were given the authority to carry out inspections for Good Clinical Practice (GCP), Good Manufacturing Practice (GMP) and Pharmacovigilance

3. But adoption of the CTD had a series of unintended consequences

- The number of clinical trial applications fell by 25% between 2007 and 2011. In UK, the number of commercial trials fell by 22% over the same period.
- The costs of the resulting bureaucracy and resource requirements to handle paperwork doubled
- Delays in starting trials increased by 90%

4. Specific problems with the implementation of the CTD include:

- Inconsistent interpretation of the Directive among member states made the conduct of multinational clinical trials difficult (of some 25,000 clinical trials being conducted in Europe, some 25% are multinational).
- The type of studies regulated by the CTD were subject to different judgements among member states. For example, in UK, a study on a feeding formula for newborn babies was judged to be a trial to be regulated under the auspices of the CTD, whereas in Netherlands the same protocol was judged to be outside the remit of the CTD.
- The concept the “one regulatory size fits all” implying that low risk studies with well understood drugs had to be regulated with the same rigour as trials of new molecular entities where their risks are unknown, was challenged.
- Academics who were not accustomed to working under strict GCP, found the new arrangements burdensome and frequently unnecessary.
- Some definitions used in the CTD and arrangements for reporting of adverse reactions were open to several interpretations.

5. In July 2012 the European Commission produced proposals to revise the CTD.

The most important of these are:

- The European authorisation of clinical trials will be carried out as Regulations (CTR), not a Directive. As a result, different interpretations of the rules by member states should diminish and multicentre multinational clinical trials should be facilitated.
- Submissions will be by a single dossier submitted via a single EU portal.
- National Competent authorities will still be responsible for local and ethical considerations of clinical trials which will be carried out within fixed time frames.
- A risk based approach to the authorisation of clinical trials would be adopted.
- New indemnity and new safety proposals have been suggested in order to reduce the burden on non commercial sponsors of clinical trials (although details of these proposals are currently sketchy and previous experience suggest that these may be unnecessarily unwieldy).
- The European Commission reserves the right to monitor the conduct of these regulations and to carry out inspections.

6. The Select Committee now wishes to gather evidence on five matters.

1) DO THE EUROPEAN COMMISSION'S PROPOSED REVISIONS TO THE CTD ADDRESS THE MAIN BARRIERS TO CONDUCTING CLINICAL TRIALS IN EUROPE AND THE CTD?

Response

The Commission's proposals are generally to be welcomed and, as shown above, should address many of the concerns which have been highlighted.

In particular, the authorisation of clinical trials under a Regulation rather than a Directive should facilitate the conduct of multicentre, multicountry trials, as will the adoption of a single submission via a EU portal. As with many of these new proposals, however, more details are needed on how they will be implemented. It is not clear whether all member states will have access to IT systems which will permit the single portal to operate as planned.

The adoption of a risk based approach to the authorisation of trials, which the UK has advocated strongly, represents an important step forward. But it is important that clear definition is made as to the terminology used e.g. "low intervention" and "non intervention" trials, phraseology not currently widely used in regulation.

Further, the proposal that studies involving licensed medicines with good safety records for already agreed indications should be classified as "low intervention" requires careful scrutiny. If the dose, route of administration of the product or type of patient studied differs from those in the licence, appropriate proportionality considerations should be applied.

2) WHAT IS THE ROLE OF THE HEALTH RESEARCH AUTHORITY (HRA) IN RELATION TO CLINICAL TRIALS AND HOW EFFECTIVE HAS IT BEEN TO DATE?

Response.

The HRA was created in 2011 to protect and promote the interests of patients and public in health research, and is now being established in primary legislation. The HRA will coordinate the regulation of health and social care research in the UK

With respect to clinical trials the HRA will work closely with MHRA and the National Institute for Health Research (NIHR) to create a unified approval process for clinical trials. A harmonious relationship between the three bodies is critical for the promotion of clinical trials in the UK. .

One of the most important role of the HRA is to coordinate the National Research Ethics Service (NRES) whose functions were previously provided by the National Patient Safety Agency and Strategic Health Authorities, both of which have been disestablished. Another important function of the HRA will be to complete service improvements such as a UK-wide e-submission through IRAS (Integrated Research Application Service).

The documentation so far provided by HRA is generally perceived as being helpful to sponsors of clinical trials.

It is too early to give an opinion on how the relationship between the various parties involved in authorisation of clinical trials will develop and this must be kept under close scrutiny.

3) WHAT EVIDENCE IS THERE THAT PHARMACEUTICAL COMPANIES WITHHOLD CLINICAL TRIAL DATA AND WHAT IMPACT DOES THIS HAVE ON PUBLIC HEALTH?

There are two aspects of this problem

- Data relevant to the registration of clinical trials
- Data relevant to the results of clinical trials

With respect to registration of clinical trials, in Europe all clinical trials reviewed by the EU since May 2004 have been entered on the data base EudraCT. Until recently, this database was accessible only to sponsors of the particular trial and to regulators, but not to the public. In March 2011, however, it was agreed that a EU Clinical Trials register should be created containing the aims of a trial, its design, name of its sponsor, and status of the trial and all these should be made available to the public.

In contrast, in the US matters moved more rapidly. Under the Food and Drugs Administration Modernisation Act (1997) the National Institutes of Health were charged with creating a public information resource (clinical trials.gov) which would contain information on all clinical trials approved as Investigational New Drugs (INDs), and would show the purpose of the trial, eligibility of subjects to participate and location of the trial. The Food and Drugs Administration Amendment Act (2007) reiterated these points and also legislated for reporting of basic results of clinical trials.

Details of public availability of the results of clinical trials present a more complex picture. A balance has to be reached between data which are commercially confidential and those whose disclosure is in the public interest. While a new medicine is undergoing review by regulatory

authorities, it is reasonable that these clinical data should be confidential to the sponsor and the regulator. Once regulatory approval has been obtained, all clinical trial data, whether beneficial to the approval or not should be accessible and in the public domain. Many of the major sponsors of new medicines have agreed to this and have made supporting statements. Facts however belie this position and there are several recent widely publicised instances of the refusal of drug companies to release relevant information on the regulatory trials by which marketing authorisation of specific products has been obtained. Further, the means by which such data is made public by companies can leave much to be desired. An abstract in a minor medical journal is not a suitable vehicle for important clinical trial information of public health interest.

In 2012, the European Medicines Agency has agreed that such clinical trial data should be publically available, but has also said that further work is necessary on the timing of this change.

The impact of the availability of clinical trial data is the assurance of the transparency of regulatory decisions. As long as important relevant clinical data remains the preserve of sponsors of new medicines and those who regulate them, concern will continue as to the veracity of regulatory decisions. Public health deserves better.

Regulators already do publish public assessment reports which give the basis of their decisions, including some clinical data supporting the licensing decisions, but more openness is needed.

4) HOW COULD THE OCCURRENCE AND RESULTS OF CLINICAL TRIALS BE MADE MORE OPEN TO SCRUTINY? WHO SHOULD BE RESPONSIBLE?

Response

From the response to question 3, it would appear logical that the responsibility for releasing clinical trial data on medicines which have been authorised for marketing should lie with regulatory authorities. The legal basis for enforcing this is not currently clear. In this way, there could be assurance that all clinical trial data was made available, including details of those trials which were not supportive of approval, i.e. negative trials. This would take considerable resource and time and the question arises if this should become part of the regulatory function.

The alternative approach would be to have a legal requirement that marketing authorisation holders must disclose all the clinical trial data that they have submitted to NCAs at submission and this should be published on grant of the licence. This would also require further legislation.

5) CAN LESSONS ABOUT TRANSPARENCY AND DISCLOSURE OF CLINICAL DATA BE LEARNED FROM OTHER COUNTRIES?

Response

The pharmaceutical industry operates as a global enterprise, and applications for marketing authorisation of important new medicines are usually made simultaneously to several regulatory authorities who maintain regular scientific contact and frequently have memoranda of understanding which permit sharing of information. In particular, decisions on major regulatory issues such as those concerning drug safety are closely coordinated by the respective agencies. Where differing decisions which are reached based on the same data these may be due to differences in legal frameworks (e.g. as in the case of rosiglitazone in US and Europe)

The scientific basis of regulations are coordinated via the International Conference on Harmonisation of technical products (ICH), which ensures that similar standards apply in the main international arenas. While in broad terms ICH standards have been an effective means of maintaining and improving medicines regulation, increasing criticism has been made of ICH, especially with respect to Good Clinical Practice(GCP) guidelines which in many instances appear obstructive and rigid. The procedures involved in the CTR should be seen as helpful to all stakeholders.

February 2013

Written evidence submitted by Privacy and Clinical Trial Data (CT13)

1. For trials which have correctly followed protocols, there should be no general privacy-based reason for non-publication of de-identified trial outputs. Where participation in a trial is based in line with protocol (full disclosure of information about the trial, post-trial process, and properly informed consent is obtained from volunteers), the privacy impact of currently required publication should already have been appropriately minimised.
2. Were any organisation conducting a trial to claim privacy as justification for secrecy or failure to publish, this could imply a serious breach of trial protocol. In any such case, a detailed investigation should be made to discover which if any protocols have been broken or improperly applied, and why - and in what other ways the trial might be invalid.
3. For good reason, UK law tightly regulates medical trials. The ability for pharmaceutical companies to use a jurisdiction of choice should not allow them to evade UK regulations on trial publication based upon trial use elsewhere.

February 2013

Written evidence submitted by the Trial Steering Committee (CT14)

1. Thank you for the opportunity to submit written evidence to the Select Committee on Clinical Trials. This submission responds to the question: *“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?”*

2. We answer this question with a focus on low risk trials of treatments already in widespread use, conducted at the point-of-care (i.e. trial participation does not impose substantial risks to patients). We are investigators of two ongoing low risk pilot trials in primary care, one comparing different types of statins and the other comparing antibiotic treatment for exacerbations of a chronic lung disease to usual care without antibiotics [1]. Both are commonly used, but it is not known which is better. The ideal is that these trials mimic real-life, except that the patient is randomised between the interventions, while usually the treatment is allocated by doctor/patient preference without good evidence. These trials do not need special monitoring visits or procedures in these trials, as we want patients or doctors to behave as they would normally do. This approach allows us to measure e.g. whether patients still take their tablets long-term without any prompting by research staff. We would want many clinicians and many patients to participate, so that these studies can represent the full spectrum of clinicians and patients and that they can be completed in months. They can then quickly inform the NHS (and the trial participants!) about which one of the routinely used interventions is better. In our studies, we use the anonymised electronic health records to measure the outcomes (such as death or heart attack), so the impact of the trial on busy clinicians can be minimal. The NHS has the capability to run these trials as part of routine clinical care creating a learning healthcare system, continuously improving the interventions. The UK has the potential to lead on this approach to evaluating treatments, due to the quality of electronic health records in primary care. However, current regulations are designed for trials of novel and potentially risky treatments, and discourage this important class of trials of existing treatments.

3. The 2012 proposed revision of the Directive includes the definition of ‘low-intervention clinical trial’ for *“authorised medicinal products, used in accordance with the terms of the marketing authorisation or their use is a standard treatment and the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects...”*. This definition is reasonable and would cover the trials we are involved in. However, the key question is whether this 2012 proposed revision of the Directive has indeed accepted the need for proportionality and risk stratification in research governance or whether it merely concerns a superficial plaster without really adopting risk proportionality in the regulations. The 2012 proposed

revision of the Directive mentions the words ‘low-intervention’ in the following sections (excluding the definition and descriptions of the regulatory process for classifying this):

- (i) *... they should be subject to less stringent rules, such as shorter deadlines for approval (comment 9 page 17).*
- (ii) *.. the extent and nature of the monitoring shall be determined ..including ...whether the clinical trial is a low-intervention clinical trial (article 45)*
- (iii) *Investigational medicinal products shall be traceable, stored, destroyed and returned as appropriate taking into account ...whether the clinical trial is a low-intervention clinical trial (article 48)*
- (iv) *The content of the clinical trial master file shall allow verification of the conduct of a clinical trial, taking account of all characteristics of the clinical trial, including whether the clinical trial is a low-intervention clinical trial (article 54)*
- (v) *For clinical trials other than low-intervention clinical trials, the sponsor shall ensure that compensation in accordance with the applicable laws on liability (article 72).*

4. This indicates that the 2012 proposed revision of the Directive has not adopted risk proportionality in any material sense. Firstly, the text relating to ‘low-intervention’ trials is vague and open to a range of interpretations. Secondly, the regulatory and bureaucratic implications of classifying a trial as ‘low-intervention’ appear to be optional. The 2012 proposed revision of the Directive therefore does not require for a clear and factually different approach to the regulatory framework of low and high risk trials.

5. Our experience with conducting two point-of-care trials in the UK indicates that the current regulatory system makes it impossible to keep low-risk trials simple. Local NHS organisations, following the legislation, require completion of extensive paperwork before a low-risk trial can start. The clinicians are required to undergo training in Good Clinical Practice, sign various forms and contracts, even for trials for medicines they have already prescribed to hundreds of patients (such as statins and antibiotics). Nurses need to provide their curricula vitae before being allowed to take a blood sample in a trial, even when they have been doing this for years in usual practice. It is not surprising that less than 10% of the 500 practices we contacted were interested in our trials and prepared to complete the paperwork. Only a minority of general practices in the UK participate in the Primary Care Research Network (set up to facilitate research), despite their best efforts.

6. The NHS needs trial evidence to guide interventions but its practitioners are unwilling to generate it. In our view, the 2012 proposed revision of the Directive does not attempt to address this fundamental challenge – the lack of clinician and patient involvement in evaluative research. There is

ample effort in the 2012 proposed revision of the Directive to control ‘bad’ clinicians but no effort to encourage the development ‘good’ clinicians whose practice is informed by research.

7. The 2012 proposed revision of the Directive states, like the current legislation, that “*the sponsor and the investigator ...shall take due account of the quality standards set by the detailed international guidelines on good clinical practice of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)*”. This 59-page guideline states that it should be followed when generating clinical trial data intended for submission to regulatory authorities. The 2012 proposed revision of the Directive does not address what guidelines are needed for trials that will not be submitted to regulatory authorities (e.g. our low risk trials). The MHRA guidance on risk-adapted approaches to the management of clinical trials mentions that “*...the European Commission proposed to publish ‘specific modalities’ guidance for non-commercial trials to indicate where certain aspects of GCP could be ‘relaxed’ for these trials specifically. This guidance, although consulted on, has never been published*” [2]. The 2012 proposed revision of the Directive still does not include any reference to the need for risk proportionality of ICH guidelines and to the relaxation of rules for low-risk trials. It has not addressed the serious criticism that ICH is inapplicable to most non-commercial research [3].

8. The ICH guideline fails to mention the concept of risk proportionality and has not adopted it. As an example, ICH states that “*in general there is a need for on-site monitoring...; in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators training and meetings, and extensive written guidance can assure appropriate conduct of the trial*”. But a site visit to a clinic that uses wholly electronic healthcare records will obtain information additional contained centrally in a research database (which obtains copies of the anonymised records). So, there is no reason to consider that central site monitoring should be exceptional in computerised healthcare systems (unlike paper-based healthcare systems). As noted by McMahon and others, the cost-effectiveness of the type of procedures required by ICH is untested [3]. Like the current Directive, the 2012 proposed revision of the Directive does not provide a rationale or evidence for the cost-effectiveness of the approaches it mandates. We challenge the assumption that a low-risk trial, with randomisation the only difference from routine clinical practice, should be subjected to a 59-page guideline designed for clinical trials of novel agents (ICH).

9. The ‘one size fits all’ approach of the current and proposed Clinical Trial directive is exemplified by the reporting requirements for serious unexpected suspected adverse drug reactions (SUSARs). While the requirements of SUSAR reporting within 15 days is most appropriate for novel interventions with unknown risks, the value of urgent reporting of SUSARs for low-risk trials of

widely used medicines is unclear, especially considering the costs of implementing urgent SUSAR reporting and considering that regulatory authorities will often already have received reports of a similar nature (about possible adverse effects not included in the drug label). In our trials, we proposed to have monthly analyses of major adverse outcomes, including comparisons with all patients not recruited into the trials, and an analysis of side-effects as recorded by the clinicians (based on the data recorded in the electronic healthcare records). This was considered to breach the Directive. We do not argue at all with the need to diligently monitor safety in trials but do not believe that the current and proposed approach in the Directive provides the most cost-effective method of achieving this. Safety reporting and other trial activities should be tailored to the risks a trial poses to trial participants.

10. The pre-amble of the 2012 proposed revision of the Directive acknowledges the negative effects of the current legislation, including the reduced number of trials conducted in Europe. But the issue is not only about a drop in the number of trials. More importantly, the question is whether the current trial system is providing the answers the healthcare system needs. A recent analysis by John Ioannidis found that only one of the 24 “blockbuster” medicines (with annual sales exceeding \$1 billion) had been studied in a trial with more than 10,000 participants. This is an important deficiency because large trials are needed to evaluate effects on major clinical outcomes. Few of the trials with blockbuster medicines included death as outcome, so we currently do not know whether these widely used medicines prevent death or may increase it due to side-effects. Five of the blockbuster medicines are used long-term to treat patients with mental-health problems yet the use by millions of patients is based on trials of short-term duration (3-4 months) enrolling only a few hundred patients [4]. Simple low-risk point-of-care trials could address these uncertainties at low cost: patients would be randomised after consent and the electronic health records would be used to record death unobtrusively. A standard trial with 20,000 patients can cost over 300 million pounds [4], while a simple low-risk point-of-care trial would cost only 5 million pounds. As outlined in a recent article about the continuously rising costs for trials, “reducing the costs of trials is absolutely crucial for the public good” [5]. The 2012 proposed revision of the Directive does not provide any evidence that trial costs will be reduced.

11. The 2012 proposed revision of the Directive states that the scope of the proposed legislation is *‘very wide in that it only excludes clinical studies that do not involve an intervention’*. We believe that this very wide scope is the core problem with the legislation, trying to cover in a single piece of legislation very diverse trials with very different levels of risk to study participants. We recommend the following:

- A. the scope of ICH guidelines should be restricted to its original scope of pre-authorisation studies (high risk studies)
- B. the Clinical Trial Directive should be revised so that it unambiguously covers risk proportionality by providing separate legislation for the different levels of risk
- C. the focus of the legislation for low risk trials should be around the appropriateness of the informed consent procedures, the need for the clinician to follow acceptable medical practice (in line with Good Medical Practice guidelines) and the quality of data in the trial
- D. the local NHS commissioning boards should be made accountable for the level of research in their area
- E. research activities should be made part of and recognised in the Continuous Professional Development of clinicians (in line with Good Medical Practice guidelines that state that clinicians have a duty to address uncertainty)

12. We must not continue on the current path of ever increasing complexity and costs of trials and decreasing competitiveness of the UK. Risk proportionality is essential in the research governance of trials and this should be made explicit in the legislation. The substantive barriers to low-risk, cost-effective trials, as we have experienced, have not been addressed by the 2012 proposed revision of the Directive.

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#This letter represents the personal views of the signatories

February 2013

Competing interests

The signatories of this letter are involved as researchers or members of the Trial Steering Committee of two pilot point-of-care trials. They do not have any personal financial conflicts of interests.

References

1. van Staa TP, Goldacre B, Gulliford M, Cassell J, Pirmohamed M, Taweel A, Delaney B, Smeeth L. Randomised Evaluations of Accepted Choices in Treatment (REACT) trials: large-scale pragmatic trials within databases of routinely collected electronic healthcare records. *BMJ* 2012;344:e55.
2. Risk-adapted approaches to the monitoring of clinical trials of investigational medicinal products. MHRA. <http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf>
3. McMahon AD, Conway DI, Macdonald TM, McInnes GT. The unintended consequences of clinical trials regulations. *PLoS Med* 2009;3(11):e1000131. doi: 10.1371/journal.pmed.1000131.
4. Ioannidis JPA. Mega-trials for blockbusters. *JAMA* 2013;309(3):239-40.
5. Roger Collier. Rapidly rising clinical trial costs worry researchers. *CMAJ* 2009; 180(3): 277–278.

Written evidence submitted by Professor Lesley Stewart (CT15)

SUMMARY

Although consideration of individual participant data (IPD) relates to *access to trial data* rather than *access to trial results*, we anticipate that others will interpret “results” as extending to IPD. Although requiring access to trial IPD would afford greatest opportunity for scrutiny and contribution to further research, this is more complex than access to summaries of trial results. We believe it important to separate issues around disclosure of trial results and aggregate data from disclosure of IPD.

Prospective registration of all clinical trials carried out in, or which recruit human participants from, the UK should be compulsory and there should be a requirement that the (suitably defined) results of these trials be placed in the public domain, with open public access to this information. However, open access to trial IPD would pose risks to patient confidentiality and has potential to unintentionally damage clinical trial recruitment and conduct. De-identification of IPD to permit public access would retain some risk of disclosure and would render the data less useful for research purposes.

Whilst developing mechanisms to increase access to clinical trial results and aggregate data should begin immediately, increasing access to trial IPD should be preceded by considered debate, and by investigation into the potential impact on clinical trials.

ABOUT US

As co-convenors of the Cochrane Collaboration Individual Participant Data Meta-analysis Methods Group, each of us has considerable experience over many years of obtaining clinical trial results and trial datasets (comprising data from each trial participant from published and unpublished trials) for inclusion IPD systematic reviews and meta-analyses. We also have been involved in running and sharing data from clinical trials and in setting up and running a clinical trials register.

DECLARATION OF INTERESTS

Professor Lesley Stewart is Director of the NIHR Centre for Reviews and Dissemination (CRD) at the University of York. She is responsible for delivering programmes of work that include systematic reviews of both aggregate and individual participant data. She is co-convenor of the Cochrane Collaboration IPD Meta-analysis Methods Group. She recently instigated development of PROSPERO an international prospective register of systematic review protocols and has previously overseen the development and management of a web-based national register of cancer clinical trials. She has been involved previously in the design of publicly funded clinical trials. She is currently a member of the advisory board of Current Controlled Trials which registers clinical trials and issues international standard randomised clinical trials numbers. She is Co-Editor in Chief of a journal that publishes systematic review protocols.

Dr Jayne Tierney is Meta-analysis Lead of the MRC Clinical Trials Unit (CTU) and Deputy Director of the MRC CTU Hub for Trials Methodology Research, London. She is responsible for the conduct of a programme of systematic reviews and meta-analyses of aggregate and particularly individual participant data. This involves collaborating with trial organisations worldwide to obtain IPD from their trials, and acting as custodian for these collated data. She also works closely with CTU clinical trials on systematic reviews to inform trial design, conduct and reporting, and was previously

involved in the development of a web-based national register of cancer clinical trials. She is a co-convenor of the Cochrane Collaboration IPD Meta-analysis Methods Group.

Professor Mike Clarke is Director of the MRC-funded All Ireland Hub for Trials Methodology Research at Queen's University Belfast, Northern Ireland, which is establishing a programme of research into ways to improve the quality and relevance of clinical trials and to ensure that their findings are available to patients, practitioners, policy makers and the public when making decisions and choices about health and social care. He is involved in the conduct of several randomised trials and systematic reviews. Some of these systematic reviews include the use of IPD. He is a co-convenor of the Cochrane Collaboration IPD Meta-analysis Methods Group.

Professor Maroeska Rovers is professor of evidence-based surgery at Radboud University Medical Center Nijmegen, The Netherlands. She received a promising VENI grant to study the challenges of IPD meta-analyses in which she showed that IPD meta-analyses provide valuable opportunities to study subgroups. Dr Rovers has been involved in many IPD meta-analysis. The results of her IPDMA into the effectiveness of antibiotics in subgroups of children with acute otitis media, which was published in *The Lancet* (2006), have been incorporated in various international guidelines. She has performed several randomized controlled trials. She is a co-convenor of the Cochrane Collaboration IPD Meta-analysis Methods Group and co-editor of the Cochrane ENT-group.

FACTUAL INFORMATION

1.0 The Cochrane Collaboration is separately submitting a response (to which we have contributed) which describes evidence of withheld data leading to harm to public health, and describes some lessons that can be learned from experience outside the UK. The bulk of that submission relates to the availability of summary results from trials, but part of it sets out the Collaboration's position regarding access to IPD. Here, although we touch on other aspects, we focus on providing some additional views on access to trial IPD, which is a more complex and difficult issue than access to summaries of trial results. We do not aim to be comprehensive in this.

2.0 Systematic review is a research technique that uses transparent methods to identify, critique and, where possible and appropriate, synthesise the results of all relevant studies that have addressed a pre-specified and clearly defined research question. Systematic reviews provide the best means of informing health decision making, but rely on the integrity of the underlying research evidence in reaching fair and unbiased assessments. If unfavourable trial results are withheld from systematic reviews, this evidence base will be biased, undermining the decisions that depend on them. It is therefore vital that the results of all clinical trials are made available.

3.0 Systematic reviews using IPD involve central collection, validation and re-analysis of data from individual participants rather than using aggregate data for each trial. They are widely regarded as a 'gold standard' approach and strengthen the quality of systematic reviews in a variety of important ways.

4.0 IPD are the data gathered for each trial participant, which are subsequently analysed to generate trial results. In our view, consideration of IPD relates to *access to trial data* rather than *access to trial results*, and so strictly speaking is outside the scope of this consultation. However, we anticipate that other respondents will interpret "results" as extending to IPD, particularly as the current consultation by the European Medicines Agency on access to trial data includes IPD.

Question 4:

Disclosure of the existence of clinical trials

5.0 The occurrence of all clinical trials should be made open to scrutiny by making prospective registration of all trials compulsory. This could be brought about by legislative requirement that any clinical trial carried out in, or which recruits human participants from, the UK is registered prospectively in a designated trials register. This should include requirement for the full trial protocol to be made available either through the register or by linking to relevant publications (increasing numbers of healthcare journals publish trial protocols). A single national register of clinical trials (linking to the WHO international clinical trials platform) could be achieved by re-developing an existing registry or by establishing a new one.

Disclosure of trial results

6.0 Any requirements to improve access to clinical trial results should relate to making available the results of all the planned analyses set out in the trial protocol, statistical analysis plan or other prospective plan.

7.0 Going forward, it will be important to define what is meant by *results*, to avoid ambiguity or misunderstanding. Trial results could be interpreted as meaning the summary statistics describing the results of statistical analyses investigating the effects of interventions. Alternatively, results could be interpreted as a descriptive summary of the characteristics of trial participants, aggregate data summarising how often particular events, such as recurrence of cancer, or measures, such as blood pressure, are observed in each of the trial treatment groups, as well as full details of all of the statistical analyses.

8.0 Ensuring access to full statistical results of all analyses planned in the trial protocol or other plan would pose no risk to patient confidentiality, but should provide full details of the potential harms and benefits of treatments as assessed in the trial. There would be no need to moderate or control access. However, this information would permit only limited scrutiny of results by third parties and would not be sufficient to allow independent re-analysis of a trial.

9.0 Extending *results* to include aggregate data would also pose little risk to patient confidentiality, but would afford greater opportunity for scrutiny. For example, allowing some third party re-analysis and cross checking of results against the data provided. However, depending on the detail of the data presented, the level of scrutiny would likely still be somewhat limited, as would be the opportunity to contribute to detailed additional research using the trial data. Given the low risk, there would be no need to moderate or control access.

10.0 Full disclosure of *clinical trial results* could be achieved by making it a requirement that any clinical trial carried out in, or which recruits human participants from, the UK must place the (suitably defined) results of all analyses described in the trial protocol or other plan in the public domain.

10.1 This could be implemented using existing mechanisms to formally publish in scientific or medical journals, or to make trial reports publicly available e.g. on company or institutional websites. Formal publishing would be preferable to website publishing because of the more permanent nature of journals and advantage of peer review of submitted reports, but may impose restrictions on the level of detail that can be included and full accessibility to all parties.

10.2 Alternatively, a registry or repository for aggregate trial results could be developed, as has been done in the USA with clinicaltrials.gov, which is described in the main response from The Cochrane Collaboration. This centralised, standardised approach might be preferable to the more haphazard approach of availability through numerous, diverse channels, but would come with associated financial and operational costs, for both those managing such a registry, and also those involved in the conduct of trials. If such a repository were to be developed it should be linked closely with trial registration, and this could be achieved through a single national registry responsible for both functions.

11.0 A reasonable time frame is required between trial completion and provision of trials results, and this may need to vary from trial to trial, depending on the nature of the disease or condition, and the outcomes being collected. Those conducting clinical trials should have a reasonable (but not unlimited) period of exclusive use of their data. Clarity is needed on what constitutes trial completion, as many trial data and results accrue long after the recruitment of participants has stopped. Ideally, a time frame would be described in the trial protocol.

12.0 Operationally, it would be important that publications and postings are linked to the trial registration record so that one can be found from the other. Trials should therefore use a unique registration/identifying number. This will also help identify multiple publications of the same trial (which can lead to a different type of bias if favourable trials are covertly reported many times).

13.0 With suitable redaction of any patient identifiers, clinical study reports produced by manufacturers for regulatory trials could be published using existing publishing mechanisms or deposited with a registry/repository. This could offer a quick solution to increasing access to trial results, but would apply only to the subset of trials that are developed or submitted for market authorisation.

Access to individual participant data

14.0 Access to trial IPD would afford the greatest opportunity for scrutiny and the greatest opportunity to contribute to further research, as data can be re-analysed in ways that link patient characteristics and outcomes, which are not otherwise possible. Many trial funders already have data sharing policies and many trials organisations already share trial IPD for research purposes at the request of other organisations.

15.0 An open-access model would pose risks to patient confidentiality. If adopted, data would need to be de-identified before being made public. That is, all variables that might either on their own or in combination with other variables, lead to potential identification of an individual trial participant would need to be removed. The level of de-identification that would be required to allow public access could render the data much less amenable to scrutiny and further research, and might make it impossible to replicate the original analyses. Therefore, we suggest that a risk-dependent approach to the de-identification of IPD would be required, depending on who would be able to access it and for what purpose.

15.1 The risk of a researcher identifying an individual trial participant would be much lower than someone who knows a trial participant and/or whose intention is to use open access as a means of obtaining personal information. For example, knowing that an individual has entered a clinical trial, the hospital at which they were treated, their age, and sex could be sufficient information to gain knowledge to sensitive information such as someone's depression score, history of self-harming or other aspects of their health or lifestyle. If information about hospital, age, and sex were to be

removed from the trial dataset, then it would mean that analyses (using the open access IPD) could not take account of these potentially very important factors and would be weakened as a result.

15.2 These concerns would be accentuated for trials in rare conditions where it might be much easier to identify individual participants because of their rarity of their condition.

15.3 Some trials and some outcomes are potentially more sensitive than others, for example, those dealing with sexual behaviour in the context of sexually transmitted infections.

16.0 Open public access to clinical trial IPD would also have the potential to unintentionally damage trials. We do not know how potential participants would react to the prospect of personal details being made available to anyone for any purpose and whether this would impact on their willingness to consent to join a trial. Investigation and research on this would be required prior to implementation of any requirement for public access to IPD.

17.0 Depositing and subsequent use by others of IPD may not be as straightforward as it might seem. Our experience of obtaining IPD directly from those responsible for trials has highlighted the difficulty of understanding datasets at face value. A detailed dialogue with the trial investigators is often required to reach a full understanding of the trial and its data. This understanding is necessary to avoid inappropriate or naive analyses.

18.0 We agree with the main Cochrane Collaboration submission that ultimately access to and scrutiny of IPD for research purposes, and with suitable safeguards in place to protect patient confidentiality and to protect trials, is desirable. However, we do not support open public access to clinical trial IPD. We believe that while open public access to trial results and aggregate data is in the public interest, open public access to IPD is not. The potential harms outweigh the benefits.

19.0 Before mandating access to IPD, there should be serious and considered debate. Increasing access to IPD is more complex than access to aggregate data. Consideration should include: ethical issues including protecting patient confidentiality; the potential impact on clinical trials (including on patient recruitment); resource and funding issues; and practical issues around data formats and curation. Consideration should also be given to how these issues might be handled in an international context.

20.0 Should, after due deliberation, mandatory access to IPD for research purposes be pursued, then various models might be considered. In a reactive approach, trial data would need to be supplied in response to appropriate and legitimate requests. This would align with many funders current policies on clinical data sharing, and is likely to be a less resource-intensive approach. However, it may be difficult to monitor. An alternative would be the development of a national repository of IPD (with access restricted to those undertaking legitimate research in the interest of public health). This would require mechanisms to ensure appropriate use, such as: registration of research protocols relating to use of data; compulsory deposition of final reports/publications from data analyses and transparency around potential conflicts of interest. Although, such a repository would be more resource intensive to manage and populate with trial data, it would permit monitoring of data provision and of subsequent access and use.

RECOMMENDATIONS

21.0 The government to introduce legislation to ensure that any clinical trial carried out in, or which recruits human participants from, the UK is registered prospectively in a designated trials register.

22.0 The government to introduce legislation to ensure that any clinical trial carried out in, or which recruits human participants from, the UK must place the (suitably defined) results of all analyses described in the trial protocol in the public domain.

23.0 Government agencies to consider developing a single linked national register of clinical trials and repository of trial results for any clinical trial carried out in, or which recruits human participants from, the UK.

24.0 Such a registry to ensure that full trial protocols are made publicly available, free of charge and in an accessible format within a specified period.

25.0 Public funding agencies to recognise the resource implications of 23.0 and 24.0 for those conducting trials and providing results, and to ensure that these costs are met within awards of research grants and programmes.

26.0 Developing mechanisms to increase access to clinical trial results and aggregate data should begin immediately.

27.0 Developing mechanisms to increase access to IPD should not, be pursued immediately but be preceded by informed discussion and by detailed investigation into the potential impact on clinical trials.

28.0 Open public access to trial IPD should not be pursued.

29.0 Any future mandatory access to clinical trial IPD should be restricted to legitimate research purposes for the good of public health, should include mechanisms to prevent misuse and be transparent about conflict of interest.

February 2013

**Written evidence submitted by The Regius Professor of Medicine, Professor Sir
John Bell, FRS, FMedSci (CT16)**

1. I am writing to provide evidence to the Science and Technology Committee's enquiry into clinical trials and data transparency. I think this is a very timely enquiry and I hope it will raise the level of discussion about the UK's position with regard to clinical trials, the advances made by the Health Research Authority, the remaining challenges with European regulation of clinical trials and also the need for consideration of increased data transparency. While President of the Academy of Medical Sciences, I was closely involved in advancing the case for reduced clinical trial regulation and am familiar with clinical trials in both an academic and commercial context. I thought the Committee might find my thoughts on his subject helpful in its deliberations.
2. In my view, the **European Clinical Trials Regulation** currently being discussed provides a significant advance over the previous Clinical Trials Directive. The MHRA has made a substantial effort to ensure that the views of the UK were heard during the process of re-drafting the directive. I believe many of us still have some concerns about the extent to which a risk-based and proportionate approach to regulation is likely to be described in the regulations. For example, it would be important that existing drugs with a good safety profile which are being used for new indications with relatively little safety risk are not considered to require the same regulatory environment as new medicines. It is not clear yet that these sorts of issues have been entirely resolved by the new clinical trials regulations and this needs to be carefully monitored. In general terms, however, these regulations are moving in the right direction although, if we expect this activity to be pursued with vigour in this country, we need to retain a major focus on attempting to reduce the amount of regulation and bureaucracy associated with undertaking clinical trials.
3. The **Health Research Authority** has now begun to deliver what was requested in the Academy of Medical Sciences Report published two years ago. As President of the Academy at the time, I was very anxious to ensure that the level of bureaucracy was reduced for those undertaking clinical trials and also that efforts were made to simplify and speed up the process. The Health Research Authority was one recommendation that successful emerged from the Department of Health and I believe its leadership has begun to deal effectively with many of the obstacles that prevent NHS ethical approval from being granted in a timely and efficient fashion. Ideally, this would result from a single sign off, but this is not legally possible, given the independence and responsibilities of independent Foundation Trust boards. However, the HRA and the NIHR seem to be able to improve the speed by which trials are approved by monitoring approval rates against national standards and reporting them back to hospital chief executives. It also appears that single sign off is occurring amongst clusters of hospital trusts that choose to work together and this may end up solving the single sign off problem without the HRA being directly involved.
4. I am encouraged that the committee has chosen this time to consider **clinical trial data transparency**. This is a complex issue and I have outlined my thoughts on this issue below:
 - 4.1 **The definition of transparency.** One of the key issues in this discussion is the degree of transparency of clinical trial data that is being considered. Some advocates suggest that the optimal level of data release is patient line data released online and available to the general public at the conclusion of each clinical study. Others have taken a more moderate view suggesting that summary data from both positive and negative trials be made available to genuine investigators on request. Other models are also being suggested, including access to trial data through an independent scientific committee structure.
 - 4.1.1 The extreme position of making all patient line data available to all comers has not been properly thought through. Such an approach would be associated with many issues including consent, data protection and privacy issues and the need for trialists and participants to

understand fully the nature of anonymisation and its limits. If introduced it could have a negative effect on patient recruitment as patients are likely to be uncomfortable with having their details circulated on the internet. Many of the trials of interest for this sort of data release will be part of a set of global studies and a unilateral position of extreme data release in the UK would be certain to drive most of the important and interesting trials to other jurisdictions. Given that the Academy and others, including the National Institute for Health Research, have made a major effort to ensure the UK attracted more clinical studies, such a move would be very disappointing and probably unhelpful to both patients and physicians. If applied forcefully for early stage trials an extreme form of transparency requirement would essentially eliminate the biotechnology sector in the UK, also with serious effects on our ability to discover drugs (half come from this sector) and for the Life Sciences sector of the economy.

- 4.1.2. Other degrees of transparency might prove more helpful. Availability of summary data from all trials associated with drug registration would be sensible and, in my view, all such studies should be published even if they are negative. Various other layers of detail could be considered (including the release of clinical study reports) but it is not clear what this achieves and the more onerous the requirements, the greater the burden on trialists. It might also be possible for an independent committee of trialists to review data that was contentious. This is an approach which has been used in the past and might be established on a more formal basis going forward.
- 4.2 A second major issue relates to the **risk of creating new regulatory barriers for clinical research**. The field of clinical trials is already the most regulated of any in medical science. Often, in the past, regulations have been introduced with good intent but, in the end, they have greatly impeded the field with layers of unnecessary regulations that are not risk-based and lead to a box-ticking mentality. The ICH-GCP guidelines are a good example of this and the Academy's report on clinical trial regulation lays out why all this extra regulation is unhelpful. We have spent an enormous amount of time trying to unpick the unhelpful parts of the EU Clinical Trials Directive and the burden imposed by unnecessary regulation in the UK has driven our share of global clinical trials to <3%. We must be careful not to add further layers of regulation unless we are crystal clear what the problem is that we are trying to fix. I believe that clarity around what we are trying to achieve with increased clinical trials transparency does not exist.
- 4.3 **Do we think the system for drug regulation is broken?** It is worth noting that, for the specific case of drug registration trials, all the clinical data is available for drug regulators. Most new drugs have the data examined by four or more major independent regulators, as well as health technology assessment regulators such as NICE. Patient line data is routinely examined by the FDA. All studies are submitted to the regulators and considered by these independent and rigorous agencies. Failure to submit data or the submission of erroneous data is illegal and subject to drug withdrawal or large fines. Decisions are often finely judged and not all regulators reach the same conclusion about all medicines based on the same data. It is clear that the FDA does not welcome the release of large amounts of patient line data as this would inevitably lead to often spurious challenges of the decisions made by regulators. Setting aside the validity of such disputes (see below) it is not clear who benefits from continual controversy over regulators' decisions. The committee will need to decide whether the structure for regulatory approval of drugs based on evaluation of full sets of clinical data is working or not. I see little evidence that it is failing.
- 4.4 It is important to consider both the **benefits and the harm that might arise from a change in the current arrangements** for making trial data available to a wider audience. The analysis of large data sets is not straightforward and there is always the concern that untrained or inexperienced investigators introduce bias in the results. It is also evident that, given the publicity associated with apparently overturning widely held beliefs about health care practises, atypical

analysis - either unintentional or intentional - can attract public attention and a certain amount of fame or notoriety. Large trial analysis can be done using multiple tools and, by parsing the data in a variety of ways, many different conclusions can be drawn. The public and the press are ill-equipped to deal with such assertions and it can take many years before the effects of such analyses are corrected. Of course, it would be helpful if the medical journals were able to weed out these results, but we are well aware these are not always effective gatekeepers for sensationalist stories.

- 4.5 One example of an approach that commonly produces results that are at odds with current practise is a variation on the use of meta-analysis. This approach does not focus on merging data but, instead, eliminates the majority of studies so that the power to detect effects is lost. A good example of this was the meta-analysis of studies of breast cancer screening for women. These were all in the public domain but the example illustrates the consequences of applying meta-analysis in a selective manner. In 2000, a paper which eliminated 8 out of 10 of these studies was published and not surprisingly had insufficient power to detect a benefit. This was widely reported in the lay press and was followed by a book by a now famous scientist laying out the grounds for a conspiracy. This has undermined confidence in a programme of screening adopted by almost all Western public health agencies and may well have cost lives. It has taken 12 years and multiple official reviews, most recently by Sir Mike Richards in the NHS, to rebut these arguments. In this case, I would argue that this sort of reanalysis contributed little to patient well-being. Similar reanalysis techniques were used to stir up the recent debate about Tamiflu, large numbers of trials were excluded from the analysis and unsurprisingly the power to detect effects also disappeared. Do we really want to release a wave of data in an unconstrained way that will fuel such analyses? Much depends on whether the **benefits** of transparency will outweigh the disadvantages. In how many cases have regulators failed to analyse the data packages presented for registration inappropriately, or failed to act on good new data relating to safety or efficacy? My sense is that regulators are relatively effective in their role and have acted when necessary in the interests of patients. There may be occasions where questions arise about trials that make further independent review helpful. In this case, it is likely that sophisticated reviewers are best equipped to consider the issues and hence the suggestion of independent expert groups being available would be appropriate. This would avoid the adverse consequences emerging from controversial analyses appearing in the public domain which, in the end, are inevitably balanced by similar independent committees but only after public confidence is undermined.
- 4.6 A new regulatory regime relating to transparency would also impact **academic investigators**. While widespread data release would be very beneficial for the meta-analysis brigade and those journals which thrive on secondary data, it would not always be welcomed by investigators with large datasets. These scientists can also occasionally be subject to mischievous attempts to undermine the main conclusions of their studies by parties who have been disadvantaged by these results. They also find themselves already trying to operate in an over regulated environment and more regulation, even if targeted at others, will be very unwelcome.
- 4.7 We should all be attempting to create an environment where competent reanalysis of data that is used for clinical decisions should be made easy to achieve, particularly by independent investigators with demonstrated experience with statistical approaches to large data sets. Transparency is, therefore, a very valuable objective. Care must be taken, however, to make this proportionate, to avoid undue regulatory burdens and to be conscious of the outcomes that might ultimately be unhelpful to patients. Consequently, some control should be exerted over who should have access to data. I personally do not see how sensible new legislation could be formulated without again creating obstacles that will severely impede the field and slow progress towards new therapies. A code of practice agreed by all parties might be the right way to proceed.

**Written evidence submitted by the Centre for Evidence-Based Medicine, University of Oxford
(CT17)**

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?

1. Clinical trials affect health through the formation of new knowledge, and whilst a thriving research sector is fundamental to the delivery of clinical outcomes it also supports economic growth. Research budgets form a substantial portion of the budgets of developed countries: somewhere between 1.5% and 3% of GDP. Moreover, in the modern world health care is big business, on average 10% of GDP is spent on health goods and services in developed countries, and health care is currently the largest and fastest-growing industry in the world.
2. Given the importance of health care research and clinical trials, it is therefore not surprising that self-interests in research combined with increased global competition can undermine scientific integrity. As a consequence regulatory systems, which aim to underpin research, are under considerable strain. For instance, the US Food and Drug Administration and the European Medicine Agency require drug testing and demonstration of safety, yet it is largely up to the country hosting trials to ensure procedures are sound and ethical.
3. Clinical trials and drug studies are big business, valued at \$30 billion across 105 countries, and in less developed countries the number of trials is growing rapidly. Yet, in direct contrast, the number of drug trials in the UK has fallen substantially, from 728 in 2008 to 470 in 2010.
4. This suggests a potentially worrying global trend whereby expediency in the conduct of trials, for example by minimising regulation in different countries around the world assumes a greater value than mechanisms to ensure that trials are conducted with integrity and quality.
5. The proposal for a regulation of the European Parliament and of the council on clinical trials on medicinal products for human use and, and repealing Directive 2001/20/EC highlights the problems that have occurred. The substantial increases in administrative burdens required in the EU at the outset of a clinical trial, lead to an increased delay for launching a clinical trial by 90%, which now takes on average 152 days.
6. This length of delay is untenable and directly contributing to relocation of many trials outside the EU and the UK, to no doubt less burdensome environments. In addition, the near 100% increase in administrative costs have not demonstrated parallel increases in safety and highlight all that is wrong with the current system. Too burdensome, too slow and beset with unnecessary administration without clear upsides.
7. The current proposals, laid out in the EU clinical trials directive do little to reduce this administrative burden. Indeed they will probably add an overly complex layer to suit just one type of trial, the multicentre pan-European studies that form only a fraction of the trials undertaken. Given there is no provision with the directive to cut the time to recruitment there is little to recommend within its current framework.
8. For industry, time is money and adding at least 150 days to the start of a trial means there is a loss of the equivalent time in direct sales. Therefore it is not surprising that there is a haemorrhaging of trials to less burdensome environments.

WHAT IS THE ROLE OF THE HEALTH RESEARCH AUTHORITY (HRA) IN RELATION TO CLINICAL TRIALS AND HOW EFFECTIVE HAS IT BEEN TO DATE?

9. It is too early to tell if the HRA has been effective, but there are a number of points worth outlining within its current remit. The role of the HRA is to streamline the burden of research whilst protecting patients and public taking part in research.
10. The HRA needs to be held accountable for its research Support Services framework directive that includes a 70-day benchmark to recruit first patients for trials. Yet, it is unclear who has oversight for this function and exactly how the HRA is to deliver on this target. This is an ambitious target; but, if it fails on this remit, it should be deemed to be overall a failure. If it doesn't stick to this clear mandate it risks adding an increase to the layers of bureaucracy, particularly given its alignment and role to deliver on the EU clinical trials directive and its application.
11. This target, of 70-days is currently unobtainable for drug trials. As a lead investigator on a NIHR funded trial, the best we can currently obtain is around the 150-day mark, which is the European average. Currently a funded trial requires the following permissions or approvals:
 - Peer review (no time limits)
 - Ethics (60 days approval time)
 - Research and development approval (30 days to get back) no time limits for local trusts
 - MHRA (28 days for 1st report)
 - University sponsor (1 week)
 - Service support costs (no time limits)
 - PCT approvals (no time limit)
 - Site participation (no time limits)

All of these specific requirements take considerable time and given there are many steps in the process, which require approvals without time limits; dealing with these should be the current priority of the HRA. Note that only one process, namely university sponsorship, currently has a realistic sense of urgency around its deliverables. There is no reason that many of the processes could be brought in line with a 7-day rule, with streamlining of the forms

12. There is nothing within the HRA remit to highlight poor publication practices. If the HRA is to protect patients then it should ensure that all trials are published in a timely manner, thus preventing further unnecessary research for treatments that may be found to be ineffective and or harmful. Yet, there is a strong sense the HRA cannot deliver on this task and has stated that it does not have the appetite for the task at hand. [1] This is an error of judgement on the HRAs part, as ensuring timely open publication is one of its chief remits. If it is not, then it is hard to understand what is the exact purpose of the HRA.
13. The HRA has the provision to operate in a closed manner. This ability to operate in a non-transparent manner is a mistake and should be changed. (1) The Authority must make such reports to the Secretary of State in such manner and at such time as the Secretary of State may direct, and must furnish to the Secretary of State such information as the Secretary of State may from time to time require. (2) A meeting of a committee or sub-committee of the Authority is not to be open to the public. The Authority may, by resolution, exclude the public from a meeting (whether during the whole or part of the proceedings) whenever publicity would be prejudicial to the public interest by reason of the confidential nature of the business to be transacted or for other special reasons stated in the resolution and arising from the nature of that business or of the proceedings.

WHAT EVIDENCE IS THERE THAT PHARMACEUTICAL COMPANIES WITHHOLD CLINICAL TRIAL DATA AND WHAT IMPACT DOES THIS HAVE ON PUBLIC HEALTH?

14. Whilst modern medicine delivers great benefits to society, its harms due to the withholding of data often prove devastating—with numerous incidents, ranging from thalidomide and antiarrhythmic drugs to Cox II inhibitors. Work from several investigators have highlighted the problems associated with withheld data in which poor regulatory practices have led to (and continue to lead to) direct patient harm, excess costs and delays in the delivery of effective treatments.
15. Firstly, the extent of underreporting should not be underestimated. A study of 546 drug trials, published between 2000 and 2006 reported only 2/3rds had published their results. Rates of trial publication within 24 months of study completion ranged from 32% among industry-funded trials, to 56% among non-profit or non-federal organization-funded trials. [2]
16. A further analysis of trials listed on Clinical Trials.Gov, found that of 677 trials completed by 2007 only 46% were published in a peer reviewed biomedical journal, indexed by Medline, within 30 months of trial completion. [3]
17. Mandatory reporting of trials appears to have made little difference. For example, the overall rate of compliance with the mandatory reporting rate for 2009 trials listed on Clinical Trials.gov within one year following completion, is only 22%. [4] A further study of clinical trials.gov data between 2009 and 2010 reported that only 52% of 152 trials had associated publications within 2 years after posting. [5]
18. Secondly, Six recent case studies are outlined which highlight the problem and the harm caused: (more cases studies can be provided upon request)

Rofecoxib: failure to disclose evidence of harm.

19. Research by Psaty et al published in JAMA is an example of the importance of withheld data. This case study, by reviewing information provided by the FDA, demonstrated two pivotal published articles of rofecoxib did not include analyses of mortality data, and because of this the studies wrongly concluded rofecoxib is "well tolerated."
20. In direct contrast, and at the same time as publication, the company's internal analyses of pooled data from the same trials identified a significant increase in total mortality. This equated to an overall 3 fold increase in mortality of 34 deaths among 1069 rofecoxib patients compared to 12 deaths among 1078 placebo patients (HR, 2.99; 95% CI, 1.55-5.77).
21. What is striking about this case is these mortality analyses were neither provided to the US FDA nor made public.
22. Of more concern was the data submitted to the FDA in a Safety Update Report in July 2001. This data, submitted by the sponsor, reported 29 deaths (2.7%) among 1067 rofecoxib patients and 17 deaths (1.6%) among 1075 placebo patients, thus masking the true mortality difference.

Rosiglitazone: research misconduct and failure to disclose harms

23. Rosiglitazone is a thiazolidinedione class of drug which was marketed as an addition and/or stand-alone drug to the oral hypoglycaemic agents available to treat patients with uncontrolled type 2 DM. Annual sales peaked at approximately \$2.5bn in 2006; the drug is now withdrawn due to safety issues.

24. Internal GSK company emails reveal a submitted journal publication, which showed rosiglitazone increased the risk of myocardial infarction, was leaked to GSK. GSK's internal analysis and their company statisticians confirmed the findings and internal company emails demonstrated the company had already come to similar conclusions yet failed to disclose this publicly. [6, 7, 8]

Oseltamivir: Lack of access to full trial programmes

25. Further to these investigations we have taken a similar approach to Psaty [9] in the analysis of the effects of oseltamivir. [10] Only in response to substantial publicity generated by a joint BMJ-Channel 4 News investigation of oseltamivir, did Roche publicly pledge to make its unpublished full clinical study reports available. [11] The subsequent work has gone on to find a high risk of publication and reporting bias in the trial programme of oseltamivir, which significantly undermines the results published in journals.

Paroxetine: withholding trial data and risk of suicide

26. GSK was caught withholding clinical trial data showing Paroxetine increased the risk of suicide in young people. The Chief Executive of the MHRA said, "I remain concerned that GSK could and should have reported this information earlier than they did. [12]

Reboxetine: effects of publication bias

27. Reboxetine was eventually found to be an ineffective and potentially harmful antidepressant after researchers found that 74% of the data from clinical trials had been suppressed during the lead up to the approval of the drug for the treatment of severe depression. [13]

Rimonabant

28. In 2007, the FDA's concluded the French manufacturer Sanofi-Aventis failed to demonstrate safety of rimonabant and did not recommend the anti-obesity treatment. The drug had been on sale in Europe for one year previously. The company spent nearly four years withholding data on the risks and benefits of two weight-loss drugs. Eventually, Acomplia had to be taken off the market: its harms outweighed its benefits. [14]

HOW COULD THE OCCURRENCE AND RESULTS OF CLINICAL TRIALS BE MADE MORE OPEN TO SCRUTINY? WHO SHOULD BE RESPONSIBLE?

29. Globally the development of new treatments is grinding to a halt. The lack of transparency means ineffective treatments continue to waste scarce healthcare resources. Putting it simply, we currently have a system that favours conflicts and deters transparency. Therefore, making the results of trials more open will not be, and should not be seen as a simple process. Voluntary arrangements will have little impact on the current status quo and will be little more than window dressing. In addition, given the complexity of the current problem it is highly likely that a number of solutions will be required.
30. The following highlights five possible means of action and there are likely to be more:
31. a) Legislation is required to make clinical study reports, of all completed trials, available within one year of trial completion.
32. b) NICE should have a remit to ensure that all the data is provided and made transparently available for any drugs that they provide guidance upon.

33. c) EMA aims to ensure that by 2014 that all data and clinical study reports they receive shall be made available. However, this does not cover pre 2014 trials. Therefore they should ensure that a full list of clinical study reports in their possession, going back 20 years are posted on the internet, and allow access for these clinical study reports upon request.
34. d) The MHRA should have a responsibility to ensure all post marketing studies, required by regulators are up to date and published in full.
35. e) Ethics committees should have a responsibility to follow up all trials that have been approved under their committees. Investigators, sponsors, manufacturers not complying should be barred from further ethical review until the position is rectified
36. f) There is a need to set up an independent body to oversee the standards and practices related to publication transparency.

CAN LESSONS ABOUT TRANSPARENCY AND DISCLOSURE OF CLINICAL DATA BE LEARNED FROM OTHER COUNTRIES?

37. The simple answer is no. This is a global phenomenon, riddled with conflicts, and in need of robust legislation to tackle the problem. As highlighted, the size of the market, the profits to be made simply means the current system is not fit for purpose. No one has yet come up with a robust solution to the problem and there is a direct to be more transparent in terms of clinical trial results

CONFLICTS OF INTEREST:

Carl Heneghan and Matthew Thompson have received research funding from the National Institute of Health Research for work related to Tamiflu and access to trial data.

February 2013

References

1. [<http://policyblog.amrc.org.uk/2013/02/01/talking-about-the-health-research-authority/>]
2. Bourgeois FT, Murthy S, Mandl KD. Outcome reporting among drug trials registered in ClinicalTrials.gov. *Ann Intern Med.* 2010 Aug 3;153(3):158-66.
3. Ross JS, Tse T, Zarin DA, Xu H, Zhou L, Krumholz HM. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. *BMJ.* 2012 Jan 3;344:d7292.
4. Prayle A, Hurley M & Smyth AR. Compliance with mandatory reporting of clinical trials results on ClinicalTrials.gov: cross sectional analysis. *BMJ* 2012; 344:d7373
5. Deborah A. Zarin, Tony Tse, Rebecca J. Williams, Robert M. Califf, and Nicholas C. Ide. The ClinicalTrials.gov Results Database — Update and Key Issues. *N Engl J Med* 2011; 364:852-860 March 3,
6. United States Senate, M.B., Chairman, Chuck Grassley, Ranking Member., Staff Report on GlaxoSmithKline and the Diabetes Drug Avandia. Prepared by the staff of the Committee on Finance. <http://finance.senate.gov/press/Gpress/2010/prg022010a.pdf>.
7. Nissen, S.E. and K. Wolski, Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*, 2007. 356(24): p. 2457-71.
8. Nissen, S.E., Setting the RECORD Straight. *JAMA*, 2010. 303(12): p. 1194-5.
9. Psaty, B.M. and R.A. Kronmal, Reporting mortality findings in trials of rofecoxib for Alzheimer disease or cognitive impairment: a case study based on documents from rofecoxib litigation. *JAMA*, 2008. 299(15): p. 1813-7.
10. Jefferson, T., et al., Ensuring safe and effective drugs: who can do what it takes? *BMJ*, 2011. 342: p. c7258.

11. Cohen, D., Complications: tracking down the data on oseltamivir. *BMJ*, 2009. 339: p.b5387.
 12. <http://www.nelm.nhs.uk/en/NeLM-Area/Evidence/Patient-Safety/500721/>
 13. <http://www.bmj.com/content/341/bmj.c4737>
 14. <http://www.acompliareport.com/News/news-061807.htm> -
- <http://www.dailymail.co.uk/news/article-2241431/Scandal-poison-pen-pushers-How-doctors-patients-kept-dark-potentially-dangerous-everyday-drugs.html>

Written evidence submitted by Medical Schools Council and Association of UK University Hospitals
response (CT18)

1. INTRODUCTION

- 1.1. The Medical Schools Council (MSC) represents the interests and ambitions of UK medical schools as they relate to the generation of national health, wealth and knowledge through biomedical research and the profession of medicine. The membership of the Medical Schools Council is made up of the Heads or Deans of the 32 UK undergraduate medical schools, plus the postgraduate London School of Hygiene and Tropical Medicine.
- 1.2. The Association of UK University Hospitals (AUKUH) is the key leadership body across the UK promoting the unique interests of University Hospitals. Its purpose is to represent the unique role and interests of UK University Hospital Trusts in the tripartite mission of service, teaching and research in partnership with other national bodies. There are currently 44 member Trusts.
- 1.3. We welcome the opportunity to submit evidence to the Science and Technology Committee inquiry into clinical trials and the disclosure of data. Clinical trials are core business for both MSC and AUKUH; therefore members have a keen interest in ensuring they are conducted to the highest standard with public support and engagement.

2. 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?

- 2.1. The EU Clinical Trials Directive has been a significant barrier to the conduct of clinical trials in the UK and EU. Proposals to create new regulation that will replace the Directive are welcome. In particular, we support the move to a more risk-based approach and the introduction of the 'low-interventional studies' concept.
- 2.2. While we are supportive of the revisions, we feel that there are a number of opportunities to improve the proposal. A summary of these considerations can be found in our response to the MHRA consultation on the proposed regulation.¹ In addition to these points, we would note that to ensure revisions truly reduce burden on those driving forward clinical research, the IT system / portal to be created by the Commission must be robust and user-friendly.
- 2.3. In addition, care must be taken to ensure that existing processes are compatible with the proposals (and vice versa) to avoid duplication (e.g. ensuring that the portal compliments the Integrated Research Application System [IRAS]). There is a risk that a dichotomy between Clinical Trials of Investigational Medical Products (CTIMPs) and non-CTIMPs will emerge

¹ Annex 1 – Not printed

if proposals are not carefully aligned with current processes. In doing this, a unification of terms and language used will be necessary.

2.4. We feel that there is an opportunity for the EU to consider 'phase zero' trials. Very often materials made and used for early trials in the USA are not admissible for use in the EU. This is anticompetitive and gives the UK a major scientific disadvantage. For example, in gene therapy for cancer, therapeutic viruses made and used for early phase trials in the US cannot be used in Europe. This places a heavy burden for translational science in Europe, particularly university-led science, and should be changed.

2.5. Internal barriers for the conduct of research in the UK have greatly reduced in recent years. Efforts to develop a more streamlined and proportionate approach to regulation have been particularly helpful in achieving this. It is heartening to see commitments to the importance of biomedical research in key Government and DH publications including, but not limited to, the Life Sciences Strategy, the NHS Constitution revision, Innovation, Health and Wealth and the NHS Mandate. We support the National Institute for Health Research and the Health Research Authority's continuing work to ensure barriers to conducting and attracting trials are removed. One key aspect of this work is efforts to improve access to patient data records for the benefit of research and ultimately patient care.

3. WHAT IS THE ROLE OF THE HEALTH RESEARCH AUTHORITY (HRA) IN RELATION TO CLINICAL TRIALS AND HOW EFFECTIVE HAS IT BEEN TO DATE?

3.1. While the HRA is a newly formed organisation, we believe that the early signs are encouraging. For example, we feel that changes to IRAS that have been proposed and/or carried out are beneficial.

3.2. It is important that the HRA ethics review programme is integrated into existing Research Ethics Committee processes, to avoid duplication of effort. The HRA appears to be aware of this risk and we are optimistic that, through careful piloting, unnecessary burden can be avoided.

4. WHAT EVIDENCE IS THERE THAT PHARMACEUTICAL COMPANIES WITHHOLD CLINICAL TRIAL DATA AND WHAT IMPACT DOES THIS HAVE ON PUBLIC HEALTH?

4.1. Publication bias in all its guises is a real issue of concern. The preference for the publication of 'statistically significant' findings is hugely damaging to the corpus of published research and is unfair to participants of unpublished trials. The more obviously dishonest practice of prohibiting/hiding research which disfavours a product causes more direct harm.

4.2. While evidence of this has not consistently been identified by members at a local level, there is a considerable body of evidence at a larger scale of withheld data.

- 4.3. Lack of clinical trial data can have both direct and indirect effects on public health and the health of individual patients. Poor treatment choices based on incomplete information will have a direct effect on patients. Care costs from the use of insufficiently evidenced treatments can lead to the waste of limited resources.
5. HOW COULD THE OCCURRENCE AND RESULTS OF CLINICAL TRIALS BE MADE MORE OPEN TO SCRUTINY? WHO SHOULD BE RESPONSIBLE?
- 5.1. We feel that the publication of all trial data would be welcome to improve scrutiny. To make this truly effective, there are a number of key considerations:
- 5.1.1. **Anonymity:** transparency of data must not have the counter-productive effect of losing patient and public trust in clinical trials through the release of identifiable information. The publication of Clinical Study Reports rather than individual patient level data may therefore be preferable.
- 5.1.2. **Commercialisation and publication:** it is important that the timeline for publication of trial data does not harm prospects for commercialisation or publication for the researcher(s) through the premature release of sensitive information. Mutually agreed, appropriate timescales will be required.
- 5.1.3. **Meaningful data:** data would need to be released at an appropriate stage to be meaningful (i.e. once analysed, verified and peer reviewed).
- 5.1.4. **Which trials?:** CTIMPs, Devices trials and other interventional trials (e.g. of a surgical intervention) would all need to be considered.
- 5.1.5. **Scrutiny by whom?:** The public, health professionals, regulators, manufacturers, researchers and sponsors all have a role in scrutinising clinical trial data. With this in mind, the format of data on trial outcomes will need to differ dependent on the intended audience.
- 5.1.6. **The global nature of trials:** Installing a system for opening all trial data to scrutiny would require concerted global effort.
- 5.1.7. **Avoiding duplication of effort:** Existing processes need to be harnessed rather than duplicated.
- 5.2. Regulators are the only bodies with the power to require the publication of all trial data and this would need their full support to be effective. A mandatory commitment to share the clinical study report of a trial could be a condition of its approval. R&D authorities could follow up on studies at regular intervals from a pre-agreed date after a study has closed to ensure this happens. After an appropriate time period of checking, a study which has not reported could be flagged as “not published within x years”. This statement (if not accompanied by a valid explanation) would then be viewed as a ‘black mark’ by the research community. This should have the effect of discouraging the suppression of clinical trials data. Any trials where one would not expect to see results published (e.g. withdrawal of a medication from approved use) should be accompanied on the database by as informative a

summary as possible. All studies on such a database would need clear links to other places the data are available (e.g. link to a peer-reviewed publication).

- 5.3. As a long-term option for the UK, the involvement of NICE could be beneficial. We believe that NICE has the competency to interpret, synthesise and communicate these data. The enlargement of the National Research Ethics Service (NRES) database may assist with this work. The Medicines and Healthcare products Regulatory Agency is another organisation that could host a publically accessible database.
- 5.4. Compelling sponsors to deposit (anonymised) trial data into an EU repository is another option to explore. This would require commitment from the EU and a sophisticated and secure database, in addition to the considerations above. There is a risk that while this would make trials more open, effective scrutiny of these data would require clear presentation and effective indexing of huge volumes of information. Systems for the registration of clinical trials already exist, on international databases such as www.clinicaltrials.gov – this could be extended to include protocols and Clinical Study Reports with better regulation and audit of their reporting.
- 5.5. Existing data could be used more efficiently as a short-term solution. NRES publishes a synopsis of all trials which go to Research Ethics Committee on its website and requires a synopsis of results when a trial is concluded. Were the synopses of results rigorously collected, of a high standard and published in an easily searchable format, it would assist in the dissemination of appropriate data. Committee members would need to interrogate results to ensure they are fit for purpose under this option.
- 5.6. An alternative proposal would be for all data to be issued on reasonable request, with the possibility that release may be subject to a time restriction. This would avoid some of the problems with release of all trial data, but the mechanism for doing this would need to be clear. Requests for access to detailed trial data would need to be accompanied with a clear rationale for their use and description of the intended analyses. Peer review of these requests by the original researchers and the competent authorities would ensure that data are not used inappropriately.
- 5.7. Another potential lever would be academic journals signing up to a code of practice that ensures that publications are only accepted from companies who make all of their trial data available. This would build on the model adopted by the *British Medical Journal*². Journals should be encouraged to review trial protocols before results are analysed, and accept them for publication in principle, unless there are overwhelming academic reasons not to do so. This may help reduce publication bias.

² <http://www.bmj.com/about-bmj/resources-authors/article-types/research>

5.8. In Ben Goldacre's *Bad Pharma*, referenced by this inquiry, medical schools are tasked with the following: "teach medical students about how to spot bad evidence from the pharmaceutical industry, and in particular how its marketing techniques work". Our publication: *Consensus Statement on Relationship between UK Medical Schools and the Pharmaceutical and Medical Devices Industries* makes it clear that:

"Students should be aware of the potential for the challenges to professionalism and clinical judgement that may be presented by certain interactions with the pharmaceutical industry. Students should be exposed to balanced information that describes both potential benefits of the relationship between the pharmaceutical industry and the healthcare sector, as well as the potential risks that inevitably derive from the commercial imperative of the industry"

Therefore, medical schools acknowledge the need to ensure students are fully informed and sensitive to the functioning of the pharmaceutical industry. This is important in ensuring the future medical workforce is equipped to scrutinise these data.

5.9. We agree that withholding appropriate data can do a disservice to the patients who participate in clinical trials and the broader population. Along with many other organisations, we are supporters of *The concordat to support research integrity*³ and its requirement for rigour, transparency and open communication when reporting research data, including the sharing of negative results.

6. CAN LESSONS ABOUT TRANSPARENCY AND DISCLOSURE OF CLINICAL DATA BE LEARNED FROM OTHER COUNTRIES?

6.1. We are not aware of other countries achieving greater success in this area.

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³ <http://www.universitiesuk.ac.uk/Publications/Documents/TheConcordatToSupportResearchIntegrity.pdf>

Written evidence submitted by Sense about Science (CT19)

This is a memorandum about patient and public support for clinical trials reporting, and in particular the support from participants in clinical trials, in response to Questions 3 and 4 set out by the Committee. Sense About Science is making a separate submission about the effects of publishing the results of clinical trials.

1. Background

- 1.1 Sense About Science established the AllTrials campaign with Bad Science, *BMJ*, James Lind Initiative and Centre for Evidence Based Medicine. AllTrials is calling for all clinical trials to be registered and results to be reported, from both industry and academia. The best available evidence shows that about half of all clinical trials have never been published, and trials with negative results about a treatment are much more likely not to be published¹. There have been years of discussions about addressing this problem but they have been slow and have failed to produce a decisive public commitment.
- 1.2 The campaign was launched on 9 January 2013. The AllTrials.net petition has been signed by over 30,000 individuals and 178 organisations including 97 patient groups. Appendix 1 contains the petition text and the names of the supporting organisations.
- 1.3 Sense About Science is a charity that equips people to make sense of science and evidence. We are a source of information, we challenge misinformation and we champion research and high quality evidence. We work with thousands of scientists, scientific bodies, research publishers, policy makers, the public, community groups and media, to promote sound science and evidence in public discussions.

2. Clinical trial participants

- 2.1 On 18 January 2013, fifty three clinical trial participants wrote to the European Medicines Agency (EMA) saying that the lack of regulations requiring clinical trials to be published is a betrayal of their trust. They said: “we all agreed to participate in the trials in the belief that we were helping to improve knowledge and treatments. We now understand that many participants in trials have been misled... This means that the findings generated from our participation and that of thousands of others in the trials may not be available to the doctors, researchers and regulators who work on particular diseases or make decisions about their treatments. It also means that some of the trials could be repeated in the future, when they do not need to be.” (Appendix 2)
- 2.2 The signatories to the letter asked the EMA to put in place measures to ensure that the protocols for all clinical trials from now on - and all clinical trials since the 1980s – are posted on a public register; and that the primary and secondary outcomes measured in all these trials and the clinical study reports are published.
- 2.3 Richard Stephens, Chair of the NIHR Cancer Consumer Liaison Group, who signed the letter as a cancer patient and clinical trial participant said, “The Department of Health report, *Innovation Health and Wealth*, sets out a goal for the NHS that every willing patient should be able to take part in research. In our publication, *Action On Access*, we call for research to be embedded in

¹ F Song, S Parekh, L Hooper, YK Loke, J Ryder, AJ Sutton, C Hing, CS Kwok, C Pang, I Harvey. *Dissemination and publication of research findings: an updated review of related biases*. Health Technology Assessment 2010; Vol. 14: No. 8 <http://www.hta.ac.uk/fullmono/mon1408.pdf>

clinical practice. Already 20% of cancer patients in the UK take part in clinical trials as part of their treatment options. We expect that the results of trials will be made freely available to researchers, clinicians and administrators, in order to deliver better treatments, better services, and better outcomes for patients. So all clinical trials should be on a central accessible register, and all trials should be reporting their results, even if they do not change clinical practice. Patients who choose to take part in clinical trials believe that by doing so, we are helping other patients in the future. I believe it is immoral to recruit patients to clinical trials and then not report or share the results. We participate in order to increase knowledge and to help others. We do not expect the knowledge to be kept secret or the help for others to be denied.” (Appendix 3)

2.4 GSK signed up to the AllTrials petition on 5 February 2013. Their statement set out their plans to publish the full results of all the trials they have conducted going back to their formation as a company. It also recognises the concerns of patients: “Our commitment also acknowledges the very great contribution made by the individuals who participate in clinical research. All those involved in the conduct and publication of clinical research, whether healthcare companies like GSK, academia or research organisations, have a role to play in ensuring that the data they generate are made publicly available to help bring patient benefit.”²

2.5 Between 16 and 18 of January 2013, Sense About Science conducted a survey through PatientView (which has access to an international network of 120,000 patient groups). The results of this survey indicated that 75% of people who have a medical condition (and 72% of all respondents) say that they would be more likely to take part in a clinical trial if they knew the results would be published. (Appendix 4)

3 Recommendations

3.1 Where they have not already been registered, all clinical trials for medicines in current use should be registered retrospectively in an approved public registry. This is because the majority of prescription drugs currently in use were licensed before 2007 (FDA regulation amendment).

3.2 Clinical trials which have not been part of a marketing authorization (licensing) application should also be registered retrospectively. This will contribute to better clinical research and avoid repetition of clinical trials (and therefore unnecessary risk to patients and expense).

3.3 For all trials (phase 2 and above) conducted since 1990:

- Full clinical study reports, or equivalent, should be made publicly available.
- Where these are not available, a written statement should be provided, signed by the current Medical Director or Principal Investigator, stating that the clinical study reports and/or results are unavailable; explaining when and why they were destroyed; stating what efforts have been made to find the relevant documents; and sharing whatever information is still available about the trials (such as protocol, clinical indication, size, etc).

3.4 For all future trials, regardless of location or indication:

² GSK announces support for AllTrials campaign for clinical data transparency
<http://www.gsk.com/media/press-releases/2013/GSK-announces-support-for-All-Trials-campaign-for-clinical-data-transparency.html>

- The trial should be registered on an ICMJE recognised registry before recruitment of the first patient.
- Summary results and full clinical study reports (or equivalent) should be available within one year of completion (with an explanation provided in any case of delay).

3.5 The EMA intends to publish data that has been submitted for marketing authorizations from 2014. It should provide registry space for trials which are not part of such applications and lead the retrospective registration and reporting in 3.1-3.4, providing space for links to be provided to clinical study reports or equivalent held on other databases.

3.6 The Association of the British Pharmaceutical Industry's response to the AllTrials campaign has been disappointing. After some initial obfuscation it has said that it is going to wait for EMA working groups to report. These groups are not directly considering the proposal to publish clinical study reports, or equivalent results for other types of intervention studies, for all trials and for all treatments in current use (i.e. the medical treatments we actually use, which are already licensed, rather than just the small percentage that will be licensed and used in the future). Clinical study reports do sometimes contain some patient level data. GSK is resolving this by redacting it where necessary.

Since AllTrials started, it has become clearer by the day that this is moving in only one direction, as thousands of doctors, researchers and members of the public sign up. In a few years time it will be hard to imagine how anyone could have defended the current situation.

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Appendix 1: AllTrials petition and supporting organisations

Thousands of clinical trials have not reported their results; some have not even been registered.

Information on what was done and what was found in these trials could be lost forever to doctors and researchers, leading to bad treatment decisions, missed opportunities for good medicine, and trials being repeated.

All trials past and present should be registered, and the full methods and the results reported.

We call on governments, regulators and research bodies to implement measures to achieve this.

Signed by:

Adelaide Health Technology Assessment
American Institute for Technology and
Science Education
American Medical Students Association
Association of Clinical Biochemistry
Association of Medical Research Charities
Association of Research Ethics Committee
Belgian Centre for Evidence Based Medicine
Berne Declaration
BioMed Central
British Library
British Nutrition Foundation
British Society for the Study of Vulval
Diseases
Canadian HIV Trials Network
Centre for Reviews and Dissemination
Centre for Statistics in Medicine
Centre of Evidence Based Dermatology
Chemist and Druggist Magazine
Clinical Pharmacist
Cochrane Collaboration
Committee On Publication Ethics
Critical Appraisal Skills Programme
Critical Appraisal Skills Programme
International Network
Critical Appraisal Skills Programme Mexico
Critical Appraisal Skills Programme Spain
Dianthus Medical Ltd
Doctors Reform Society
Drugs and Therapeutics Bulletin
eCancer
Equator Network
European Continuing Medical Education
Forum

European Federation of Clinical Chemistry
and Laboratory Medicine
Faculty of Intensive Care Medicine
German Network for Evidence Based
Medicine
GIMBE Foundation
GSK
HealthWatch
Health Action International Europe
Health Action International Global
Healthy Skepticism UK
Hospital Pediátrico de Sinaloa
IBase
Idea Pharma
Ideal
Institute for Quality and Efficiency in
Healthcare
Intensive Care Foundation
Intensive Care Society
International Coalition for treatment
preparedness in Eastern Europe and Central
Asia
International Institute for Advanced Studies of
Psychotherapy and Applied Mental Health
International Society for Evidence Based
Health Care
Journal of Cognitive and Behavioural
Psychotherapies
Journal of Kathmandu Medical College
London School of Hygiene and Tropical
Medicine
Medical Research Council
Medicos Sin Marca
Medsin
Minervation

National Physicians Alliance
Netherlands Epidemiological Society
NICE
No Grazie Pago Io
North London Humanist Group
Norwegian Knowledge Centre for Health Services
Nottingham Clinical Trials Unit
Open
Open Knowledge Foundation
Open Science Federation
Oxford Vaccine Group
Pharmaceutical Journal
Pharmaware
PLOS
Royal Statistical Society
Russian Society for Evidence Based Medicine
Sabre Research UK
Tatarstan Medical Student Association
Thinkwell
Trip
UK Clinical Pharmacy Association
UK Dermatology Clinical Trials Unit
UK Research Integrity Office
Wellcome Trust
World Association of Medical Editors

Patient Groups

AIDS Coalition to Unleash Power Paris
AIDS Treatment Activists Coalition
Action for M.E
Age UK
Action for Sick Children
Afiya Trust
Alkaptonuria Society
Alpha 1 Awareness UK
Alzheimer's Society
Anticoagulation Europe
Arrhythmia Alliance
Arthritis Care
Asthma UK
Beat
Bliss
Blood Pressure Association
Bowel Cancer UK
Brain and Spine Foundation UK
Breakthrough Breast Cancer
Brains Trust

Brain Tumour Charity
Bristol and Avon Chinese Women's Group
British Dupuytren's Society
British Heart Foundation
British Obesity Surgery Patients
British Lung Foundation
Cancer Research UK
Cardiomyopathy Association
Changing Faces
Crohn's and Colitis UK
Counsel and Care
CSV
Cystic Fibrosis Unite
Diabetes UK
Different Strokes
Disabilities Trust
Ear Foundation
Enccephalitis Society
Epilepsy Action
Epilepsy Society
Genetic Alliance UK
ITP Support Association
INPUT
James Whale Fund for Kidney Cancer
June Hancock Mesothelioma Research Fund
Kidney Alliance
La Leche League GB
Leukaemia CARE
Lyme Disease Action
Lymphoedema Support Network
Lymphoma Association
Macmillan Cancer Care
Macular Society
MDS UK Patient Support Group
Migraine Trust
Motor Neurone Disease Association
Mouth Cancer Foundation
Muscular Dystrophy Campaign
Myeloma UK
MS Society
National Ankylosing Spondylitis Trust
National Association of Deafened People
National Childbirth Trust
National Osteoporosis Society
National Rheumatoid Arthritis Society
National Voices
NI Chest & Stroke
Norwegian Cancer Society

No Panic
Pain UK
Parkinsons UK
Patients Association
Patients Involved in NICE
Pelvic Pain Support Network
The Pernicious Anaemia Society
The Pituitary Foundation
Prostate Cancer UK
Positive People Armenian Network
PXE (PiXiE) Europe
Rare Disease UK
Rethink
Royal National Institute of Blind People
Royal Society for Public Health NGO forum

Sarcoma UK
Sarcoma Patients Euronet
Scleroderma Society
STARS
Stichting Tekenbeetziekten
Stonewall
Target Ovarian Cancer
Terrence Higgins Trust
Treatment Action Campaign
Treatment Action Group
Together for short lives
Urostomy Association
Well UK
Young Minds

Appendix 2: Letter to the EMA from clinical trial participants

We have participated in clinical trials in the last 30 years.

Some of us are healthy individuals and some of us have medical conditions. Some of us probably received the treatment under investigation in the trial and some of us were given the control treatment or placebo.

Whatever the case, we all agreed to participate in the trials in the belief that we were helping to improve knowledge and treatments. We now understand that many participants in trials have been misled. Current evidence shows that, overall, about half of all clinical trials have not been published and that this proportion has seen only a small improvement over the past few years. Furthermore, both companies and independent researchers can withhold information about clinical trials from doctors and researchers even when asked for it.

This means that the findings generated from our participation and that of thousands of others in the trials may not be available to the doctors, researchers and regulators who work on particular diseases or make decisions about their treatments. It also means that some of the trials could be repeated in the future, when they do not need to be.

This is dangerous and expensive and it holds back good medicine. It is also a betrayal of our trust in clinical trial regulation, and the trust of the families of those patients who volunteer for trials having had a terminal diagnosis.

The Clinical Trials Regulation is currently being debated in the European Parliament. We want you to put in place measures to ensure that the protocols for all clinical trials from now on - and all clinical trials since the 1980s – are posted on a public register; and that the summary results, the “primary and secondary outcomes” measured in all these trials and the Clinical Study Reports are published.

Name	Description of trial	Date of trial
Iain Chalmers	Oxford Vaccine Group’s test of a new pneumococcal vaccine	c 2008-2009
Richard Stephens	Trial of drug combinations in Lymphoma	1998
	Trial of PET scans as prognostic indicators in Lymphoma	1999
	Trial of blood anti-clotting agents in heart patients	2007
Lauren Gore	Test of potential new eczema treatment on healthy volunteers.	August 2012
Richard Smith	The trial was a double blind randomised controlled crossover trial to see if the polypill would reduce blood pressure and blood lipids. It lasted about six months. The polypill did reduce blood pressure and blood lipids.	2011

Sarah Stevens	Undertaken at St Barts Hospital for GW Pharma to assess effectiveness of Sativex for muscle spasms (trial was double blind). Condition: multiple sclerosis.	c 2006
Dominic Haigh	TREK Study Description: Participants from several different European countries were given either a patch immunising against traveller's diarrhoea or an inert placebo and dispatched to countries where they might become infected with the disease. I went to stay in Guatemala City for a week.	January 2010
Nancy Kane	Beta SNP trial; study examining whether differences in genes affect how vitamin A is used by the body.	October 2012
Ralph Cantellow	The PACE trial was a randomised controlled trial of treatments for chronic fatigue syndrome also known as myalgic encephalomyelitis or myalgic encephalopathy. The trial, which involved 640 patients, was conducted in six hospitals in England and Scotland and compared the safety and effectiveness of four treatments: Specialist medical care (SMC) alone, and SMC plus one of the following therapies: adaptive pacing therapy cognitive behaviour therapy, and graded exercise therapy.	March 2003- January 2010
Mei Lee	Phase 3 trials of Novartis's vaccine against neisseria meningitides B	2009-2010
Sam L	It was an antidepressant study looking at drugs affecting glutamate (ketamine and a new drug AZD6765)	February-March 2010
Charis Croft	The trial is between subcutaneous injections and sublingual tablets as a mechanism for administering immunotherapy to relieve hay fever arising from grass pollen.	September 2012- ongoing
Joanne Evans	Trialling BMN110 enzyme replacement therapy for Morquio's Syndrome (Mucopolysaccharide IVA)	August 2011- January 2012
Phil Booth	Trials of anti-epilepsy and pre-diabetes treatments	1988-1989

Rachel Pearce	My trial is called SOFT (Suppression of Ovarian Function Trial) and is a 3-arm trial testing the benefits and disadvantages of: Tamoxifen, Tamoxifen + ovarian function suppression, Exemestane + ovarian function suppression in premenopausal women with hormone receptor positive breast cancer.	2003- 2011
Thomas Edward Hills	Single dose of a generic formulation of bicalutamide (anti-androgen for prostate Ca) – pharmacokinetic study.	c June 2005
Helen Ap-Rhisiart, on behalf of my daughter, now aged twelve	Oxford Vaccine Group (Univ Oxford) meningitis C/pneumonia combination vaccine study.	2000-2003
Brian Sewell	Trial for a drug to control high blood pressure	1992
Caroline Richmond	Vitamin C and the common cold MRSA in denture wearers COPD	c 1984 c 2005 2013
Ryan Geleit	First into human trial to assess a new compound for the treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome	February 2012
Richard Desmond	Concorde trial into the efficacy of treating infection with HIV	1989-1991
A'Llyn Ettien	Yearlong trial of drug combination to prevent bone thinning 3-month trial of birth control patch comparing usability to ring	2005-2006 Summer 2007
James Warwick	Final phase RCT for a new meningitis vaccine developed by Novartis	October 2010-2011
Kevin Nickells	Clinical trial into the affects of alcohol on nicotine dependency	August 2010

Michael Wing	The trial was based at St Georges Hospital, Tooting, London. I underwent 12 hours of an intravenous infusion of deuterium enriched water preceded and followed by a blood test. I also had a repeat blood test 2 weeks later. The study was to identify the maturation rate of lymphocytes.	2001-2002
Khairil Hodgson	FluCamp a phase 2a, randomized, double blind, placebo controlled study to Investigate the effects of VX 787 administered to adult volunteers experimentally inoculated with live influenza virus	August 2012
Dr Aaron Dale	Addenbrookes Hospital for GSK for a painkiller FluCamp to test an influenza vaccine	2007 December 2012
Kathryn M Burke	The trial was Fingolimod (Gilenya) phase III. The trial was to test safety and efficacy.	2007
Harry Purser	Trial for a peripheral system analgesic.	April 2010
Gillian Lang	During pregnancy my blood pressure was monitored and samples of placenta taken following the birth	March - November 2002
Hester Tidcombe on behalf of my son Chris Murphy	Post-authorisation safety study of GSK's pandemic flu vaccine in the UK For diabetes	November 2009 Autumn 2004
Hilary Foote	The effects of natural bran food supplement on irritable bowel syndrome	c 1994
Michael James Fox	The trial was for the norovirus	Summer 2009
Darran Shepherd	Malaria vaccination trial	January 2010
Christopher Parlett	John I participated in three medical trials at the Department of Respiratory Medicine and Allergy, King's College, London All trials were said to be for the testing of alternatives to current corticosteroid treatments for asthma.	2001 -2003

Denise Syndercombe Court	Tamoxifen +/- (Zoladex) randomised- given for 2 years duration. Given for stage I/II breast cancer in premenopausal women (including those with positive nodes)	1994-1995
Linton Lahoud	Effects of light on sleep	c 2011
Dr Gemma Bashevoy	A trial for a malaria vaccine	January 2011- September 2012
Dr Maxim Bashevoy	A clinical trial for hay fever using a drug called rPhleum (immunotherapy)	c 2009
Nicola Branch	Trialling a gel to help reduce the spread of HIV amongst heterosexuals in Africa	2004- 2005
Leslie Rose	Phase I study of effects of a beta-blocker on muscle blood flow. Injection of a radio-label into anterior tibialis muscle, followed by treadmill exercise testing.	1980
	Acupuncture in neck pain. The purpose of the study was to evaluate electro-acupuncture in comparison with normal acupuncture and placebo electro-acupuncture.	2004
Adam Barnett		
Katherine Hunter		
Kieran Crean		
Matthew Valentine, MD	Roche trial of Oseltamivir (Tamiflu). Recruited with active flu-like illness as a medical student at Oregon Health and Sciences University in Portland, Oregon, USA for randomized controlled trial of Oseltamivir	Autumn 1998
Amanda Burls	The intervention was probiotic yoghurt versus non-probiotic yoghurt for IBS	2005
Martin Law	Get Moving run by the MRC epidemiology Unit	October 2012- February 2013
Carmen Major		

Cynthia Dumas Phase III randomized study of treatment based on April 2001- July
response to induction chemotherapy in patients with 2003
higher risk childhood acute lymphocytic leukaemia

Amanda Kerr on Infant vaccine trial 2008-2009
behalf of my son

Sean Murphy Interaction of an antihistamine and an anti-fungal drug 1993
Interaction of a 5HT1A receptor agonist and alcohol. 1993

Veronica Klein

Michelle Fraser

Appendix 3: Note on publication of the open letter from clinical trial participants to the EMA

Fifty-three clinical trial participants have written to the European Medicines Agency pointing out that the lack of regulations requiring clinical trials to be published is a betrayal of their trust.

Tracey Brown, Director, Sense About Science: “There is no good reason to delay full reporting of clinical trial results. It will have huge benefits for patients, health workers, doctors, pharmacists, regulators and researchers. It will benefit treatment decisions now and research into future options and it will encourage more people to be involved in clinical trials. The first tranche of results from our international patient survey¹ is showing that 78% of people who have a medical condition (and 72% of all respondents) say they would be more likely to take part in a clinical trial if they were assured the results would be published.”

Ben Goldacre, doctor and author of *Bad Pharma*: “We need the results of clinical trials to make informed decisions about which treatment is best, but half of all such trials have never been published, which exaggerates and distorts the evidence we have. This is medicine’s dirty secret, so it’s great to see patients speaking out, and so many eminent organisations joining up, to finally fix this problem. Withholding trial results is indefensible, and should never have been allowed to happen.”

Carl Heneghan, Director, Centre for Evidence-Based Medicine, University of Oxford: “When trial results aren’t published substantial harms occur, patients die and ineffective treatments waste precious health care resources. Is this what patients expect when they sign up to consent in a trial? Certainly not.”

Comments from signatories to the letter:

Richard Stephens who signed the letter as a cancer patient and clinical trial participant: “The Department of Health report, *Innovation Health and Wealth*, sets out a goal for the NHS that every willing patient should be able to take part in research. In our publication, *Action On Access*, we call for research to be embedded in clinical practice. Already 20% of cancer patients take part in clinical trials as part of their treatment options. The *National Cancer Patient Experience Survey* (2012) showed that two thirds of cancer patients are open to being asked about participating in research, and of those who are approached, 95% are glad to have been asked, even if they choose not to participate themselves.”

“Patients who choose to take part in clinical trials believe that by doing so, we are helping other patients in the future. We expect that the results of trials will be made freely available to researchers, clinicians and administrators, in order to deliver better treatments, better services, and better outcomes for patients. So all clinical trials should be on a central accessible register, and all trials should be reporting their results, even if they do not change clinical practice. I believe it is immoral to recruit patients to clinical trials and then not report or share the results. We participate in order to increase knowledge and to help others. We do not expect the knowledge to be kept secret or the help for others to be denied.”

Iain Chalmers took part in the Oxford Vaccine Group’s test of a new pneumococcal vaccine, c2008- 2009: “I agreed to a request from the Oxford Vaccine Group to participate in a trial of a new formulation of pneumococcal vaccine. I asked to be sent the results of the study, and was assured that I would be; but I wasn’t. When I received a request to volunteer for another vaccine trial being done by the same group I rang to ask to see a copy of the protocol, but I was informed it was confidential. I

declined that invitation, and will do so for any future invitations I receive from this research group until this problem is solved.”

Phil Booth took part in trials of anti-epilepsy and pre-diabetes treatments, 1988-1989: “I volunteered to do clinical trials on the understanding they would help people. If the results of any trial aren't published, how can doctors know what'll help their patients and what might harm them? Had someone with diabetes reacted to the test drug I took in the way I did, they might have died. There's no excuse for hiding data like that.”

A'Llyn Ettien took part in a yearlong trial of drug combination to prevent bone thinning, 2005 – 2006: “I would hate to think that the time and effort I and other participants invested in multiple visits to the trial centre, repeated evaluative tests, and complying with a drug regimen for an entire year was wasted because the data wasn't made public. The compilation of that many person-hours (never mind the time of the researchers themselves!) deserves to be put to use by being made available to help inform the next people who want to study this topic--regardless of the outcome.”

Charis Croft took part in a trial comparing different ways to administer immunotherapy for hayfever, September 2012- ongoing: “As a trial participant, I had a couple of motivations for signing up. One, of course, is the hope that in the course of the trial I receive an active therapy that improves my condition. But the odds of receiving the placebo are relatively high, and the therapy may not be effective. So there has to be an additional motivation. And certainly for me, and I think a large number of my fellow participants, there is a very strong motivation in the knowledge that we are contributing to scientific knowledge and understanding of our condition and ways to treat it. It's at least half of the reason we do it. If the results are not released, then we are not contributing to the wider scientific understanding. That is a massive betrayal of our trust and the implicit contract between researchers and patients. This must be addressed. There are no options except action.”

Hilary Foote took part in a trial on the effects of natural bran food supplement on irritable bowel syndrome, c 1994: “When I was asked to take part in the study I wasn't very keen on the idea as it would intrude on my daily personal life in an intimate manner. However I felt a sense of duty because I was aware that I have benefited from other people taking part in trials in the past. Having found out about how trials often go unreported I would be very reluctant to take part in any trial in the future. I will certainly not take part in any commercially funded trial unless suitable legislation is brought in.”

Dr Aaron Dale took part in a trial for a painkiller in 2007 and in FluCamp to test an influenza vaccine in December 2012: “It is essential that data from all clinical trials, both positive and negative, is accessible to doctors and their patients, to enable them to make the most informed and suitable decisions about their treatments and medications.”

Dominic Haigh took part in a trial on treatments for traveller's diarrhoea in January 2010: “Trials are the best tools that we have to test ideas in medicine. Ideas and medicines which may in theory be beneficial may in fact do great harm. Only trials can separate facts from theories.”

Nicola Branch took part in a trial on a gel to help reduce the spread of HIV amongst heterosexuals in Africa, 2004-2005: “I think trials are very important to enable scientists to develop drugs and other medical products to improve treatments for people around the world. Trials are not risk averse and people who participate in them should be given full access to information about what's

involved hence the need for a register. And one where we as 'guinea pigs' can leave uncensored comments about our experiences.”

Appendix 4: Survey of patient groups and members on clinical trial participation.
Circulated by PatientView to their international network of patient groups. Responses collected between 16/1/13- 18/1/13

Total number of respondents: 195

Would you be more likely to take part in a clinical trial if you knew the results would be published?

More likely	139	71.28%
The same	44	22.56%
Less likely	4	2.05%
Don't know/ not relevant to me	9	4.62%

Have you ever participated as a volunteer in a clinical trial?

Yes	55	28.35%
No	139	71.65%

Have you ever been asked to participate as a volunteer in a clinical trial but didn't do so?

Yes	29	14.87%
No	166	85.13%

Number of respondents who are patients: 111

Would you be more likely to take part in a clinical trial if you knew the results would be published?

More likely	83	74.77%
The same	25	22.52%
Less likely	1	0.90%
Don't know/ not relevant to me	2	1.80%

Have you ever participated in a clinical trial?

Yes	39	35.14%
No	72	64.86%

Have you ever been asked to participate as a volunteer in a clinical trial but didn't do so?

Yes	15	13.51%
No	96	86.49%

Further written evidence submitted by Sense About Science (CT19a)

The rationale for full and retrospective clinical trial registration and reporting, for research, innovation and effective healthcare

1. Improving treatments for patients

- With full information about effects and side effects, a better risk/benefit calculation can be made by doctors, and individual patients. Healthcare commissioners and regulators can make a more accurate cost/benefit assessment which ensures that the treatments available are those that are truly the most effective.
- With full information we would expect greater confidence all round that full information about risks and benefit is known. It will also reduce the potential for flipping between 'wonder drug' and 'killer drug' stories and their associated effects among patients of overoptimistic demand (people failing to report side effects, taking others' medication etc) and suddenly stopping medication.

2. Improving research and innovation

- The effect of publishing the full reports of clinical trials will be to provide a richer research base for both industry and academia. This means greater potential for collaboration and interdisciplinary work, more productive research, and potential value from unused Intellectual Property.
- Scientific research is self correcting. Research advances through critical analysis and review, which are essential for identifying flaws in study design, statistical errors, missed observations of both benefits and risks and the best ways to conduct further research. This process has been necessarily partial because of partial publication. Full publication will restore this vital part of the research checking process, which is the basis of greater confidence in research findings whatever their provenance.
- Efficient reviews. A large proportion of the time currently spent on systematic reviews by organisations such as the Cochrane Collaboration, publicly funded clinical researchers as well as by companies seeking information about proposed applications, goes on attempting to discover what has been done already rather than on assessing it.

3. Avoiding the waste of pointless repetition of studies

- Clinical trials cost; UK cost per patient of a clinical trial: 9, 758 euros¹.
- Contractors report that they are asked to conduct research for one entity and do so even though they have already conducted similar work under a confidential contract for another entity and know that the intervention does or doesn't work².

¹ Economics Europe. (2011). The Economic Environment for Clinical Research & Development in the UK. Funded by Novartis

² Chalmers, I (2006) TGN1412 and the Lancet's solicitation of reports of phase 1 trials. Lancet; 368, 2206-2207

- Conducting clinical trials on patients to discover something that has already been discovered, however unintentionally on the part of those conducting the research, is misleading participants, wasting resources on expensive and unnecessary research and putting patients at unnecessary risk³. For years, patients who had suffered a heart attack were prescribed drugs to prevent heart rhythm abnormalities. By 1990, it was estimated they were killing between 40,000 and 70,000 per year. Had a trial conducted in 1980 suggesting the drugs were lethal been published, this catastrophe might have been prevented⁴.

The 'burden'

It is necessary, in the case of full Clinical Study Reports and their equivalent, to ensure that any data that would identify patients are not made public. GSK, in its undertaking to make reports available going back to its formation as a company, has made clear that it can achieve this through redacting that information. Other companies are considering doing this too, and yet others are considering whether as a first step they should retrospectively publish all summaries, with redaction taking place on receipt of a request for the full report.

In the case of future reports, greater care can be taken to separate information which cannot be published, so this administrative burden is temporary and should be viewed as part of the necessary remedial measures to overcome failures in transparency to date.

Academics are already required, according to the Helsinki Declaration, to make the results of trials available: "Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting."

This means all results according to what was planned in the trial protocol, not just a summary of the results (we already know that summaries of results are generally highly misleading, see, for example: Gøtzsche PC. Believability of relative risks and odds ratios in abstracts: cross-sectional study. *BMJ* 2006;333:231-4).

March 2013

³ McGauran *et al.* (2010) *Trials*; doi:10.1186/1745-6215-11-37 Table S2: Examples of reporting bias in the medical literature

⁴ Moore, T (1995) *Deadly medicine*. New York; Simon and Schuster

Annex 1: Statements by the pharmaceutical industry on clinical trial transparency

1. Correspondence between the AllTrials campaign and the Association of the British Pharmaceutical Industry
2. GSK statement announcing support for the AllTrials campaign and our response
3. Roche statement on new process for accessing clinical trial data and our response
4. ABPI statement on new clinical trial transparency measures

1. Correspondence between the AllTrials campaign and the Association of the British Pharmaceutical Industry

Association of the British Pharmaceutical Industry (ABPI) statement on AllTrials.net

18th January 2013

The pharmaceutical industry has been and continues to be committed to evolving and addressing the issues relating to transparency in clinical research.

Throughout the industry, companies are publishing increasing amounts of clinical data. Following a change to the ABPI Code of Practice in 2012, companies are obliged to publish all clinical trial results within one year of marketing authorisation and publically register new clinical trials within 21 days of the first patient being enrolled.

In common with alltrials.net, the ABPI believes greater transparency of clinical trial results, and appropriate access to trial data, past and present, is in the best interests of patients and medicine. However, this can only be true where proper attention is given to some crucial considerations.

Firstly, there is a need to protect patient confidentiality and personal data. At present, disclosure policies protect patients' personal data and consent is not given for their data to be utilised by other third parties, for different purposes and at different times.

In addition, the release of commercially confidential information could undermine investment in the research and development of future medicines. This is ultimately not in the interests of patients, who would not be well served by dis-incentivising research based biopharmaceutical companies and commercial organisations from other life sciences sectors from making the substantial investments and shouldering the risks that are necessary to develop new innovative medicines.

Furthermore, the disclosure of all clinical trial results, past and present, would involve making vast amounts of data, held in an enormous variety of formats across the world, accessible for medicines long established as safe and effective by the clinical community. Release on reasonable request, via a transparent and accountable process, may be a more pragmatic way forward and this debate is ongoing. We believe there must be measures in place to ensure that the raw data from clinical trials can

only be shared with trustworthy and competent scientific institutions that are capable of conducting appropriate analyses.

Throughout these discussions, it is important to recognise that research is a truly global activity, with the UK supplying less than 2% of patients to global clinical trials. As part of a global industry, we are actively engaging with our European and international counterparts, as well as many other stakeholders, to input into these on-going discussions.

Finally, the debate around clinical trial transparency is important but it is essential that patients have confidence that the medicines their doctors prescribe for them are appropriately safe and effective. However much data is published - or not - the regulatory authorities have access to all the relevant data as part of the approval process for new medicines.

Response from AllTrials to ABPI statement

23rd January 2013

On 18th January 2013 the ABPI put out a statement on AllTrials, but the statement does not address the things that AllTrials is calling for.

AllTrials calls for the publication of clinical study reports from all clinical trials since the 1990s and for all trials to be registered. It is not a campaign for releasing individual patient data. The only mention made of publishing clinical trials results in the ABPI response is with reference to the ABPI Code of Conduct, which is only for new trials rather than earlier trials relating to treatments currently in use. The ABPI's statement appears to contradict the Code by saying that there are commercial reasons not to follow it.

The development of new treatments, patient confidence and regulatory oversight can only benefit from having full information about the trials that have been done before and what they have found. It is important that industry engages with this issue. We are not campaigning on access to individual patient data; that is a separate issue. Please can you respond to our call for access to clinical study reports and summary trial results on all trials for currently used treatments.

Reply from ABPI to AllTrials statement

24th January 2013

Many thanks for your email to Stephen Whitehead which has been passed to me to respond on behalf of the ABPI.

Like you, we do believe that greater transparency of clinical trial results, and appropriate access to trial data, past and present, is in the best interests of patients and medicine. We also agree that all trials should be registered, which is a requirement of the ABPI Code of Practice.

Regarding the call from the AllTrials campaign for the publication of clinical study reports from all clinical trials since the 1990s, we support greater access to trial data but as you are aware, this is a complex issue since research and development is an international endeavour. As such, the UK cannot act in isolation. This is why we support the European Medicines Agency's initiative to disclose trial information and the creation of working groups to examine the many complexities in making disclosure feasible. We believe it is necessary to wait for the outcomes of the working groups in order to establish systems and processes to disclose CSRs in line with the EMA final recommendations.

As we acknowledge in our statement, the debate around clinical trial transparency is important but it is also essential that patients have confidence in the medicines their doctors prescribe and understand that the regulatory authorities have access to all the relevant data as part of the approval process for new medicines, regardless of how much data is 'published'.

The ABPI welcomes your contributions to this important debate and we do believe there is much common ground. Please do feel free to contact me if you would like to discuss this in person.

AllTrials asks ABPI some direct questions

29 January 2013

Thank you for your reply. Your comments are still on the subject of individual patient data. As our last response to you emphasised, AllTrials is calling for publication of clinical study reports for all treatments in use internationally. Your position on this is as unclear as it was before you issued two replies. There is no need to wait until 2014 for an EMA consultation on individual patient data to end before answering our questions on clinical study reports. Attempts to address transparency have suffered from these kinds of irrelevant delays since first being raised in the 1980s, which suggests that industry does have objections to the publication of clinical study reports for treatments in current use. If so, these should be set out clearly and specifically. Perhaps a better way to clarify it would be for ABPI to answer directly the following questions:

Do you agree that clinical study reports etc should be provided for all treatments in current use (and that where these are not available an account given of this by the Principal Investigator)?

Do you agree that this information should be publicly available?

Will you amend your 2012 guidelines to this effect?

Will you support an amendment to the EU Clinical Trials Regulation to this effect?

What, if any, are your commercial objections to publication of clinical study reports?

What kind of situations do you think would justify withholding clinical study reports?

ABPI answers

1st February 2013

Many thanks for your email and questions. We have responded below.

Our overarching belief is that greater transparency of clinical trial information is in the best interests of patients. We are supportive of the EMAs efforts to identify the best way to do this and are engaged in the discussion on how it can be done.

Do you agree that clinical study reports etc should be provided for all treatments in current use (and that where these are not available an account given of this by the Principal Investigator)?

In principle, ABPI is in favour of sharing CSRs; however this needs to be done in a way that is responsible, reliable and reproducible across the world since clinical research is a global activity. The EMA working groups are going to report on the mechanics of exactly how to do this, therefore it would be prudent to await the results of their work, which will be later this year.

Do you agree that this information should be publicly available?

In principle yes. But there has to be a process involving the company in identifying what elements should not be disclosed due to data privacy concerns or to protect commercially confidential information. Our industry would urge civil society to prioritise what studies are most important to release. It is simply impossible for regulators and companies to release all study reports at once. Companies would rather spend time developing new medicines than going through millions of pages of historic data. Also, there must be a process of coordinating this process among the regulatory agencies - the same study reports have been submitted to agencies all around the world.

Will you amend your 2012 guidelines to this effect?

The discussions on release of data are being carried out at a European level through EMA and, from an industry perspective, through the European Federation of Pharmaceutical Industries and Associations (EFPIA). EFPIA has indicated it is open to discuss future changes to its Code depending on on-going discussions with EMA. ABPI would ensure its Code was aligned to the wider European position.

Will you support an amendment to the EU Clinical Trials Regulation to this effect?

We support rules that require the publication of all clinical studies. For studies intended to support marketing authorisation applications, the studies should be made public once the product is approved.

What, if any, are your commercial objections to publication of clinical study reports?

As clinical study reports, until now, have been written for a regulatory audience and assuming confidentiality, they may describe commercial plans of the company. For instance, the development strategy for future studies on new indications may be described to put the particular study in context. In some cases, companies may consider that a particular study design is a trade secret that competitors can learn from. Furthermore, study reports often include appendices with detailed information on analytical methods (chemical and physical) and on the manufacturing of the clinical trials material. This is a key area the EMA working groups will examine.

What kind of situations do you think would justify withholding clinical study reports?

In general patient identifiable data and commercially sensitive information can be redacted rather than the study report withheld. However, when a company does not have a patent for a product it relies on "regulatory data protection" to get the necessary market exclusivity to recoup the investment made. This period is 10 years in the EU. If the entire file with all studies is released other companies can get approvals around the world. Anyone can get an approval as long as they submit the necessary data - regulators do not require that they generate the data themselves. This would not support the development of innovative medicines.

2. GSK statement announcing support for the AllTrials campaign and our response

GSK announces support for AllTrials campaign for clinical data transparency

5th February 2013

GSK today further demonstrated its commitment to clinical trial transparency by announcing its support for the AllTrials campaign. The campaign is calling for registration of clinical trials and the disclosure of clinical trial results and clinical study reports (CSRs) to help drive further scientific understanding.

GSK already publicly discloses a significant amount of information about its clinical trials. The company registers and posts summary information about each trial it begins and shares the results of all its clinical trials – whether positive or negative – on a website accessible to all. Today this website includes almost 5,000 clinical trial result summaries and receives an average of almost 11,000 visitors each month. The company has also previously committed to seek publication of the results of all of its clinical trials that evaluate its medicines to peer-reviewed scientific journals.

Expanding on this, GSK is committing to make CSRs publicly available through its clinical trials register. CSRs are formal study reports that provide more details on the design, methods and results of clinical trials and form the basis of submissions to the US Food and Drug Administration (FDA), European Medicines Agency (EMA) and other regulatory agencies. From now, GSK will publish CSRs for all of its medicines once they have been approved or discontinued from development and the results have been published. This is to allow for the data to be first reviewed by regulators and the scientific community. Patient data in the CSRs and their appendices will be removed to ensure patient confidentiality is maintained.

In addition, while there are practical challenges, the company also intends to publish CSRs for clinical outcomes trials for all approved medicines dating back to the formation of GSK. This will require retrieval and examination of each historic CSR to remove confidential patient information. Given the significant volume of studies involved, the company will put in place a dedicated team to conduct this work which it expects to complete over a number of years. Posting will take place in a step-wise manner, with priority given to CSRs for its most commonly prescribed medicines.

Patrick Vallance, President, Pharmaceuticals R&D, GlaxoSmithKline, said: “We are committed to being transparent with our clinical trial data to help advance scientific understanding and inform medical judgment. Our commitment also acknowledges the very great contribution made by the individuals who participate in clinical research. All those involved in the conduct and publication of clinical research, whether healthcare companies like GSK, academia or research organisations, have a role to play in ensuring that the data they generate are made publicly available to help bring patient benefit.”

Separately, in October 2012, and going further than the call made by the AllTrials campaign, GSK announced it would develop a system where researchers will be able request access to detailed anonymised patient level data that sit behind the results of clinical trials to enable additional scientific inquiry and analyses to help further scientific knowledge.

Response to GSK statement from Tracey Brown, Director, Sense About Science

6th February 2013

“GSK signing up to the campaign is very important, of course, because they are a large global player in clinical research so they have a lot of potentially useful information to share, but also because they are finding a way to put in place the infrastructure needed to do this. Which makes it realistic for others and sets a new standard. Their position will also make it possible to have a sensible discussion with regulators about the way that they make information available. And it will hopefully put a stop to the ridiculous obfuscation and foot-dragging that have characterised reactions to AllTrials from some other parts of industry.

I think that since AllTrials went live it is becoming clearer by the day that this is moving in only one direction, as thousands of doctors, researchers and members of the public signed up and organisations have joined them. It’s clear from their statement about the practical details that GSK has been thinking about this issue for some time; AllTrials’ influence has really been in getting the decisive public commitment.

GSK say in their statement that they owe it to patients who have taken part in their trials. I think that is very, very true. Companies who have yet to take this seriously should ask themselves where they want to be on that duty a few years from now.”

3. Roche statement on new process for accessing clinical trial data and our response

26th February 2013

Roche launches new process for accessing clinical trial data

Independent body to grant access to patient-level data for scientific review

Roche today announced that it is expanding access to its clinical trial data for third party researchers. Roche will work with an independent body of recognised experts to evaluate and approve requests to access anonymised patient-level data. Roche will support the release of full clinical study reports (CSRs) for all its licensed medicines via regulatory authorities and make available any CSRs that cannot be provided by these authorities upon a researcher's request.

“We understand and support calls for our industry to be more transparent about clinical trial data with the aim of meeting the best interests of patients and medicine,” said Daniel O’Day, Chief Operating Officer of Roche Pharma. “At the same time, we firmly believe that health authorities need to remain the gatekeeper for drug assessment and approval. We believe we have found a way in which patient data can be provided to third party researchers in a legitimate environment that ensures patient confidentiality and avoids the risk of publishing misleading results or giving rise to public health scares and consequences.”

Roche continues to provide all information requested by health authorities who approve medicines for patient use. Public access to results from clinical trials is also provided via rochetrials.com and clinicaltrials.gov in a summary form. Roche will also submit results to the European Union database, EudraCT as soon as this public archive becomes operational.

Roche is supporting the European Medicines Agency (EMA) in its commitment to the proactive publication of data from all clinical trials supporting the authorisation of medicines. Roche is a member of one of the EMA advisory groups working on the new EMA data access guidelines. The policy is scheduled to come into force early 2014.

Amendments to the Roche data transparency policy include:

Access to patient data sets: An independent body will assess the scientific validity of requests for anonymised patient-level data, with the requested data made available within a secure system following agreement. Access to patient data will be available for those clinical trials which have been submitted together with an application for a medicine's registration and will be available after the completion of regulatory reviews in the U.S. and European Union. This process will come into effect in 2013. Roche is in discussions with other pharmaceutical companies to see if this can be an industry-wide initiative.

Access to CSRs: Roche supports the release of full CSRs, summaries and safety updates for its approved medicines by the EMA. In line with relevant country or regional laws, this information will

be edited in consultation with Roche to ensure patient confidentiality and to protect legitimate commercial interests, including intellectual property rights. Roche will provide any CSR on request that cannot be obtained from the EMA for third party researchers with this specific process coming into effect by April 2013. This will enable access to all Roche CSRs for researchers.

Tamiflu (oseltamivir) data

Roche acknowledges the specific public interest in data transparency concerning the antiviral Tamiflu. Health authorities worldwide have received all the information they have requested regarding Tamiflu.

Of 74 completed Roche sponsored Tamiflu trials, 71 (or 96%) are in the public domain either as a primary publication or secondary publication or on rochetrials.com. Arrangements are underway for the three sponsored trials which are completed but not yet in the public domain to be posted.

Roche supports a fair, transparent and independent way of addressing data transparency regarding Tamiflu. To do this, a MUlti-party Group for Advice on Science (MUGAS) will be set up by four renowned scientists in the field of influenza to look at data on Tamiflu, identify any unanswered questions and agree on a statistical analysis plan. Following an agreement, Roche will provide access to all requested Tamiflu clinical trial data for the analyses.

The four scientists will invite independent experts and third parties to their meeting, which is scheduled to take place in June. The four scientists are Prof Albert Osterhaus, Erasmus Medical Centre Rotterdam; Prof Menno De Jong, Academic Medical Centre Amsterdam; Prof Arnold Monto, University of Michigan and Prof Richard Whitley, University of Alabama.

Response to Roche statement form Tracey Brown, Director, Sense About Science

26th February 2013

“Does Roche expect applause for announcing that it will continue to keep clinical trial findings hidden? They’re on another planet. Thousands of people are calling for all clinical trials to be registered and the findings published. Patients, researchers and practitioners are petitioning organisations and regulators for change all over the world. Just today the UK’s Health Research Authority signed up, joining a throng of research organisations, regulators, patient groups and professional bodies. GSK has announced that it will publish all the CSRs available since its formation as a company. That is genuine progress and an answer to patients who participated in those trials. Roche’s response is poor. Which bit of All and Trials do they not understand?”

4. ABPI statement on new clinical trial transparency measures

27th February 2013

ABPI announces new clinical trial transparency measures

The ABPI has today announced that it will put in place measures to monitor compliance to the clinical trial transparency provisions contained in the ABPI Code of Practice. An independent, third party service provider will be appointed to undertake this work, and the ABPI will take on the responsibility for reporting to the PMCPA non-compliance with trial registration and posting of summary results.

These measures support the current requirement in the ABPI Code of Practice which stipulates that current and future trials must be registered within 21 days of enrolling the first patient, and results must be published within one year of marketing authorisation or one year from completion for marketed products.¹

From quarter three this year, a new toolkit is also to be introduced that will provide good practice guidelines, compliance checklists and template standard operating procedures for pharmaceutical companies.

In addition, the ABPI will host a series of workshops with all relevant stakeholders to explore how best to address the issue of historical data, and disclosure requirements, to meet two distinct needs – firstly, improve transparency for patients, public and health care professionals in general and secondly, access to the relevant data that are necessary for the advance of certain types of research.

Commenting, Stephen Whitehead, Chief Executive of the ABPI, said:

“The ABPI is a strong advocate for transparency in clinical trial data and so I am pleased to announce the introduction of new measures which will encourage greater compliance. Hiring a third party provider to ensure that companies fulfil their obligations in the ABPI Code of Practice to register clinical trials and publish summary results, is a significant step and illustrates how seriously we take this issue.”

“On the issue of historical data we also want to ensure that we work collaboratively with all health stakeholders and international colleagues to agree a pragmatic approach which is in the interests of patients while protecting the commercial research model. The pharmaceutical industry has always accepted that making data more transparent is important, but all parties must now decide together how exactly this is achieved.”

¹ Specifically, these measures support the current ABPI Code of Practice which requires in Clause 21.3 disclosure of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication

of Clinical Trial Results in the Scientific Literature. The joint positions include requirements that current and future trials must be registered within 21 days of enrolling the first patient, and results must be published within one year of marketing authorisation or one year from completion for marketed products.

Written evidence from PLOS (CT20)

Executive Summary

1. Clinical trials on humans cannot be considered as private undertakings, since they require the participation of human volunteers. However, it has become the norm for information generated from commercially sponsored trials to be held as private by default with the release of much of this information happening only according to commercial needs and in way that is dictated by the sponsors. There is now substantial evidence of harm as a result of this withholding of clinical trial data.
2. Mechanisms are in place or under discussion that could ensure all clinical trials are tracked and data from them are made available. However, these mechanisms are not currently complied with, legally mandated nor sufficiently enforced.
3. This is an international problem, but one in which the UK could usefully show leadership by mandating registration of all trials in a World Health Organization (WHO)- or International Committee of Medical Journal Editors (ICMJE)-approved registry, prospectively requiring reporting of all data from ongoing and future trials within a specific time frame after completion, as well as requiring release of data from previously completed trials.

Background on PLOS

4. PLOS is a not-for-profit organisation headquartered in San Francisco, USA with an office in Cambridge, UK, with a mission to transform scholarly communication. PLOS publishes peer-reviewed research papers in the science domain with a focus on biomedical sciences.
5. PLOS publishes seven journals: two highly selective journals, *PLOS Medicine* and *PLOS Biology*; four community journals, which are based on a publishing model that is similar to journals published by scholarly societies and focus on specific domains of Computational Biology, Genetics, Neglected Tropical Diseases, and Pathogens; and *PLOS ONE*, the world's largest journal, which publishes across science and medicine.
6. PLOS applies the Creative Commons attribution license (CC-BY [1]) by default to all the content it publishes. Under this Open Access (OA) agreement, all the papers it publishes are freely and immediately available to read and, crucially, to reuse.
7. Since publishing its first articles in 2003, PLOS has seen phenomenal growth. In 2012, *PLOS ONE* published more articles registered in the PubMed bibliographic database as being funded by the Wellcome Trust, Medical Research Council (MRC), Biotechnology and Biological Sciences Research Council (BBSRC), Cancer Research UK (CRUK), Canadian Institutes of Health Research, and the US National Institutes of Health (NIH), than any other journal. PLOS published 11% of all Wellcome Trust research in 2012, 9.3% of CRUK, 8.5% of BBSRC, and 6.9% of MRC. PLOS has published many hundreds of trials since it began publishing in 2003.
8. PLOS is a leader in high-quality peer-review processes. All of the journals are peer reviewed, and PLOS applies the highest ethical standards to the peer review and publishing process. For instance, unlike most other biomedical publishers, PLOS journals do not accept advertising for drugs or devices. PLOS has also taken a leadership role in promoting higher reporting standards and reproducibility of research.

Declaration of Interests

9. PLOS publishes clinical trials in several of its journals. We have specifically stated we are interested in publishing clinical trials regardless of outcome; this and any mandate for clinical trial reporting are likely to lead to increased numbers of papers being submitted to our journals and potentially more income. To provide Open Access, PLOS journals use a business model in which expenses—including those of peer review, journal production, and online hosting and archiving—are recovered in part by charging a publication fee to the authors or research sponsors for each article they publish. The fees vary by journal. PLOS offers to waive or reduce the payment required of authors who cannot pay the full amount. Editors and reviewers have no access to information on authors' ability to pay; decisions to publish are based only on editorial criteria [2].

10. PLOS has also publicly supported the AllTrials campaign [3], which calls for all trials to be registered and all results reported. Our position in this area is therefore well known.

The Committee sought submissions on the following questions:

- a) 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?
 - b) What is the role of the Health Research Authority (HRA) in relation to clinical trials and how effective has it been to date?
 - c) What evidence is there that pharmaceutical companies withhold clinical data and what impact does this have on public health?
 - d) How could the occurrence and results of clinical trials be made more open to scrutiny? Who should be responsible?
 - e) Can lessons about transparency and disclosure of clinical data be learned from other countries?
11. We address points c-e in this submission.

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

12. There is substantial evidence that systematic bias exists within the published medical literature due to companies withholding clinical data [4]. This bias begins very early in the planning stages, in which trials and publications are planned in order for drugs to appear in as good a light as possible. "Positive" (e.g., reporting results favourable to the drug) trials are targeted at specific high-profile journals, and "negative" trials are either not published or are targeted at lower-profile journals [5] [6] [7].
13. The lack of negative trials in the literature was acknowledged by medical journals when in 2004 the ICMJE adopted a policy [8] that all trials should be registered in an approved registry before the first participant was enrolled, and unregistered trials would not be considered for publication

in these journals. This policy was applied to all trials initiated after July 1, 2005. Since then many other journals, including all the PLOS journals, have adopted this policy. Unregistered trials can have their results alone submitted to ClinicalTrials.gov [9]. However, a 2012 study showed that registration is not universal, and that, even if registered, the study's registration number is not always included in the journal report of a trial [10]. In addition, the quality of data included in the registry is highly variable and often not complete [11]. PLOS regularly receives submissions of unregistered trials; we reject these submissions along with a suggestion that the authors submit the results to ClinicalTrials.gov. We do not know the ultimate fate of these trials.

14. Many trials are not submitted for publication. A 2009 study showed that trials primarily sponsored by industry (40%, 144 of 357) were less likely to be published when compared with non-industry/non-government-sponsored trials (56%, 110 of 198) [12]. A study of a national registry – the Netherlands Trial Register – showed that 48% of trials registered in the NTR had not been published at least two years after completion [10].
15. Even if a trial is published, the results in a journal article are often a biased subset of the full dataset generated by the trial, and often skewed towards framing the intervention in a light favourable to the sponsor – an effect known as outcome reporting bias [13].
16. Currently, journals – especially high-profile journals – are more likely to receive for publication trials which are “positive”. A study of six high-profile general journals showed that industry-supported trials were more frequently cited than trials with other types of support, and publication of industry-supported trials was associated with an increase in journal impact factors, a favourable outcome for the journals [14]. These journals obtain a large proportion of their income from selling reprints of industry-sponsored trials [14] – a potential source of bias.
17. A downstream effect of the lack of negative trials in the published literature is that secondary analyses, such as systematic reviews and meta-analyses, will not include all relevant studies and may therefore inadvertently conclude overall evidence of benefit that would not have been found had all the trials, regardless of outcome, been included. This effect has been known and demonstrated statistically for many years [15], and has more recently been conclusively shown in a systematic review [13].
18. There are numerous examples of harms to the public that have resulted from the withholding of trial data. For example, harms to patients treated in routine practice may arise if the clinical approach is informed by incomplete data or leads to treatment with drugs for which the harms may have been evident from prior trials, but which have not been made public; harms may also occur if patients are treated with drugs that are ineffective or less effective than other treatments, information which could have been evident from trial data, but which had not been made public. Two prominent examples are the increased risk of death from myocardial infarction from the use of Avandia (rosiglitazone) [16], which was not apparent in initially published studies; and the increased risk of breast cancer from the use of menopausal hormone replacement therapy Prempro [17]. In these cases, the existence of much data came to light only after court cases in which many drug company documents were released. Many other examples exist.

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

19. To prevent the abovementioned sources of bias and potential patient harms, all steps in the information chain of clinical trials need to be as transparent and accessible as possible. This chain starts from the point of planning of trials and extends through to publication of trial reports in journals or elsewhere, and to the reports and data submitted to regulators.
20. Everyone involved in clinical trials therefore has a responsibility to examine the processes for which they are responsible to ensure that their part of the chain is transparent and the associated data are available. Thus, funders and sponsors of trials, those who run and report trials, those who publish trials and those who oversee trial registration and drug regulation all have a role. Currently there is insufficient oversight and regulation to ensure complete transparency for some parts of this chain.
21. Clinical trial registration for all trials, even early phase, if mandated by funders, regulators and journals, and if properly followed up and enforced, will ensure that all trials that are started are adequately tracked.
22. Trial registration needs to be coupled with a mechanism for the reporting of all trial results. This reporting can occur in the form of journal articles, but need not exclusively to be done this way. Alternative mechanisms, which are adequately resourced and overseen, should be put in place to allow reporting of clinical trials into a database.
23. Journals should publish articles reporting clinical trials based on the value of the question asked and the soundness of the methodology, not the direction of the results. Journals should require that trials are well reported, according to the accepted CONSORT criteria [18], should require submission and publication of protocols alongside articles reporting on trials and should have policies that require access to the data underpinning trials and provide a mechanism to link to such data.
24. In addition, the UK government should support the initiative of the European Medicines Agency (EMA) [19], which has stated that by 2014 it will release publicly clinical-trial data submitted as part of drug regulatory approval. This availability should, however, apply to drugs already submitted for approval, not just future drugs, and should include drugs for which approval was not granted.

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

25. Clinical trials are increasingly an international business. Although examples of good practices are available from other countries, it is also clear that regulatory differences among countries have in the past led to lack of transparency. Ideally, any new initiatives will not be limited to just one country.
26. One specific example is the requirement in the US, under Food and Drug Administration Amendments Act (FDAAA) legislation, for mandatory reporting on ClinicalTrials.gov of specified trials of summary clinical trial results within one year of completion of the trial. A 2012 study showed that only 163/738 (22%) had reported results in this way. Enactment of legislation without enforcement is obviously ineffective [20].

Recommendations for Government Action

27. Require prospective registration of all clinical trials of all phases in a WHO- or ICMJE-approved registry [21] with specific penalties for non-compliance.
28. Require reporting of all clinical trial results within a specific time frame after trial completion in a properly resourced public site with enforced penalties for non-compliance.
29. Support EMA initiatives to require release of clinical trial data related to all drugs submitted for marketing approval, both approved and unapproved, and for historical as well as forthcoming trials.

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References/Notes

1. PLOS (2013) Open-access license. Available: <http://www.plosmedicine.org/static/license>. Accessed February 20, 2013.
2. PLOS (2013) Publication fees. Available: <http://www.plos.org/publish/pricing-policy/publication-fees>. Accessed February 20, 2013.
3. AllTrials (2013) All trials registered – all results reported campaign. Available: <http://www.alltrials.net>. Accessed February 17, 2013.
4. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R (2008) Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 358:252-260. doi:10.1056/NEJMsa065779
5. Vedula SS, Li T, Dickersin K (2013) Differences in reporting of analyses in internal company documents versus published trial reports: Comparisons in industry-sponsored trials in off-label uses of gabapentin. *PLoS Med* 10(1): e1001378. doi:10.1371/journal.pmed.1001378
6. Sismondo S (2007) Ghost management: How much of the medical literature is shaped behind the scenes by the pharmaceutical industry? *PLoS Med* 4(9): e286. doi:10.1371/journal.pmed.0040286
7. Melander H, Ahlqvist-Rastad J, Meijer G, Beermann B (2003) Evidence b(i)ased medicine—Selective reporting from studies sponsored by pharmaceutical industry: Review of studies in new drug applications. *BMJ* 326: 1171. doi:10.1136/bmj.326.7400.1171
8. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, et al. (2004) Clinical trial registration: A statement from the International Committee of Medical Journal Editors. *N Engl J Med* 351: 1250–1251.
9. ClinicalTrials.gov (2013) Trial registry. Available: <http://www.clinicaltrials.gov>. Accessed February 20, 2013.
10. van de Wetering FT, Scholten RJPM, Haring T, Clarke M, Hooft L (2012) Trial registration numbers are underreported in biomedical publications. *PLoS ONE* 7(11): e49599. doi:10.1371/journal.pone.0049599

11. Viergever RF, Gherzi D (2011) The quality of registration of clinical trials. *PLoS ONE* 6(2): e14701. doi:10.1371/journal.pone.0014701
12. Ross JS, Mulvey GK, Hines EM, Nissen SE, Krumholz HM (2009) Trial publication after registration in ClinicalTrials.gov: A cross-sectional analysis. *PLoS Med* 6(9): e1000144. doi:10.1371/journal.pmed.1000144
13. Dwan K, Altman DG, Arnalz JA, Bloom J, Chan A-W, Cronin E, Decullier E, Easterbrook PJ, von Elm E, Gamble C, Gherzi D, Ioannidis JPA, Simes J, Williamson PR (2008) Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PLoS ONE* 3(8): e3081. doi:10.1371/journal.pone.0003081
14. Lundh A, Barbateskovic M, Hróbjartsson A, Gøtzsche PC (2010) Conflicts of interest at medical journals: The influence of industry-supported randomised trials on journal impact factors and revenue – Cohort study. *PLoS Med* 7(10): e1000354. doi:10.1371/journal.pmed.1000354
15. Egger M, Smith GD, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315: 629. doi:10.1136/bmj.315.7109.629
16. Nissen SE, Wolski K (2007) Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 356: 2457-2471. doi:10.1056/NEJMoa072761
17. Fugh-Berman AJ (2010) The Haunting of medical journals: How ghostwriting sold “HRT”. *PLoS Med* 7(9): e1000335. doi:10.1371/journal.pmed.1000335
18. CONSORT (2013) Home page. Available: <http://www.consort-statement.org>. Accessed February 17, 2013
19. European Medicines Agency (2013) Release of data from clinical trials. Available: http://www.emea.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&mid=WC0b01ac0580607bfa. Accessed February 17, 2013.
20. Prayle AP, Hurley MN, Smyth AR (2012) Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: Cross sectional study. *BMJ* 344: d7373. doi:10.1136/bmj.d7373
21. WHO (2013) International Clinical Trials Registry Platform. Available: <http://www.who.int/ictrp/network/primary/en/index.html>. Accessed February 20, 2013.

Written evidence submitted by Parkinson's UK (CT21)

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?

1. Parkinson's UK welcomes the proposed changes made by the European Commission to the Clinical Trials Directive. The proposed Clinical Trials Regulation appears to help overcome some of the barriers to conducting clinical trials in the UK and EU and addresses key criticisms of the Directive, such as reducing the administrative burden for clinical trials, clarifying the scope of clinical research so it is not interpreted differently across Europe, and introducing tight deadlines so clinical trials will not be delayed.
2. Introducing the concept of a low-interventional trial is an important step to adopting a risk based approach in clinical trials legislation. This would allow trials of medicines already authorised for use with minimal risk to go ahead more efficiently. This risk proportionate approach would recognise that the requirements associated with application and monitoring processes of a trial can be reduced for medicines with well-known safety profiles without compromising the safety of participants.
3. It is still unclear how the Regulation will reduce the requirements for trials of marketed products used for a new purpose, which are not included in the low-interventional trial category. Trials of these products are particularly important for Parkinson's research. Drug repositioning (finding new uses for previously authorised drugs) has great promise for quickly bringing new treatments to people with Parkinson's. Trials are currently underway to examine the effects of isradipine (an anti-hypertensive drug) and desferrioxamine (a drug to decrease blood iron levels) on Parkinson's. As these are drugs that are currently in routine clinical use in the UK, it is vital that any beneficial effects are translated as fast as possible into the clinical arena.
4. A single application portal with a single application dossier is particularly attractive to streamlining and harmonising the application process for clinical trials. This will reduce the administrative work of sponsors who would otherwise have to submit the same documentation to all the Member States separately.
5. Efficient operation of the IT systems associated with a single European portal will be crucial to the success of all of the measures set out in the Regulation. The Commission should outline how it will go about creating and implementing the IT systems associated with the Regulation.
6. We strongly support the provision that the patients' views must be sought in this process – it is crucial in order to assess the relevance of the trial to patients' needs, and to obtain an accurate risk-benefit assessment. Patients, who ultimately bear the personal risks of participation in research, have the right to be involved in assessing its risks. They may be more willing to take up higher risks for different benefits, such as quality of life. For example, Parkinson's UK surveyed our Research Support Network to ask if having to have a lumbar puncture (*spinal tap*) would stop them from taking part in a drug trial. Whilst 50.4% of respondents agreed that it would put them off, 29.8% responded that they would still take part despite this invasive procedure. One respondent commented, "A lumbar puncture is nothing compared to slogging it out with Parkinson for 11 years plus". Whilst another respondent said "Depends on whether the drug trial would be likely to make substantial strides towards a cure". Patients with serious conditions will very often have a different perception of risk compared to that of investigators or regulators.

7. Patient involvement is also shown to contribute to better protocol design and the identification of new issues that researchers may not have considered. These can include for example practical questions such as treatment schedules or transportation that may affect patients' participation and drop-out rate.
8. We welcome the provision for the publication of summary results of trials, but this should be more strongly and precisely framed. We recommend that clear standards should be developed for what the summary needs to contain e.g. descriptions of the methodology, the way the researchers eliminated or minimised biases, blinding and randomisation arrangements etc. These standards should be developed with the involvement patient organisations and researchers, to ensure they address all groups' information needs.

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

9. The process of obtaining research permissions from NHS Trusts has been identified as a significant barrier to research projects and trials in the UK, introducing delays and increasing costs. This process remains the responsibility of NHS providers which can result in submitting separate applications at each site. We welcome action taken by the NIHR and HRA to streamline this process.
10. We welcome the role of the Health Research Authority (HRA) to promote a unified and fair approach for approving research and producing standards for compliance for researchers.
11. As the HRA has only been in place since December 2011, we feel it is too soon to identify how effective it has been to date with regards to enabling clinical trials to take place.
12. Metrics will need to be developed to measure the effectiveness of the HRA. Researchers and patient organisations should also be consulted to gain an understanding of the level of the HRA's effectiveness.

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

13. It is crucial to research that there is transparency regarding how trials are conducted. Ensuring results are published provides essential information to future research, helping researchers learn and make further advances. Data from trials must be published to help future research build on results and improve treatments based on new discoveries. For example, recently the British Biotech company Phytopharm announced their new Parkinson's drug Cogane failed in Phase 2 clinical trials. In week 28 participants taking Cogane showed no benefit compared to those taking a placebo. Whilst these results are disappointing, they have been crucially been made public for scientists, professionals and people affected by Parkinson's so they are available for others to learn from.

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

14. Pharmaceutical companies should have a legal responsibility to publish all trial data regardless of findings. However, it is important that the data is published in a useful format. For example, ensuring confidentiality issues are adhered to and published results should be clear and accessible.

15. The EU Clinical Trials Regulation should include measures that ensure registration and reporting of trials takes place.
16. The HRA should work alongside other bodies to ensure transparency.

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

17. We are currently unaware of other countries having improved transparency protocols. As we all come under the EMA umbrella, our national agencies fall under the same level of European law regarding disclosure. We are not aware of any that insist on the release of more data than is required by law.

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Written evidence submitted by Glyn Moody (CT22)

1. My name is Glyn Moody, and I am a journalist who has been writing about technology for over 30 years. More recently, I have been exploring the advantages of openness – notably open source (such as GNU/Linux), open content (Wikipedia, for example), and open data. My perspective is therefore from an open data, rather than a clinical viewpoint. I have no interests to declare.
2. In general, open data brings a number of benefits. It automatically increases transparency, it allows data to be used in new ways, and can also generate new economic activity. I believe that all of these are possible if clinical trials information were made available as open data.
3. Of these, transparency is perhaps the most important, because in this case it will save many lives and much money. Given the exhaustive treatment of this issue by Ben Goldacre in his book "Bad Pharma", referred to on the Inquiry's home page, I won't repeat details here. I would, however, like to mention the particularly egregious case of Roche's Tamiflu. As the Committee will know, this has provoked a letter from a group of MPs to the Public Accounts Committee to request action on hidden trials and Tamiflu.
4. This paragraph captures their - and my - concerns: "There are failings at every level, from ethics committees which allow trials to proceed without insisting on data being published, to organisations like the National Institute for Clinical Excellence and the European Medicines Agency which do not insist on receiving all the evidence – and then making it available to all interested medical researchers – before granting regulatory approval for drugs, appliances and implants. Sharing information can be a very powerful way to protect patients, because then “many eyes” can be brought to bear on what are often complex questions. Problems with Rosiglitazone, Tamiflu, Vioxx, and many devices were spotted by the global community of independent academics, rather than by individual countries’ regulators acting behind closed doors.

Most manufacturers claim they release data. However, unless they publish relevant data in a form accessible to UK regulators and researchers, it may be useless or incomplete."

5. In the light of this widespread lack of transparency, I would therefore like to urge that the UK require drug companies to make available the full clinical study reports as well as the raw data (but only in an anonymised form, of course.)
6. The benefits would be many. As well allowing external experts such as the Cochrane Collaboration to examine the data, and to combine it with information from elsewhere to produce statistically significant results, making the data available would allow many other uses, including commercial ones that would produce further benefits for healthcare in this country, as well as boosting its leading position in the open data world thanks to the Open Data Institute.
7. There is no justification for not providing this information. It is based on research carried out with public volunteers, who have placed themselves and their health at the disposition of drug companies in the expectation that the greatest benefit for society would result. Withholding the anonymised data is a betrayal of that trust, and is motivated by purely selfish reasons on the part of the pharmaceutical industry, which we now know has much to hide about the medicines we have been taking. The recent scandals involving high-profile players demonstrates that the current system does not work; instead we must have real transparency in the form of clinical trials information released as open data.

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Evidence submitted from the Editor and Deputy Editor of the British Medical Journal (CT23)

The BMJ (British Medical Journal) appreciates the opportunity to contribute to this inquiry. We would be pleased to also provide oral evidence if necessary, and we look forward to the Committee's conclusions.

Here is our response to the Committee's questions:

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?

1.i. Not entirely, although the revisions will greatly improve the regulation of clinical trials (Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. European Commission. 2012 http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal). We agree with Dr Peter Gøtzsche of the Nordic Cochrane Centre, whose recent peer reviewed article in the BMJ said "The new European Union Regulation on Clinical Trials ... aims to simplify the process for application and approval of trials and make it more uniform throughout the EU. It also includes a lighter regime for low risk trials—for example, those using licensed medicines. It contains much good sense, but there are still deficiencies in providing access to information and protection to patients" (Gøtzsche PC. Deficiencies in proposed new EU regulation of clinical trials. BMJ 2013;345:e8522 doi: <http://dx.doi.org/10.1136/bmj.e8522>).

1.ii. How the EU regulation will improve applications and approvals for drug trials:

- It provides for a single EU portal for applications, set up and maintained by the European Commission
- It allows lighter regulation for low risk trials
- All application information will be publicly accessible unless confidentiality is justified to protect personal data or commercially confidential information
- Summary results must be reported to the single EU database (which will be controlled by the European Commission) within one year of the end of the trial
- Each trial protocol should include a description of the publication policy for results
- All information given to trial participants, including the form for informed consent, must be included in each application

1.iii The BMJ endorses Gøtzsche's evidence based recommendations for further amendments to the proposed EU Regulation on Clinical Trials, as summarised here:

- Citizens' right to know should override commercial confidentiality. The EU database will contain no personal data on trial participants, and the European ombudsman has declared that there is no commercially confidential information in trial protocols or clinical study reports. Patients volunteer for research to benefit society and future patients, not to benefit industry
- Results and data should be provided within one year after trial completion, with no exceptions. The current proposal for the EU Regulation allows for postponement for substantiated "scientific reasons"
- Violations of the one year deadline should be punished
- A public audit process should be established
- Clinical study reports, raw anonymised patient level data, and statistical codes should be published on the portal, not simply summaries of results
- Trial protocols should be easily accessible and all amendments should be dated and submitted to the EU portal
- The protocol should contain the full statistical analysis plan and case report forms
- The scientific and ethical justification for a trial should be based on a systematic review of similar trials, whether registered or not. Many old, unregistered trials are highly relevant for evaluating the scientific and ethical justifications for new trials
- Trial populations should be similar to the populations expected to use the drug
- Certificates of analysis of both active drugs and any placebos should be submitted together with visual records (images): even in "double blind" trials active drugs and placebos sometimes differ in texture, colour, and size and the study is not truly blinded
- The consent form for trial participants should state that all results and anonymised trial data will be made publicly available within a year after the end of the trial
- The clinical trial master file should be stored indefinitely (not just for the proposed five year period), in preserved electronic formats: data may be essential for interpreting trial results or for litigation at any time in the future
- All serious adverse events - including those occurring in trials conducted outside the EU - should be reported without delay. The current proposal for the EU Regulation requires sponsors to report adverse events that affect the benefit-risk balance, but only if these events are unexpected and only from trials in the EU
- Patients should be followed up closely for some time after they come off a trial drug. Such follow up is not currently provided for in the proposal.

All of the above points come from this detailed article: Gøtzsche PC. Deficiencies in proposed new EU regulation of clinical trials. *BMJ* 2013;345:e8522 doi: <http://dx.doi.org/10.1136/bmj.e8522>.

2. WHAT IS THE ROLE OF THE HEALTH RESEARCH AUTHORITY (HRA) IN RELATION TO CLINICAL TRIALS AND HOW EFFECTIVE HAS IT BEEN TO DATE?

2.i The HRA is relatively new and is finding its feet. However, we are encouraged by the statements made by Janet Wisely of the HRA's National Research Ethics Service about how she plans to monitor compliance on registration and reporting of the results of trials. <http://www.bmj.com/content/345/bmj.e7304/rr/613776>

2.ii We would recommend that the NRES and HRA take a firm line against trialists and sponsors who fail in their responsibilities to publish the results of trials, and that any failures to comply should be sanctioned by withholding ethical approval on future trials until results are fully reported.

3. WHAT EVIDENCE IS THERE THAT PHARMACEUTICAL COMPANIES WITHHOLD CLINICAL TRIAL DATA AND WHAT IMPACT DOES THIS HAVE ON PUBLIC HEALTH?

3.i. What evidence is there? As the BMJ states at <http://www.bmj.com/open-data>, hidden clinical trial data are systematically undermining doctors' ability to prescribe treatment with confidence. Many widely used drugs across all fields of medicine have been represented as safer and more effective than they are, endangering people's lives and wasting public money. It is well documented that researchers and companies often withhold clinical trial results from doctors and patients. Half of all trials are never published (Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ, Hing C, Kwok , Pang C, Harvey I. Dissemination and publication of research findings: an updated review of related biases. Health Technology Assessment 2010; Vol. 14: No. 8). In many cases—such as those of oseltamivir (Tamiflu) and rimonabant—direct requests for information about trials have been refused. The US government's requirements for timely reporting of clinical trial results at its register <http://www.clinicaltrials.gov/> have been ignored by the authors and sponsors of four out of five eligible trials. Numerous studies have shown strong evidence of publication bias, where unfavourable or negative results are not published.

3.ii. The BMJ has shown, through publishing research, investigative journalism, and commentaries, that current knowledge about the effectiveness and safety of specific medicines and medical devices is seriously incomplete. Doctors cannot always make fully informed and accurate decisions about which tests and treatments to offer their patients. Well documented cases in which hidden clinical trial data have had or may have serious consequences for human health include the cases of these drugs:

- paroxetine (GSK) (Lenzer J. Manufacturer admits increase in suicidal behaviour in patients taking paroxetine. BMJ 2006; 332 doi: <http://dx.doi.org/10.1136/bmj.332.7551.1175>)
- oseltamivir (Roche) (Doshi, P. Neuraminidase inhibitors - the story behind the Cochrane review. BMJ 2009;339:b5164 doi: <http://dx.doi.org/10.1136/bmj.b5164>)
- reboxetine (Pfizer) (Wieseler B, McGauran N, Kaiser T. Finding studies on reboxetine: a tale of hide and seek. BMJ 2010;341:c4942 doi: <http://dx.doi.org/10.1136/bmj.c4942>)
- rosiglitazone (GSK) (Cohen D. Rosiglitazone: what went wrong? BMJ 2010; 341 doi: <http://dx.doi.org/10.1136/bmj.c4848>)
- rimonabant (Sanofi-Aventis) and orlistat (Roche) (Gøtzsche PC, Jørgensen AW. Opening up data at the European Medicines Agency. BMJ2011;342:d2686 doi: <http://dx.doi.org/10.1136/bmj.d2686>).

3.iii. What impact does withholding clinical trial data have on public health?

This is not simply an academic matter. Missing data about the risks of medical interventions in trials can skew the evidence base (body of knowledge) that drives medical practice and policy, can harm patients by exposing them to drugs and devices that may be less effective and safe than we currently think, and can lead to futile priority setting and expense by health systems. Moreover, researchers or others who deliberately conceal trial results have breached their ethical duty to trial participants. A BMJ editorial last year said: “Concealment of data should be regarded as the serious ethical breach that it is, and clinical researchers who fail to disclose data should be subject to disciplinary action by professional organisations. This may achieve quicker results than legislation in individual countries, although this is also desirable” (Lehman R, Loder E. [Missing clinical trial data](#). BMJ 2013;343:d8158 doi: <http://dx.doi.org/10.1136/bmj.d8158>).

Fiona Godlee, editor in chief of the BMJ, was coauthor of the briefing note at www.alltrials.net on missing trial data.

3.iv One key example is that of the neuraminidase inhibitors oseltamivir (Tamiflu). In 2009, during the swine flu (H1N1 influenza) pandemic, the BMJ published an updated Cochrane review on neuraminidase inhibitors in adults with influenza (Jefferson T, Jones M, Doshi P, Del Mar C. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review

and meta-analysis. BMJ 2009;339:b5106).The review and a linked investigation undertaken jointly by the BMJ and Channel 4 News cast doubt not only on the effectiveness and safety of oseltamivir (Tamiflu), but also on the system by which drugs are evaluated, regulated, and promoted, which is giving doctors, patients, and the public a false sense of security (Cohen D. Complications: tracking down the data on oseltamivir. BMJ2009;339:b5387). Jefferson et al concluded that they had no confidence in claims that oseltamivir reduces the risk of complications and hospital admission in people with influenza. In doing so they reached a similar conclusion to the Food and Drug Administration in the United States and a health technology assessment performed for the UK's National Institute for Health and Clinical Excellence (NICE), which both found insufficient evidence on complications. Yet claims that oseltamivir reduces complications have been a key justification for promoting the drug's widespread use. Governments around the world have spent billions of pounds on a drug that the scientific community has found itself unable to judge. The BMJ has made public key correspondence with the drug's manufacturer, Roche, and with international organisations that recommend or regulate drugs (<http://www.bmj.com/tamiflu>). Currently:

- The World Health Organization (WHO) recommends Tamiflu, but has not vetted the Tamiflu data.
- The European Medicines Agency (EMA) approved Tamiflu, but did not review the full Tamiflu dataset.
- The US Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Control and Prevention (ECDC) encourage the use and stockpiling of Tamiflu for influenza epidemics, but have not vetted the Tamiflu data.
- The majority of Roche's Phase III treatment trials of oseltamivir remain unpublished over a decade after completion.
- In Dec 2009 Roche publicly promised independent scientists access to "full study reports" for selected Tamiflu trials but, to date, the company has not made even one full report available.

4. HOW COULD THE OCCURRENCE AND RESULTS OF CLINICAL TRIALS BE MADE MORE OPEN TO SCRUTINY? WHO SHOULD BE RESPONSIBLE?

4.i. Governments: Voluntary agreements have been shown to be ineffective in achieving transparency on the results of clinical trials. Calls for greater transparency have been made for the past 20 years with little visible effect. Where individuals have made important strides, as for example 20 years ago at GSK, a change of leadership at an organisation can reverse any temporary gains. Legislation is the only certain way of mandating publication of trial results. This should be enacted at the European

level. Experience at the FDA shows that legislation is not in itself enough. Rigorous audit and sanctions for trialists and sponsors who fail to comply will also be needed.

4.ii Regulators: The European Medicines Agency (EMA) announced in November 2012 that, from 1 January 2014, it would proactively publish all clinical study reports in order to allow reanalysis of clinical trial data by stakeholders. The BMJ sees this as a major and essential step towards improving the evidence base for medicine and healthcare. At the moment, the EMA's policy is the only ray of light on a dark horizon. Working through the detail of how it will work, and fighting off attempts to block the policy, will require steadfast support from all parties interested in the public good.

4.iii Ethics committees: As mentioned above, ethics committees have an important role to play but have not so far seemed able to live up to their responsibilities. It should be a pre-requisite of approval that trials will be registered and the results published in a timely manner. Ethics committees need to be charged with auditing compliance and should be required to report to the HRA any trials that fail in this regard. Approval of further trials by the same trialists or sponsors should then be withheld until the results of completed trials are reported in full.

4.iv Study sponsors and funders: It should be their legal responsibility to register and report the results of all trials they have sponsored. They should withhold some of the funds until the results have been published, as the UK HTA does to good effect.

4.v Investigators: It is or should be ultimately the principle investigators responsibility to ensure that the trial is registered and the results made public in a timely manner. The extent to which this might be enshrined in legislation is obviously a matter for consideration.

4.vi Journals: Journals can and should act as advocates for transparency and integrity in medical science. Through its open data initiative the BMJ aims to achieve appropriate and necessary independent scrutiny of data from clinical trials (<http://www.bmj.com/open-data>). Working with others, we seek to highlight the problems caused by lack of access to data and to call for and support ways to release the data. Journals can also apply pressure directly on trialists and sponsors who still value publication in a journal for academic and marketing purposes. To this end, the BMJ announced in January 2013 that we will no longer publish any trial of drugs or devices where the authors do not commit to making the relevant anonymised patient level data available upon reasonable request. Whether or not a request is reasonable will be adjudicated by readers of the BMJ through our rapid response system. Those making the request will be asked to post an account of what they wish to do with the data, and the trial's authors will be asked to respond, giving details for any refusal.

4.vii. campaigners: The BMJ is a joint founder of the current AllTrials campaign (<http://www.alltrials.net/>). The campaign calls on governments, regulators, and research bodies to ensure that the aims and methodological details of all clinical trials, past and present, are publicly registered and their full methods and results reported. By 19 February 2013, just over a month after launch, the AllTrials online petition had more than 30,800 signatories including many international organisations concerned with medical research and treatments and more than 80 patients' organisations (<http://www.alltrials.net/supporters/>).

4.viii If all of the above fails, pharmaceutical and medical device companies should be prevented from evaluating their own products. A central fund could be established, as exists in Italy, into which companies would pay if they wanted their drugs to be licensed. The fund would be used to support independent phase 3 and 4 trials comparing new treatments with existing treatments. For more on how such a system might work, read Garattini S, Chalmers I. BMJ 2009;338:b1025. BMJ 20<http://www.bmj.com/content/338/bmj.b1025>

5. CAN LESSONS ABOUT TRANSPARENCY AND DISCLOSURE OF CLINICAL DATA BE LEARNED FROM OTHER COUNTRIES?

It is not clear that any country has cracked the problem of hidden clinical trial data. (Major discrepancies in how regulators in different jurisdictions interpret the clinical trial data available to them is itself a sign of how mad the current situation is – see Doshi P. Neuraminidase inhibitors: the story behind the Cochrane review. BMJ 2009;339:b5164). The USA has taken the legislative route but has so far failed to enforce the law adequately. Other countries have retained a voluntary approach but with variable and mainly little effect. This is why the EMA's recent announcement has been greeted with such enthusiasm, and why it is essential that we all give the EMA as much support as possible in working through the difficult issues it will face in delivering on its promise. Italy has shown innovative thinking in setting up a fund for supporting independent head to head trials, drawn from a proportion of the marketing revenues of pharmaceutical companies. This is an approach that other countries should consider.

Submitted by:

Dr Fiona Godlee, Editor in Chief, BMJ, and Dr Trish Groves, Deputy Editor, BMJ.

Dr Fiona Godlee has been Editor in Chief of the BMJ since 2005. She qualified as a doctor in 1985, trained as a general physician in Cambridge and London, and is a Fellow of the Royal College of Physicians. Since joining the BMJ (British Medical Journal) in 1990 she has written on a broad range

of issues, including the impact of environmental degradation on health, the future of the World Health Organisation, the ethics of academic publication, the problems of editorial peer review, and the need for greater openness in medicine and research. In 1994 she spent a year at Harvard University as a Harkness Fellow evaluating efforts to bridge the gap between medical research and practice. On returning to the UK, she led the development of BMJ Clinical Evidence, which evaluates the best available evidence on the benefits and harms of treatments and is now provided worldwide to over a million clinicians in 9 languages. In 2000 she moved to Current Science Group to establish the open access online publisher BioMed Central as Editorial Director for Medicine. In 2003 she returned to the BMJ Group to head up its new Knowledge division. She has served as President of the World Association of Medical Editors (WAME) and Chair of the Committee on Publication Ethics (COPE) and is co-editor of Peer Review in Health Sciences.

Dr Trish Groves is Deputy editor, BMJ and Editor-in-Chief, BMJ Open. Trish qualified in medicine and psychiatry before moving to the BMJ in 1989. Trish leads the team that peer reviews original research and articles on research methods, and is responsible at both BMJ and BMJ Open for policies on open access and sharing of raw research data from studies. She has been a member of the council of the Committee on Publication Ethics and of international groups including those developing guidelines on transparent reporting of clinical trials and trial protocols (CONSORT2010, SPIRIT); those working with the European Medical Research Councils and European Science Foundation on the effectiveness of medical; and the IDEAL collaboration that is developing stronger surgical research methods and is working with the US FDA devices division on improving regulatory pathways.

The BMJ: The BMJ (British Medical Journal) is an international peer reviewed medical journal published online at bmj.com with more than 14.5m unique users internationally (1.6m unique users a month). It also appears in weekly print and iPad editions. The print BMJ's weekly circulation is 122,000, of which 10,000 copies are distributed outside Britain. International editions reach another 55,000 readers. The BMJ has been published without interruption since 1840. The journal's mission is to lead the debate on health and to engage, inform, and stimulate doctors, researchers, and other health professionals in ways that will improve outcomes for patients. We aim to help doctors worldwide to make better decisions.

Conflicts of interest: Both authors of this statement are full time editors employed by the BMJ. A small proportion of our remuneration is affected by the performance of the journal and the publishing group, which could in a very small way be boosted by the success of the BMJ's open data campaign. Both authors are long standing advocates for transparency in research and for open access to peer reviewed research.

February 2013

Joint written evidence submitted by Cardiff University School of Medicine and Cardiff and Vale University Health Board (CT24)

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?

1.1. Anything that makes the setting up and undertaking of clinical research should be applauded. The changes may marginally help low risk drugs or biosimilars, but we have concerns that they do not address the fundamental problem of extremely costly overregulation. Every small change still has to go through a 4week review process and the paper trail will be as immense. The plan to introduce a "lighter regimen" for low risk studies is welcome but the proposals could have gone further. The restriction that "...investigational medicinal products are used in accordance with the terms of marketing..." could have been more generous. We have a phenomenal amount of knowledge of drugs by the time they have gone off patent and a less regulated way of using a drug in a slightly different way to the "terms of marketing" should be accepted, especially as such a change would still have to be approved by a REC.

1.2. For already licensed medications with many years of usage in clinical populations there is still a level of approvals and monitoring burden in excess of that needed for safety purposes. This hampers our ability to ensure that what is used in practice is evidence based. We are still in the situation where a clinician can chose between treatments in a relatively arbitrary way (possibly influenced by drug representative), but if they were to randomise between two treatments they would have to go through approximately 6 months of approvals. The example given in Goldacre's book is of comparing two statins, but there are similar prescribing choices being made every day on a poor evidence base and we cannot address this unless we find a new governance approach for this type of study.

1.3. There remains a view that a fundamental re-think and re-engineering of the approval and monitoring process is required and until this is done, opportunities for improved patient care and economic income will continue to be lost. One colleague favours a model of approval of Clinical Trials and monitoring by a "Responsible Officer" (like a building of fire safety inspector) as is done for many if not most other high risk activities (radiation protection, data protection, hygiene etc) but there may be other options. A major concern is the delay at individual NHS Organisation R&D offices. Monitoring and publishing individual institution performance would be likely to help.

2. WHAT IS THE ROLE OF THE HEALTH RESEARCH AUTHORITY (HRA) IN RELATION TO CLINICAL TRIALS AND HOW EFFECTIVE HAS IT BEEN TO DATE?

2.1. The HRA is positively perceived but felt to be moderately effective with no major impact in Wales to date. It is felt that some studies that have been adopted - certainly in the cancer field - have been poorly scrutinised and are virtually impossible to deliver in large parts of the NHS.

3. WHAT EVIDENCE IS THERE THAT PHARMACEUTICAL COMPANIES WITHHOLD CLINICAL TRIAL DATA AND WHAT IMPACT DOES THIS HAVE ON PUBLIC HEALTH?

3.1. It is felt that this goes on, more in smaller companies than major Pharma, but that it also happens in the academic sector. The danger to future patients is that if a trial fizzles out because of toxicity and it is not recorded a repeat could happen (e.g. Northwick Park). The option not to submit a final report should be removed. One local investigator reports having seen areas where the reporting clinician of a certain adverse event wishes to register a particular AE as "possibly or probably" related to a given drug but the sponsor hasn't been completely in agreement.

3.2. There are a number of systematic reviews published which show that there is a significant difference in the proportion of trials published with pharma involvement that show a positive finding compared to those trials published with no pharma involvement. This has been taken to be evidence

that pharma must be avoiding publishing studies. However there is little distinction made between early and late phase trials in these discussions and it is possible that more phase 3 trials are positive if there is a better decision making process made at phase 2. However if those early phase trials are not published then this still distorts the picture of what products are successful when we come to have an overview of the evidence in a systematic review.

4. HOW COULD THE OCCURRENCE AND RESULTS OF CLINICAL TRIALS BE MADE MORE OPEN TO SCRUTINY? WHO SHOULD BE RESPONSIBLE?

4.1. Publication bias in all its guises is a big issue. The more benign kind, nevertheless devastating to the corpus of published research, is where 'statistically significant' findings are preferred for publication. The more blatant kind is an organisation prohibiting publication of research that disfavors its product. The present research governance system should be helping a little but changes in the publication system so far haven't really addressed this issue at all.

4.2. The obvious solution is a system in which research governance approval entails a mandatory commitment by the researchers that a basic report on the study - consisting of the final protocol and a brief summary of how the study progressed (such as the CONSORT flowchart) and of the main findings - would be placed in the public domain within a mutually agreed, appropriate timescale. The appropriate placing would be a freely accessible website, a single one to cover all the approved research in the health domain in the UK (?HRA). The final protocol would be published at the start of the study, the summary of progress and findings would be published later and would have a link back to the protocol. Both would have the same reference code which would identify the year, the competent authority, and a serial number.

4.3. Researchers would normally be expected to seek publication of a definitive article in a peer-reviewed publication. When this occurs, clear links should be made in both directions between the publication(s) and the material for the study on the database described above. The R&D authority would follow up the investigators at six-monthly intervals from a pre-agreed date a few months after the study close for say 3 years, to ascertain progress towards this objective. If this has not been achieved within this time period, the study would then be flagged on the database as 'not published within 3 years' - which, if left as it stands without any explanation, would be construed by the research community as a black mark.

4.4. An exception, where one would not expect to see results published, are studies that collapsed for some valid, unforeseen reason such as withdrawal of a medication from approved use, actual recruitment rate grossly below what was anticipated, or death or serious incapacity of the main researcher to complete the project. Here, we would expect a summary on the database, linked to the approved protocol - this summary to be as informative as possible, including regarding lessons to be learnt from the failure of the study where this is applicable.

4.5. The scrutiny of a particular study largely resides with the Sponsoring company, MHRA and in the end Referees of the particular journal the Chief Investigator chooses to submit the manuscript to. Sponsoring companies seem to vary in their particular vigilance but the MHRA are very sound in their work. Following publication some journals allow quick, free access but many do not. Whether it would be possible to only License drugs if the results are published in free to access journals is open to debate but this would certainly broaden access.

4.6. The sponsor should be responsible for ensuring that trials are registered and that the results are made available (preferably open access) and that there is a mechanism for access to original datasets

for independent verification of results and conclusion. While publication of results is laudable, the strength of the evidence base would be increased if there was sufficient scrutiny of the methodology used.

4.7. To take a concrete example, in trials of cholinesterase inhibitors in Alzheimer's disease, many of the original trials on which decisions were made failed to follow-up patients who ceased therapy. They then imputed results using last observation carried forward; i.e. the last result while on treatment was used following withdrawal. In a declining disease this will artificially bias results in favour of the treatment with greater toxicity; and the active treatment in these trials suffered greater early dropout. If the methodology is flawed in this way, journals (say those which find it difficult to get access to high quality statistical review) will generally accept the paper, meaning that clinicians, who should not be expected to understand this issue in detail may gain an inflated opinion of a treatment's efficacy; alternatively, the journal will reject on the grounds of scientific value, meaning that the trial is lost forever.

4.8. This is not a simple problem to solve; this sort of issue would probably be caught at the funding stage by one of the larger funding councils; but in trials that do not go along that route, there may be a need for greater scientific review at some point. Conversely, data should be made available following publication as a safeguard – but again one needs to guard against the production of “results” of spurious validity obtained by looking at subgroups of data, or using the sort of analytical methods given above. Clearly independent scientific review of proposals is required – but resources would need to be found; and an arbitration system introduced to stop people with a vested interest, faced with a negative trial, being allowed to massage or dredge the data for spurious signs of hope.

5. CAN LESSONS ABOUT TRANSPARENCY AND DISCLOSURE OF CLINICAL DATA BE LEARNED FROM OTHER COUNTRIES?

5.1. We are not aware that any given country is particularly superior to the UK in this respect. We consider this to be a global issue, not least because evidence doesn't stop at our country's borders.

6. CONFLICT OF INTEREST.

6.1. We have no conflict of interest to declare.

February 2013

Written evidence submitted by The Migraine Trust (CT25)

1. The Migraine Trust is the health and medical research charity for migraine in the United Kingdom. We are committed to supporting people living with migraine by providing them and their families with evidence based information. We seek to raise migraine as a serious public health issue. The Migraine Trust funds and promotes research into migraine in order to better understand it, to improve diagnosis and treatment and ultimately to find a cure for this debilitating condition.

Migraine

2. Migraine is a complex condition with a wide variety of symptoms. For many people the main feature is a painful headache. Other symptoms include disturbed vision, sensitivity to light, sound and smells, feeling sick and vomiting. There are approximately 8 million migraine sufferers in the UK and, there are an estimated 190,000 migraine attacks every day. One third of sufferers will experience significant disability as a result of their migraines at some stage of their lives. The World Health Organisation ranks migraine in the top 20 most disabling conditions, stating that a day with migraine is comparable to a day with dementia, quadriplegia and active psychosis. Treatment options exist for sufferers but there is no known cure for migraine.

Migraine Research and Clinical Trial Data

3. Despite the prevalence of the condition funding for research into migraine and headache worldwide is not prioritised. Migraine is the least publically funded neurological illness relative to its economic impact. In the UK very little clinical trial data is collected from sources other than pharmaceutical companies. This is because independent research bodies have not shown willingness to sponsor clinical trials in this area. The overall effect of these funding decisions is to reduce the likelihood of research developments changing the course of the condition for people with migraine.

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

4. Openness and transparency of clinical trial data is essential to ensure that clinicians have access to the best data to make decisions about how to treat their patients. Greater transparency in clinical trials can be achieved by public sector part or full sponsorship. The involvement of public sector would necessitate greater scrutiny in the peer-review process which would mean more openness and rapid assessment. Funding streams provided by independent public bodies would ensure that smaller organisations could take responsibilities for clinical trials that may otherwise be unable to compete with large organisations.

5. Independent co-sponsorship could also be provided by charitable organisations. This can be facilitated by educational grants provided by the pharmaceutical industry which enables independent people to carry out the research. Strong and well regulated charity policies, for example requiring clinical trial registration and transparency of methodology, data and results would require the trial data to be more open to scrutiny. Strict regulations would be required to ensure that pharmaceutical companies adhere to the terms and conditions of the trials. Part of the educational grant could also be used for independent scientific research beyond the clinical trials.

6. This system could also be managed as “Research Deposit Fees” provided by pharmaceutical companies to fund independent research for each commercial led study that occurs. Monies could be returned on registration and open availability of the trial data by the pharmaceutical companies. This would allow funded research to occur and cash flow availability to the researchers independent of pharmaceutical companies. The allocation of these grants via public sector funding would ensure accountability and transparency and ensure trials were accountable to peer scrutiny.

7. Co-sponsorship and ownership of clinical trials is important to independent organisations such as charities as it enables these sponsors involvement in clinical trials who would otherwise be restricted by finances. Imposing this requirement on the pharmaceutical industry will lead to more openness and accountability of the system in the UK.

8. Statutory legislation to ensure that all parties adhere to the requirements of openness and transparency of clinical trials is required to effectively change the current system.

February 2013

Written evidence submitted by the National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre (CT26)

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?

- 1.1. The proposed EU regulation on clinical trials represents a substantial and important change from the current regulatory framework. The changes proposed address important issues required to increase clinical research activity within the NHS, and so deliver evidence and information of importance to patients, public, NHS and wider government.
- 1.2. Overall the revisions proposed appear to be in line with the required amendments identified by several key bodies and organisations. The proposal for a simpler authorisation procedure, a more risk proportionate approach for lower risk trials, establishment of co-sponsorship model, simpler safety reporting, informed consent arrangements for trials in emergency situations, and consolidation of rules for the manufacturing, importing and labelling of medicinal products should all help improve clinical trial conduct.
- 1.3. There are other barriers / areas of concern for the conduct of trials in the UK which are not covered by the EU regulations. Some of these are related to the interpretation and implementation of regulatory and legislative requirements, and these will need to be addressed centrally by organisations such as the HRA and MHRA. In addition the implications of additional legislation in areas such as data protection need to be considered for research more generally.

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

- 2.1. The HRA is part of a wider network of bodies, including the MHRA and NIHR, working together to try and improve and unify the research approvals process. It is hoped that this activity will lead to the delivery of some key legal requirements to permit clinical trial conduct in a quicker, more streamlined manner. This includes activity to promote proportionate standards for compliance and inspection within a consistent national system of research governance.
- 2.2. The HRA is still establishing itself but has begun to make important improvements to the current ethical approval processes which will hopefully deliver results quicker. In addition proposals to develop opportunities for information sharing and reporting could deliver important results in terms of reduced bureaucracy and improved transparency. The HRA has been making important connections with key partners and has already established effective working relationships and collaborative activity. However it remains unclear as to the extent of the influence the HRA can have on activity and practice across the NHS, given the current legal arrangements with NHS Trusts being independent legal entities.

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

- 3.1. We have no comments or evidence to be considered.

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

- 4.1. Research funders have a responsibility to produce the knowledge from the research and ensure that it is in the public domain. This serves a number of purposes including: transparency of public money spent, assurance of the validity of the work, patient safety (through publication of negative results), information sharing and engagement.
- 4.2. There is an increasing focus on the results of research being published. Studies from different countries repeatedly show a 40-50% publication rate, and the recent BMJ article by

Chalmers, Glasziou and Godlee “All trials must be registered and the results published”, reported that only around half of all registered trials have published at least some of their results¹).

- 4.3. The DH/NIHR is a partner in the European version of PubMedCentral – Europe PMC. On the NIHR website there is a statement that the DH and NIHR support the principles that:
- Ideas and knowledge derived from publicly funded research must be made available and accessible for public use, interrogation and scrutiny as widely, rapidly and effectively as possible
 - Published research outputs must be subject to rigorous quality assurance through effective peer review mechanisms
 - The models and mechanisms for publication and access to research results must be both efficient and cost effective in the use of public funds
 - The outputs from current and future research should be preserved and remain accessible for future generations.
- 4.4. The standard NIHR contract enables enforcement of many key mechanisms that ensure transparency and openness of clinical trial data. In particular funded researchers must undertake compulsory trial registration before any monetary awards are paid, and in addition they are obligated the release of data to the funder on request. A number of NIHR programmes also publish full protocols or summaries on their websites.
- 4.5. Publication and dissemination of trial results are also included within the standard NIHR contract which states; ‘The Contractor shall ensure that the outcome of the Research is prepared for publication in a suitable peer-reviewed journal’. Despite this, the rate of publication from NIHR-funded research is varied, ranging from some research programmes and projects which do not publish their findings to others with a publication vehicle through the NIHR Journals Library.
- 4.6. NIHR-funded researchers are actively encouraged to submit articles of their research findings to peer-reviewed journals, however this does not guarantee publication for all results through this route.
- 4.7. In order to address this potential bias in reporting trial results, the NIHR HTA programme achieves near total and complete publication for its research findings (estimated to be in the region of 98%¹), whether positive, neutral or negative, through its dedicated journal ‘Health Technology Assessment’. This process is now being extended to four other NIHR research programmes through the establishment of the NIHR Journals Library. The final reports within the NIHR Journals Library are subject to a full editorial process prior to publication in the relevant journal. It is not until the report meets the quality expected from a journal that it is approved for publication by the editor.
- 4.8. A current area of NIHR activity is concerned with reducing avoidable waste in research, and an intention to ‘ensure that all NIHR funded research is published’ is a central part of this.
- 5. Can lessons about transparency and disclosure of clinical data be learned from other countries?**

5.1. We have no comments or evidence to be considered.

Declaration of Interests

The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the National Institute for Health Research (NIHR), and plays an important role in improving the health and wealth of the nation through research. NETSCC has been contracted by the Department of Health to manage evaluation research programmes and activities primarily as part of the research work strand of the NIHR. The NETSCC managed NIHR funding programmes have a national and international reputation for high-quality research and research management.

¹ Chalmers I, GLasziou P, Godlee F. All trials must be registered and the results published. BMJ. 2013; 346:f105

February 2013

Written evidence submitted by NHS European Office (CT27)

The NHS European Office has been established to represent NHS organisations in England to EU decision-makers. The office is funded by the strategic health authorities and is part of the NHS Confederation.

In submitting our response we have limited our comments to those questions that are most relevant to our role and remit representing the interests of NHS organisations to EU decision-makers.

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 the EU?

1. The NHS European Office welcomes many of the changes in the proposed Clinical Trials Regulation, as overall it addresses a number of the areas in the current EU Clinical Trials Directive which form barriers to conducting clinical trials in the UK and across the EU.
2. The revision of the Clinical Trials Directive is particularly important to the NHS as over 99 per cent of NHS hospital trusts are involved in research studies, which often take the form of clinical trials. Involvement in these studies allows NHS trusts to develop new treatments and to improve the quality of healthcare they provide. In addition clinical trials allow participating patients to benefit earlier from innovative drugs and treatments to which they would not otherwise have access.
3. While the Clinical Trials Directive has improved the safety and ethical soundness of clinical trials, it has led to a significant increase in the cost and administrative burden for conducting these studies and has significantly extended the time required for launching new trials. These difficulties have contributed to making the EU a less attractive location to conduct clinical trials, which has, in turn, resulted in a significant fall in clinical trial activity in the UK.
4. The proposed Regulation represents a significant improvement to the current Directive and takes positive steps to streamline the existing rules to reduce the administrative burden and speed up time for the authorisation of new clinical trials. Of the proposed changes, in particular we welcome:
 - a. *A simplified authorisation process:* The Regulation proposes that a single application dossier is submitted via an EU portal. While all countries in which the sponsor intends to conduct the trial will be involved in the assessment of the application, they will have to cooperate in several areas of the process with one Member State leading and coordinating on their behalf. We believe that these changes should reduce the bureaucratic burden, speed up the authorisation process and reduce the lengthy delays that have hindered many clinical trials applications.
 - b. *A lighter regime for 'low risk' trials:* Another positive proposal is the recognition that trials which pose no or very limited additional risk to participants compared to normal clinical practice should be subject to a lighter regulatory regime. The Regulation identifies a new category of clinical trials, called 'low intervention', which would be subject to more proportionate rules for different aspects of the clinical trial process, including timelines for authorisation, monitoring, reporting, and insurance requirements. This is a positive step forward especially for non-commercial bodies, such as NHS trusts, which often sponsor non-commercial trials that aim to compare

the efficacy of medicines which are already authorised and for which there exists extensive knowledge of their safety and tolerability.

- c. *Enabling co-sponsorship*: The explicit introduction of the concept of co-sponsorship is also a very positive development, particularly for non-commercial sponsors like NHS trusts, which often are unable to lead clinical trials on their own due to different regulatory and practical difficulties and, therefore, decide to share the sponsor's responsibilities with their partner university to overcome these obstacles.
5. The NHS European Office has consulted extensively with organisations across the NHS to identify areas where further improvements can be made to the proposed Regulation and have briefed EU decision-makers on NHS views.

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

1. The EU database proposed in the new EU Clinical Trials Regulation will achieve greater transparency of the results of clinical trials. It will contain much more data and information on clinical trials, which will have to be made publically available through it.
2. Overall NHS organisations are in favour of making the results of clinical trials more accessible, provided that all appropriate steps are taken to ensure that necessary personal confidentiality is maintained, and also to ensure that results are only published when it is certain that the results of the clinical trial are both robust and reliable. In order to achieve this, consideration would have to be given to the following:
 - a. Sufficient information would need to be provided in a format which is accessible to the public, as well as practitioners, while maintaining sufficient levels of personal and commercial confidentiality.
 - b. The required format for the presentation and publication of the results of clinical trials data should be consistent across all member states.
 - c. Appropriate steps should be taken to ensure that the amount of clinical trials data sets housed on the EU database will be manageable. It is likely that the European Commission database would not be able to store unlimited amounts of information.
 - d. Full consideration would need to be given to who would have access to full datasets to ensure that personal confidentiality would be maintained at all times.
 - e. For more detailed information, relevant interested parties would have to contact the sponsor directly.
3. If non-commercial sponsors of clinical trials, such as NHS organisations, were to be required to undertake additional measures to ensure greater transparency of the results of their clinical trials than currently required, careful consideration should be given to the cost implications that additional administrative requirements would bring.
4. In the proposals for a new EU Clinical Trials Regulation, significant efforts have been made to reduce the costs and administrative burden for sponsors. It is important to ensure that significant costs and administrative requirements will not be introduced as a result of new requirements to publish the results of clinical trials. This is especially important for non-commercial sponsors not seeking marketing authorisation at the conclusion of their clinical trial.
5. The sponsor should always be responsible for making the results of clinical trials more accessible, while ensuring appropriate safeguards with regards to confidentiality are maintained.

February 2013

Written evidence submitted by the BioIndustry Association (BIA) (CT28)

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?

1. The conduct of clinical trials in the EU is a highly regulated process ensuring patient safety and the reliability and robustness of data that is generated. These rules are set out in the 'Clinical Trials Directive' (2001/20/EC). Limitations of this legislation have been highlighted in the years since its introduction by a wide range of stakeholders for its disproportionate regulatory requirements, high costs, and in particular a lack of harmonisation of the applicable rules necessary for multinational clinical trials. This has contributed to a decline of clinical trials in the EU of 25% between 2007 and 2011.
2. The BIA fully supports the European Commission's proposal for a new Regulation on clinical trials (hereafter referred to as the proposed Regulation). The proposed Regulation can achieve more harmonisation, transparency and consistency in the approval and conduct of clinical trials across the European Union (EU), while maintaining high standards of patient safety, robustness and reliability of clinical data.
3. The proposed Regulation offers an improved, simplified and more efficient regulatory framework for clinical trials. This is critical to strengthen Europe's competitive position as a global player for translational research and clinical development of medicines.
4. To ensure the benefits are realised and multi-state clinical trials are made easier to conduct care should be taken in legislation drafting of any amendments to ensure that the obligations and requirements are sufficiently precise, clear and unconditional.
5. While the proposed Regulation is very welcome and does, on the whole, represent a progressive change to the European framework for the conduct of clinical trials, there are specific points worthy of further consideration and refinement. Such issues are raised below before comments on more specific aspects of the proposed Regulation are also provided.
6. The BIA has concerns that the European Commission has defined new terms in the proposed Regulation. A distinction between clinical trial and clinical study (articles 2(1) and 2(2)) is unnecessary and should be aligned with agreed international guidelines to ensure no unintended consequences particularly taking into account the different types of clinical research undertaken in the EU.
7. The proposed Regulation cannot be looked at in isolation and must be considered alongside other existing pharmaceutical law, for instance the obligations on post-authorisation studies to gather further long term data outlined in the EU pharmacovigilance legislation.
8. Once the clinical trial authorisation has been granted and accepted by all participating Member States, a faster process to extend a clinical trial to additional Member States is essential.
9. There also appears no scientific justification for the longer assessment timelines for advanced therapy medicinal products.
10. The BIA can make the following more specific observations relating to key aspects of the proposed Regulation. These specific aspects are relevant as they address some of the main barriers clinical trial applicants face when conducting multi-state trials.

Authorisation procedure

11. The BIA supports the submission of one clinical trial application dossier in accordance with defined and harmonised requirements through a single EU portal for consideration by all the Member States where the clinical trial is to be carried out. The designation of one contact point per Member State is also welcomed in order to facilitate coordination and management of a clinical trial application. The proposal to introduce a clear distinction between aspects that are assessed through collaboration between Member States from those aspects that have to be assessed individually by each concerned Member State is a pragmatic and welcome approach.
12. Moreover, removal of the duality of national competent authorities and ethics committees' decisions by mandating a single decision on the conduct of a clinical trial by each concerned Member State is another welcome feature.
13. We further support the defined timelines for each Member State to take a single decision on the conduct of a clinical trial on its territory. It is important these timelines are not lengthened. The tacit approval of a clinical trial application based on the Part I assessment conclusion if the defined timelines are not met is also welcome.
14. Where additional reviews by institutions are required by national law for a clinical trial, this must be coordinated as part of the overall assessment and provided within the timeframe specified.
15. Finally on this point, the BIA welcomes the flexibility provided by the proposed Regulation for continued support by Member States for single country trials and early phase research.

EU Portal and EU Database

16. The BIA welcomes the proposed establishment of a single EU portal to manage regulatory submissions and accompanying database for storage of all the relevant information and data.
17. Building on this it will be crucial to involve all stakeholders, including small and medium-sized enterprises (SMEs), academic institutions and research charities, in the process of developing the future EU portal. This can ensure the new portal is efficient, user friendly, secure and improves on current practice.

Risk Adaptation of the Regulation

18. The introduction of a risk-adapted approach to the regulation of clinical trials which is proportionate to the extent of current knowledge and takes account of prior experience with the product or the same class of products, as well as the type of intervention, is welcome. It will be crucial that the same approach to conducting clinical trials is applied by all academic / non commercial and commercial sponsors in the interests of patient protection.
19. The concept of a 'low-intervention clinical trial' is also a merited step. It is right that, for such trials, the assessment timelines are reduced and requirements for such trials further simplified.

2) WHAT IS THE ROLE OF THE HEALTH RESEARCH AUTHORITY (HRA) IN RELATION TO CLINICAL TRIALS AND HOW EFFECTIVE HAS IT BEEN TO DATE?

20. The HRA is a newly formed NHS organisation established on 1 December 2011 as a Special Health Authority. The purpose of the HRA is to protect and promote the interests of patients and the public in health research. Moreover, the HRA was established following the government's Arms Length Bodies review and *A new pathway for the regulation and governance of health research* report by the Academy of Medical Sciences (AMS). This work was considered of importance by a wide range of stakeholders due to the perception that the UK was becoming an

increasingly difficult location in which to conduct clinical trials. This was due to a number of factors including increased costs, bureaucracy and difficulty with patient recruitment and trial start up times.

21. The HRA was therefore also set up to ensure the environment for conducting clinical trials in the UK was streamlined, transparent and competitive as per other jurisdictions. The BIA was an active participant in this review conducted by the AMS.
22. The BIA has welcomed the establishment of the HRA and believes it can play a powerful role in reducing the cost and improving the speed of initiating clinical trials in the UK whilst promoting proportionate standards. The HRA has displayed an open and transparent spirit of engagement since its establishment which has been warmly welcomed by the sector.
23. The UK National Research Ethics Service (NRES) is now housed within the HRA. The BIA supports this move and would welcome additional consolidation of other relevant functions or competencies within the HRA to ensure, as far as is practically possible, a single point of contact for clinical trial applicants. This is particularly important for bioscience SMEs where any unnecessary delay or bureaucracy can have a detrimental effect on their ability to operate in future or raise finance.
24. The competencies of the HRA should be considered alongside other organisations involved in the clinical trial application and assessment process. The HRA therefore must work closely with the Medicines and Healthcare products Regulatory Agency (MHRA) and the National Institute for Health Research (NIHR) with the aim of creating a unified approval process which is proportionate and easily navigable for stakeholders. The HRA should not seek to duplicate activity undertaken elsewhere.
25. Activities undertaken by the NIHR should be considered here as they seek to improve the ease of conducting clinical trials in the UK. The NIHR does this, primarily, through its Translational Research Partnerships (TRPs) and Clinical Research Networks (CRNs). The BIA supports these initiatives which can also have a positive impact on the UK's clinical trial environment.
26. Underpinning all of these activities are Research and Development approvals at individual NHS Trusts (known as R&D Trust approvals). These have long been recognised as a key delaying factor which affects the competitiveness of the UK as a location for clinical trial activity.
27. BIA members often highlight the added cost, both in terms of staff and time and financial outlays, which are incurred because of the administrative burden of obtaining R&D Trust approvals from NHS Trusts. While it is fair to state there are Trusts with an excellent research history this is not uniform across the UK. This is an issue for any clinical trial sponsor that wishes to undertake clinical trials in numerous sites across the UK. Sponsors will clearly often want to perform trials in different sites to ensure the best chance of recruiting the necessary patients from across the UK. Different NHS Trusts will often request additional information that either duplicates requests from other authorities, concerns information already provided or is not materially necessary for the research in question. This leads to the situation whereby conducting trials can be demonstrably cheaper and more efficient in other jurisdictions.
28. This point regarding the financial cost of R&D Trust approval is an important one to emphasise and while is of concern to companies of any size has a particular effect on SMEs. Innovative bioscience companies are often pre-revenue and equity-backed as they develop their products for areas of unmet medical need. Delays to the commencement of clinical trials, which can be ongoing for months if not longer, act as a significant drain on the companies' finite resources. It also often delays the triggering of any milestone payments that have been agreed by a company with its partners as such payments will be dependent on completion of recruitment of patients to a

- clinical trial for example. Investors are aware of these additional costs and delays caused by R&D Trust approval practices and can perceive the UK negatively as a result.
29. The government are taking steps to address this issue. For example, NIHR funding is now dependent upon NHS Trusts meeting recruitment targets. Furthermore, the HRA is looking into the feasibility of single assessment procedures encompassing all relevant NHS Trust approvals relating to the sites in which a trial will take place.
 30. Such an approach holds promise to improve the environment for conducting clinical trials in the UK and would provide the best opportunity for other government initiatives to succeed also.
 31. It remains the BIA's hope that the establishment of the HRA will foster a more streamlined and favourable environment for conducting clinical trials in the UK although it is too early to make a judgement on progress.
- 3) WHAT EVIDENCE IS THERE THAT PHARMACEUTICAL COMPANIES WITHHOLD CLINICAL TRIAL DATA AND WHAT IMPACT DOES THIS HAVE ON PUBLIC HEALTH?
 - 4) HOW COULD THE OCCURRENCE AND RESULTS OF CLINICAL TRIALS BE MADE MORE OPEN TO SCRUTINY? WHO SHOULD BE RESPONSIBLE?
 - 5) CAN LESSONS ABOUT TRANSPARENCY AND DISCLOSURE OF CLINICAL DATA BE LEARNED FROM OTHER COUNTRIES?
32. As these questions all relate to transparency and disclosure of clinical trial data the BIA will answer them together.
 33. The BIA and its membership fully support the need for sensible and proportionate regulatory policies underpinning the legal framework designed to promote openness and transparency in clinical development. The BIA believes that all stakeholders in the life sciences sector, be they academic, medical research charities or industry, are supportive of transparency on clinical trials information. Clinician and patient confidence regarding the safety and efficacy of medicinal products are recognised as of vital importance to the sector and appropriate transparency has a key function in this regard.
 34. There should be an expectation that the results of all trials relating to the marketing authorisation of a medicine should be publicly available to ensure patient and clinician confidence in the prescribing of such medicines. The European Public Assessment Reports (EPARs) which are made available to the public by the European Medicines Agency (EMA) provide a summary of the data upon which a marketing authorisation is granted.
 35. It is worth pointing out there are many existing provisions already in place to facilitate public access to clinical trials information, for example EU Clinical Trials Register and US Clinicaltrials.gov. Dedicated web portals have also been created to facilitate public access to information pertaining to the on-going clinical trials and their results, for example IFPMA Clinical Trials Portal.
 36. Given that such information exists it is important to understand what transparency and disclosure is required and at what stage of a product's clinical development. Of course, patient safety is the core underpinning concern in all clinical trials but beyond this a large amount of data is involved in the running of a clinical trial and regard should be given to the value of know-how and expertise in the clinical development process and an appreciation of the ongoing investment into the sector. These issues are relevant in so far as they relate to products that have not yet been approved and where clinical development is ongoing before a marketing authorisation application is submitted.

37. To provide context, such know-how or trade secrets could relate to methods of manufacture and certain underlying technological approaches or processes involved in the development of an innovative product. They represent a considerable investment in intellectual effort, inventive skill, time and money, but may not be capable of protection by the mainstream law of intellectual property.
38. This should be considered alongside the changing nature of drug development and that increasingly many of the innovative developments in the sector are based on collaborations and partnerships between a variety of stakeholders including academia, medical research charities, SMEs and multinational biopharmaceutical companies. Protection of know-how provides a key factor underpinning such partnerships (examples of which are provided in the appendix of this submission). The loss of such protection would dramatically impact upon investment into the sector, thus removing a key pillar for collaborative research and development of medicines designed to improve patient outcomes and care.
39. Whilst Regulation (EC) 1049/2001 regarding public access to documents held by European institutions promotes greater openness in the works of the institutions, it also considers the need to ensure that certain specific public and private interests should be protected by way of exceptions. Article 4(2) of the Regulation provides, amongst other things, that European institutions shall refuse access to a document where disclosure would undermine the protection of commercial interests of a natural or legal person including intellectual property.
40. BIA members also highlighted as a key legal challenge for clinical trial sponsors the need to reconcile between the disclosure of clinical data as proposed and the compliance with EU data privacy rules as set forth by Directive 95/46/EC (on the protection of individuals with regard to the processing of personal data) and reflected in the scope of the informed consent form signed by the patient. It should be noted that for trials carried out so far the patient has not consented to the disclosure of personal data identifiers to the public nor to the regulatory authorities under such a new process.
41. Beyond the legal considerations and the EU strict data privacy framework, the limitations of the informed consent given by the trial subject with regard to the possible uses of the clinical trial data are also an important ethical/medical consideration and cannot be understated in the current discussion. These aspects are currently being considered by the EMA developing its policy on access to clinical trial data.
42. It is the BIA's considered view that a balanced approach should be taken to ensure that the means to achieve greater transparency should not be done in such a way that will undermine Europe's international competitiveness in basic, applied and translational life sciences research.
43. Finally, the BIA would consider regulatory bodies as the appropriate and natural holders of clinical trial data. As such, it should be these bodies that are responsible for the release of clinical trials information in discussion with the data holder. Furthermore, the premature release of patient level data prior to the granting of a marketing authorisation would allow other individuals to conduct analyses of the data which could compromise the regulatory agency review of the data, and undermine the public confidence in the decisions of the regulators.

Appendix

Listed in the table below are some examples of partnerships and collaborations. These are all recent examples announced within the last six months and represent only a sample of all such activity. Such partnerships and collaborations are increasingly a part of medical developments as the expertise of different organisations are brought to bear on a specific product or technology. A single drug, for

example, could easily pass through the ownership of four or more organisations before it is finally available for patients. Each aspect of this development chain brings different expertise and know-how of importance to the development of the medicine and the value of confidential information, referred to above, is of paramount importance in such collaborations.

Historically, the UK has a rich tradition of being considered as a hub for strategic partnerships between academia, medical research charities, SMEs and established pharmaceutical/biotechnology companies. Many important and revolutionising discoveries and inventions through applied and translational research originated here. Examples include the discovery of atracurium, the first non-depolarising non-steroidal skeletal muscle relaxant, at the University of Strathclyde in the 1970s, and temozolomide, an orally active alkylating agent authorised for treating an aggressive form of brain tumour, in the 1980s at University of Aston, Birmingham. Both are commercially successful medicines.

UK Medical Research Council and AstraZeneca	Collaborative agreement worth initially £7million to discover 22 compounds
Apitope and Merck Serono	Collaborative agreement to develop new drugs for the treatment of multiple sclerosis
UK Health Protection Agency and US government	£14million funding from the US government to develop anthrax vaccine
Led by GlaxoSmithKline and University of Manchester, collaboration of six pharmaceutical companies, thirteen Universities and four SMEs from across Europe	A public-private partnership worth £21.2 million to develop sustainable biological and chemical alternatives to finite materials, such as precious metals, which are currently used as catalysts in the manufacture of medicines
University of Oxford as the academic lead institution for StemBANCC	Five-year research programme worth £53 million involving academic and industry partners across eleven countries. Its objective is to develop human-induced pluripotent stem cells
Summit plc and Wellcome Trust	Award, up to £4 million, to support translational research of a novel compound being developed as a specific antibiotic for treating infections caused by <i>C. difficile</i> .
Oxford Biotherapeutics and Menarini	A strategic collaboration, potentially worth up to £800m, to develop and manufacture a portfolio of novel antibody-based cancer drugs.

About the BIA

Established in 1989, the BioIndustry Association (BIA) exists to encourage and promote a financially sound and thriving bioscience sector within the UK economy and concentrates its efforts on emerging enterprises and the related interests of companies with whom such enterprises trade. The BIA represents innovative healthcare-focused bioscience companies, including over ninety per cent of biotech medicines currently in clinical development in the UK. BIA members are at the forefront of

innovative scientific developments targeting areas of unmet medical need and this innovation will lead to better outcomes for patients, the development of the knowledge economy, and economic growth.

February 2013

Written evidence submitted by the General medical Council (CT29)

Introduction

1. The General Medical Council is the independent regulator for doctors in the UK. Our role is to protect patients by ensuring proper standards in the practice of medicine.
2. We do this by controlling entry to the medical register and setting the standards for medical schools and postgraduate education and training. We also determine the principles and values that underpin good medical practice and we take firm but fair action where those standards have not been met - if necessary, by removing the doctor from the register and removing their right to practise medicine.
3. We have a statutory duty to set standards for doctors on medical ethics. Our core guidance, *Good medical practice*, defines what it means to be a good doctor in the UK. But we also provide more detailed guidance on a wide range of issues, including *Good practice in research* and *Consent to research*¹.
4. This memorandum provides information on this guidance for doctors and how we help doctors to meet the standards expected of them.

Providing guidance on research to the profession

5. Research involving people directly or indirectly is vital in improving care and reducing uncertainty for patients now and in the future, and improving the health of the population as a whole.
6. Our guidance, *Good practice in research* and *Consent to research*, sets out the good practice principles that doctors are expected to understand and follow if they are involved in research, including clinical trials. It brings together all the GMC's advice to doctors involved in research including *Confidentiality*², which covers, for example secondary uses of data; and *0-18 years*³, which covers involving children and young people in research.
7. The guidance provides a framework to guide doctors' decisions throughout all stages of a research project, from research design, recruiting participants, seeking consent and the publication and dissemination of research. The guidance acknowledges the complexity of research work and that it is essential for improving care for patients now and in the future.
8. It reminds doctors that they must put the protection of participants' interests first, act with honesty and integrity and follow the appropriate national research governance guidelines. It includes advice about avoiding conflicts of interest, doctors' responsibilities to ensure that research is free from discrimination and about involving vulnerable patients or those who lack capacity.

¹ http://www.gmc-uk.org/static/documents/content/Research_guidance_FINAL.pdf

² http://www.gmc-uk.org/static/documents/content/Confidentiality_0910.pdf

³ http://www.gmc-uk.org/static/documents/content/0-18_0510.pdf

9. The guidance is also clear on the importance of openness to protect participants and maintain public confidence in research. On publishing research results *Good practice in research* says:

"Whenever possible, you should publish research results, including adverse findings, through peer-reviewed journals.¹⁷ (Paragraph 24). This references more detailed advice from the UK Research Integrity Office, *Code of Practice for Research: Promoting good practice and preventing misconduct*.

10. On openness in the conduct of research it says:

"You should make sure that details of a research project are registered on an eligible, publicly available database that is kept updated, where such a database exists." (Paragraph 11)

"You should make sure that commercial and other interests do not stop or adversely affect the completion of research. If you are concerned about this you should follow the guidance on raising your concerns in paragraph 19." (Paragraph 14)

"You must report adverse findings as soon as possible to the affected participants, to those responsible for their medical care, to the research ethics committee, and to the research sponsor or primary funder where relevant. You must make sure that bodies responsible for protecting the public, for example, the Medicines and Healthcare products Regulatory Agency, are informed." (Paragraph 16)

11. We would investigate any allegations against a doctor of fraud or misconduct in research and serious or persistent failure to follow this guidance will put a doctor's registration at risk.

Helping doctors to meet our standards

12. We are committed to being a proactive regulator and this means we want to make sure doctors are supported in meeting our standards.

13. A new system of checks for doctors, called revalidation, will put the UK at the forefront of making sure medical practice is of a high quality and that doctors are supported in their professional development. It will also mean that all licensed doctors, including those involved in research, are regularly checked against the professional standards that we and the public expect them to meet.

14. We have three local liaison services which work across the UK to meet face-to-face with doctors, employers, patients and educators to help explain our guidance and to work with employers to manage any concerns about doctors' fitness to practise.

15. We intend to follow up on the Health Select Committee's recommendation in its recent report on NICE that the GMC '*reiterates its guidance on drug trials to its members, and reminds them that failure to abide by these principles could lead to fitness to practise proceedings being taken against them*'. We will include an item in *GMC News*, our monthly e-bulletin which goes to over 200,000 registered doctors, on *Good Practice in Research*; and this message will also be cascaded to the profession locally via our liaison services.

16. We are always looking for new ways we can help make sure doctors know what is expected of them and have the support to meet those expectations. We have launched a mobile version of our website so doctors can access our guidance from their phones and other devices and have started piloting induction training to help doctors new to UK practice understand the standards expected of them.

February 2013

Written evidence submitted by the Committee on Publication Ethics (COPE)

Executive Summary

1. There are several stages in the review process for clinical trials at journals which could enable improvements in transparency of trials and their reporting.
2. COPE is committed to improving the transparency around clinical trial reporting and data disclosure. Specific actions that editors and journals can undertake are improving compliance with the requirement for registration of trials, clinical trial reporting and enabling increased availability of data from these trials.
3. However, it not realistic to assume that journals alone can enforce compliance with requirement for trial registration and trial reporting without overarching mandates from funders and government, accompanied by specific penalties for non-compliance.

Background on COPE

4. COPE [1] is a forum for editors and publishers of peer-reviewed journals to discuss all aspects of publication ethics. COPE was established in 1997 by a small group of medical journal editors in the UK but now has over 8500 members worldwide from all academic fields. Membership is open to editors of scholarly journals and others interested in publication ethics. Several major publishers have signed up all their journals as COPE members.
5. COPE does not investigate individual cases of publication ethics but encourages editors to ensure that cases are investigated by the appropriate authorities (usually a research institution or employer).
6. COPE also funds research on publication ethics, organises annual seminars worldwide and produces guidelines on a wide range of issues relevant to publication ethics. COPE has also created an audit tool for members to measure compliance with its Code of Conduct and Best Practice Guidelines for Journal Editors.

Declaration of Interests

7. I am an employee of the Public Library of Science (PLOS), whose journals belong to COPE. I am Chair of COPE; this is an unpaid position. COPE receives subscriptions from member journals and publishers, which fund its work.

The Committee sought submissions on the following questions:

- a. 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?
- b. What is the role of the Health Research Authority (HRA) in relation to clinical trials and how effective has it been to date?
- c. What evidence is there that pharmaceutical companies withhold clinical data and what impact does this have on public health?

- d. How could the occurrence and results of clinical trials be made more open to scrutiny? Who should be responsible?
 - e. Can lessons about transparency and disclosure of clinical data be learned from other countries?
8. We address point d only in this submission, and only from the perspective of journal publication ethics.

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

9. There are several steps that are essential in opening up trials to more scrutiny: ensuring that all trials are registered, that summary results are reported and that all the data behind trials are available.
10. Journals and the editors that run them have a crucial role in the dissemination of clinical trial results, as medical journals are the place where currently most of the final results of trials are published. Journal editors have expertise in the assessment of clinical trials and have led the way in several important initiatives around opening up trials to more scrutiny.
11. A key part of ensuring that trials are available for scrutiny is for there to be universal registration of clinical trials in an internationally or nationally recognized registry. In 2004 the International Committee of Medical Journal Editors (ICMJE) adopted a policy [2] that from July 1, 2005 all trials submitted to ICMJE member journals should be registered in an approved registry before the first participant was enrolled. They further indicated that unregistered trials would not be considered for publication in ICMJE member journals. Since then many other journals have adopted this policy. The COPE Code of Conduct endorses clinical trial registration [3] However, registration is not universal, and even if registered the registration number is not always reported in the journal report of a trial [4]. In addition, the quality of data included in the registries is highly variable and often not complete [5].
12. COPE has supported the AllTrials initiative, which is calling for all trials to be registered and all results reported. In our support of the initiative we said: “COPE supports the AllTrials initiative for all trials to be registered and all results reported. Publication ethics is not just about such issues as prevention of plagiarism and managing conflicts of interest, but is, more widely, about ensuring the integrity of the scholarly literature. Registration of trials and full reporting of results is a critical step in counteracting the bias towards positive results in the medical literature.” [6].
13. A further critical aspect of making clinical trials open for scrutiny is to ensure that they are fully reported. The CONSORT group has been the leader in raising the standards for reporting of clinical trials [7] and is part of a wider initiative to improve reporting guidelines overall, the EQUATOR initiative [8]. However, despite the CONSORT guidelines having been available since 2001 and then revised in 2010 and endorsed by many journals, implementation remains far from complete and there remain many poorly reported trials in the medical literature [9]. There is a clear need for funders to require and journals to enforce better reporting of trials.

14. A further problem contributing to lack of scrutiny of body of evidence from trials is the bias within the published literature against trials that are perceived to be “negative”. This bias stems from many causes, including unwillingness of sponsors and authors to submit negative trials for publication but can also be the result of journals being unwilling to consider such trials for publication as they are perceived as being less interesting. The COPE Code of Conduct specifically states that “Studies reporting negative results should not be excluded.” [3].
15. One specific effect of the relative lack of negative studies is that systematic reviews and meta-analyses of these studies can preferentially be skewed towards a more positive interpretation of the literature overall. This has been demonstrated in a number of different places, including a recent systematic review [10].

Recommendations for Government Action

16. There is a role for UK legislation to ensure that all clinical trials, of all phases, ie from early phase to post marketing, which are conducted within the UK or which are funded or co-funded by UK organisations, are registered, with specific penalties for non-compliance
17. The government should support requirements for all clinical trial results, both summary and underlying data, to be made available within a specific time frame after trial completion in a journal or a publicly available independent site. There should be oversight and enforced penalties for non-compliance.

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References/Notes

- 1] Committee on Publication Ethics (2013). Available: <http://www.publicationethics.org> Accessed Feb 17 2013
- 2] De Angelis C, Drazen J. M, Frizelle F. A, Haug C, Hoey J, et al. (2004) Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *N Engl J Med* 351: 1250–1251.
- 3] COPE code of conduct. Available: http://publicationethics.org/files/Code_of_conduct_for_journal_editors.pdf Accessed Feb 17 2013
- 4] van de Wetering FT, Scholten RJPM, Haring T, Clarke M, Hooft L (2012) Trial Registration Numbers Are Underreported in Biomedical Publications. *PLoS ONE* 7(11): e49599. doi:10.1371/journal.pone.0049599
- 5] Viergever RF, Ghersi D (2011) The Quality of Registration of Clinical Trials. *PLoS ONE* 6(2): e14701. doi:10.1371/journal.pone.0014701
- 6] AllTrials campaign. Available: <http://www.alltrials.net/> Accessed Feb 17 2013
- 7] The CONSORT Statement Website. Available: <http://www.consort-statement.org/> Accessed Feb 17 2013
- 8] EQUATOR Network (2013). Available: <http://www.equator-network.org/> Accessed Feb 17 2013

9] Turner et al.: Does use of the CONSORT Statement impact the completeness of reporting of randomised controlled trials published in medical journals? A Cochrane review. *Systematic Reviews* 2012 1:60.

10] Dwan K, Altman DG, Arnalz JA, Bloom J, Chan A-W, Cronin E, Decullier E, Easterbrook PJ, von Elm E, Gamble C, Gherzi D, Ioannidis JPA, Simes J, Williamson PR: Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PLoS ONE* 2008, 3:e3081. doi:10.1371/journal.pone.0003081

Written evidence submitted by the British Heart Foundation (CT31)

Summary

- The proposed replacement of the Clinical Trials Directive with a new **Clinical Trials Regulation** presents an opportunity to significantly improve how research is regulated in the UK
- The draft Regulation proposed by the European Commission requires further refinement to ensure that additional clarity is added to ensure a **proportionate approach** to regulating clinical trials
- Several barriers on regulation and governance in the UK still need to be addressed, in particular **NHS Research and Development (R&D) permissions**, which should be prioritised by the Health Research Authority
- Ensuring that research and clinical trial data are publicly open to scrutiny is important to ensure research findings are both **robust and transparent**
- Failure to publish research and clinical trial data **can hinder medical and scientific progress** and have a damaging effect on public health
- **Peer-review** is important in helping to ensure that the data in published research are robust
- Action to improve transparency needs to be **proportionate** in nature so as not to add to the regulatory burden medical researchers currently experience

1. The British Heart Foundation (BHF) is the nation's heart charity. From new discoveries about how the heart develops in the womb, to developing the treatments that could mend broken hearts in the future, we are the single biggest independent funder of cardiovascular research in the UK – funding around £100 million each year.

2. We welcome the opportunity to respond to the Committee's inquiry on clinical trials and the disclosure of data. The UK is a world-leader in medical research and has historically been an attractive location for researchers to carry out clinical trials for new treatments for a range of diseases – including cardiovascular disease. However, unintended consequences resulting from legislation such as the Clinical Trials Directive have made it more difficult for researchers funded by the BHF to conduct clinical trials in the UK. The Clinical Trials Regulation proposed by the European Commission to replace this legislation has the potential to significantly improve how research is regulated within the UK – providing effective safety for patients and greater transparency in results.

Q1: 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?

3. A number of the issues surrounding the existing Directive are addressed in the proposed Regulation, which we welcome. We have signed a joint statement from non-commercial and commercial organisations on the Proposal for an EU Regulation on Clinical Trials, which identifies these positive changes and highlights further areas where clarity is needed.

A risk based approach to regulation

4. A key criticism of the existing Directive has been the ‘one size fits all’ approach which fails to discriminate between trials of varying levels of risk. This approach currently applied by the Directive has proved to be unfit-for-purpose, and has exacerbated the problems associated with the Directive’s broad scope. The review of regulation and governance published by the Academy of Medical Sciences two years ago highlighted a number of examples where a lack of a proportionate approach has been shown to be problematic for UK medical research.¹

5. Introducing the concept of a low-interventional trial is therefore an important step towards achieving a risk-based approach in clinical trials legislation. Many clinical trials can involve medicines where their safety has already been established – this is in contrast to, for example, a new drug being tested in people for the first time. It is appropriate that the Regulation reflects this range in risk. However, uncertainty remains over the extent to which the proposed Regulation will adapt the requirements for trials of marketed products used for a new purpose, which are not included in the low-interventional trial category. **Further clarity is therefore needed on the two category risk based approach proposed in the draft Regulation.**

6. It also needs to be established whether there is sufficient flexibility to apply greater risk differentiation within the Regulation. A recent paper by the MRC, DH and MHRA proposed that the potential risks of participation in a clinical trial should be balanced against the level of risk that a trial participant would be exposed to outside of the trial – suggesting a three-level categorisation of risk.² The bi-partite system suggested in the proposed Regulation could mean that the majority of studies would be placed within the high risk group. **A three-level categorisation would allow greater scope for the proportionate regulation of research. We believe the Commission should give this proposal greater consideration.**

Clarity in the scope’s definitions

7. Inconsistent interpretation of the current Directive across the EU has to date contributed to inconsistencies in application. It is important that the definitions proposed in the Regulation do not result in similar problems. Additional clarity would therefore be helpful on the new concept of ‘clinical studies’ to reduce the possibility of confusion in these proposals.

8. Similarly, some of the terms used in the proposed Regulation will add confusion without further clarification. For example, ‘low intervention trials’ and ‘non-interventional trials’ are not scientifically meaningful terms. There is a danger that confusion around terminology will lead to interpretations of the final regulation that could inhibit research.

IT systems associated with the Regulation

9. The timelines that have been set by the proposed Regulation both for Member States to gain ethical and regulatory approval and also for sponsors to respond to regulatory queries are ambitious. We welcome the efforts to speed up the assessment process – efficient operation of the IT systems

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

² Medical Research Council, Department of Health, Medicines and Healthcare Products Regulatory Agency. Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products; 2011. Available at: <http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf>

associated with the single portal proposed will be essential to ensure this. We believe the EU institutions should therefore outline to the community how it will go about creating and implementing the IT systems associated with the Regulation. **The introduction of a single application portal with a single application dossier is particularly attractive to streamlining and harmonising the application process for clinical trials, so it is important that this is sufficiently supported by the necessary infrastructure.**

Co-sponsorship

10. The requirement under the current Directive for trials to have a single sponsor for the application continues to provide practical difficulties for academic sponsors, as it is difficult for an academic sponsor to hold the responsibility for clinical trials performed in another Member State – particularly when there have been differences in the way the Directive has been implemented. **We therefore welcome the introduction of the concept of co-sponsorship for clinical trials in the proposed Regulation.**

Emergency trials

11. In addition, the current Directive does not sufficiently address the issue of consent for clinical trials in emergency situations – in situations such as myocardial infarction where it may not be feasible to obtain informed consent from the patient. Since the Directive was transposed, the UK legislated to allow clinical trials in emergency situations, with many other Member States similarly amending their own legislation. We are pleased that this gap is being addressed in the proposed Regulation, though the specific requirements in the proposals that this type of trial should not impose more than minimal additional risks or burdens on patients are potentially too broad. **We believe the requirements for entry into clinical trials in emergency situations should be reviewed to ensure they do not inadvertently limit the intended provision.**

Indemnity scheme

12. The introduction of a Government-run indemnity scheme for clinical trials is of potential interest – a more detailed outline of this proposal from the Commission needs to be provided before it is given full consideration.

Improvements to regulation and governance in the UK

13. While there are a number of improvements that can be made at European level to the regulation of clinical trials, there remain several barriers specifically within the UK that contribute to delays in clinical trials.

14. The BHF strongly supports the Academy of Medical Sciences' report on research and governance, which has identified the main obstacles to medical research in the UK. The complexity of the regulatory pathway, delays and duplication for permissions from NHS Trusts, and the problems within the culture of the NHS to facilitate research were all areas that we highlighted in our response to the Academy's call for evidence. The creation of the Health Research Authority (HRA) is the first step towards helping to simplify the regulatory pathway, facilitate research and ensure that governance does not impede progress. We believe the Government should ensure the full implementation of the Academy's recommendations is completed as soon as possible.

15. A key barrier to date has often been that research is not seen as a core function by many within NHS Trusts. A much more research-oriented mentality is needed, particularly among health service managers, to ensure that R&D departments promote and facilitate research. The Health and Social Care Act 2012 placed duties on all the main commissioners and providers to promote research – it is vital that this supportive attitude towards research is now embedded into practice on the ground.

16. The UK Government has taken a number of encouraging steps to implement many of the recommendations of the Academy of Medical Sciences review, but there are several that have not been implemented that would further streamline regulation and governance. But we remain concerned that some of the roles recommended for a single health research regulator, specifically around incorporating NHS R&D permissions, have not been included within the remit of the new HRA. Researchers continue to raise this as a major barrier to cardiovascular research being conducted. One recent example is the BHF-funded PATHWAY study (Prevention And Treatment of resistant Hypertension With Algorithm based therapy). **This study took more than a year to get started because of delays caused by governance and NHS funding issues.** The study comprises of three clinical trials in eight centres – five based in England, three in Scotland. The longest delays occurred in agreeing the contracts between the lead site at the University of Cambridge and seven other centres. For combined university and health trust sign-up, some sites wanted separate agreements for each trial, which would have amounted to 21 agreements for the University of Cambridge to prepare for just one grant.

Using patient data to help clinical trials

17. Patient records provide useful data that medical researchers can use in a variety of different ways, from evaluating current healthcare interventions to looking at links between disease and someone's lifestyle. These data are also used to help identify patients that would potentially benefit from participation in clinical trials. The NHS holds the medical records for the largest single patient pool in the world and therefore potentially provides researchers in the UK with an invaluable resource for research. There are a number of barriers currently preventing researchers from readily using these data to their full potential in medical research, which we have highlighted in our report *Clear and Present Data*.³ These concerns have also been reflected in our response to the Department of Health's Information Governance Review.

Q2: What is the role of the Health Research Authority (HRA) in relation to clinical trials and how effective has it been to date?

18. As part of the Academy of Medical Sciences review of regulation and governance, we responded to the second call for evidence highlighting our support in principle for the creation of a single research regulator, which could provide a number of opportunities to improve the system of approval. We hope that the HRA will develop a streamlined system whereby there is a single point of entry and exit for researchers' applications.

19. It is still too early to judge the effectiveness of the HRA in improving how research is regulated in the UK. However, we are encouraged that one of its first initiatives has been to commence a study to examine the feasibility of establishing an HRA assessment that would combine and replace aspects of the current review by NHS R&D and Research Ethics Committees (RECs). While this has the potential to speed up the approval process, ultimately we believe bringing NHS R&D permissions

³ British Heart Foundation. Clear and present data; 2012. Available at: <http://www.bhf.org.uk/patientdata>

within control of the HRA, in line with the recommendations of the Academy of Medical Sciences review, would have the greatest benefit in improving this barrier.

Q3: What evidence is there that pharmaceutical companies withhold clinical trial data and what impact does this have on public health?

20. The pharmaceutical industry makes a vital contribution to medical research in the UK, and has been key to the development of many of the treatments used in the treatment of cardiovascular disease today. As a funder of medical research, the BHF predominantly supports the basic science and pre-clinical work that results in new medicines reaching the stage where it is tested in clinical trials. It therefore often takes the resources provided by a pharmaceutical company to conduct the large-scale clinical trials required to ensure safety and efficacy before a new medicine is ultimately prescribed to patients.

21. Clinical trial data are essential in establishing whether a new treatment is both safe for patients and effective. Ensuring that these data are publicly open to scrutiny is important to ensure research findings are robust and transparent. Publishing data in a form where this can be achieved is therefore essential.

22. However, there are some examples in the past where clinical trial data have been withheld by pharmaceutical companies. One instance within cardiovascular research concerns anti-arrhythmic drugs. Several Class 1 anti-arrhythmic drugs were the subject of two Cardiac Arrhythmia Suppression trials (CAST and CAST-II) that ran from 1986. The trials found that these Class 1 anti-arrhythmia drugs, rather than reduce mortality, actually increased mortality in the results published in 1991.⁴ The finding led to a dramatic reduction in the usage of these agents, particularly in Europe and Australasia.⁵ Earlier unpublished research from 1980 on another Class 1 anti-arrhythmia drug could have highlighted the dangers posed. This research looked at the use of the drug lorainide in 95 patients with suspected acute myocardial infarction in a double-blind study, and while finding it to be an effective anti-arrhythmic agent found that there were nine deaths among the 49 patients treated with lorainide compared with only one in the patients given placebo. An analysis part-funded by the BHF found that the results of this unpublished study were consistent with those from the later CAST and CAST-II trials.⁶ This highlights the importance of publishing results from clinical trials, as this mortality link could have potentially been established earlier. The issue of pharmacovigilance – whereby the safety and efficacy of drugs or devices used in healthcare is monitored – is also one where better access to patient records would be beneficial.

23. Failure to publish research and clinical trial data can therefore hinder medical and scientific progress and have a damaging effect on public health. Clinical trial data showing that a particular treatment is not effective are just as useful to research as data showing a benefit. Much of the clinical

⁴ Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, Arensberg D, Baker A, Friedman L, Greene HL. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med.* 1991 Mar 21;324(12):781-8. Available at:

<http://europepmc.org/abstract/MED/1900101>

⁵ Campbell TJ, Williams KM. Therapeutic drug monitoring: antiarrhythmic drugs. *Br J Clin Pharmacol.* 1998 October; 46(4): 307–319. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1874159/>

⁶ Cowley AJ, Skene A, Stainer K, Hampton JR. The effect of lorainide on arrhythmias and survival in patients with acute myocardial infarction: an example of publication bias. *Int J Cardiol* 1993, 40(2):161-166. Available at: <http://europepmc.org/abstract/MED/8349379>

research in the UK is undertaken by academic and NHS clinicians with no financial interest in the outcome of that research, but the importance of publishing trial results applies to both commercial and non-commercial research. We recognise that transparency is an important issue for clinical trials – not only for those that make use of the results, but also for those that fund, conduct and participate in trials. For research that we fund, our conditions of award state that the findings from the research funded by the grant should be made freely available to the broader scientific community as soon as possible. In addition, the conditions state that grant holders must comply with the BHF's Policy on Open Access and deposit within Europe PubMed Central an electronic copy of each paper funded wholly or in part by the BHF, which is accepted for publication in a peer reviewed journal, within 6 months of publication.

Q4: How could the occurrence and results of clinical trials be made more open to scrutiny? Who should be responsible?

24. Public registration of clinical trials is important in ensuring transparency and researchers in the EU have a legal responsibility to register clinical trials of investigational medicinal products on the EudraCT clinical trials database. This registration is also a pre-requisite for applying for authorisation from the MHRA and for research ethics committee approval. Information on many UK trials that are currently recruiting is also included on the online UK Clinical Research Network portfolio database, which is beneficial in helping patients find out about suitable clinical trials to take part in. The EU Clinical Trials Register website was also launched to provide the public with information held in the EudraCT database of clinical trials.

25. Sponsors of trials also have a legal responsibility under the Medicines for Human Use (Clinical Trials) Regulations 2004 to provide an end-of-trial report 12 months from the end of the trial. The EudraCT database does not, however, collect the results of clinical trials and there is no single place where clinical trial results are published. Current plans from the European Commission would lead to EudraCT collecting results and making them publicly available.⁷ This could go some way towards improving transparency.

26. It is important that published clinical trial data accessible to the public is in a form that is of use to researchers and has been collected using sound clinical trial methodology. Publishing data that is not sufficiently robust can be potentially damaging because such data may lead to misinterpretation and incorrect conclusions as a result. Peer-review in this regard is therefore important in helping to ensure that the data are robust, which normally takes places via journals.

27. Ideally, clinical trials would publish results within a year of completion, but publishing data can be delayed for valid reasons – for example, more data may be required or there may be questions from reviewers during the peer-review process that require a resolution.

The act of finalising results can therefore take time, particularly if this involves presentation in a series of papers. This also often occurs alongside other pressures on researchers. For example, the reports of the Heart Protection Study took substantial time to write, at a time when those that conducted the trial were conducting other trials during this period.

⁷ http://ec.europa.eu/health/files/eudralex/vol-10/2012_302-03/2012_302-03_en.pdf

28. As highlighted above, medical researchers currently experience a complex environment for regulation and governance in the UK. Legislation has, as shown by the Clinical Trials Directive, been disproportionate in its application on medical research. Any actions taken to improve transparency of clinical trial data therefore need to be proportionate in nature – a one-size-fits-all approach on publication within a certain timeframe is unlikely to be appropriate if it fails to take into account the consideration of large-scale trials. The issue of improving transparency for clinical trials should also not be taken by the UK in isolation – the new Clinical Trials Regulation provides a means for this to be applied across all Member States.

February 2013

Written evidence submitted by the Academy of Medical Sciences (CT32)

Summary

- Clinical and health research is vital to the health and wealth of the UK. The Academy of Medical Sciences has been at the forefront of calls to strengthen the support, regulation and governance of this area.
- The Clinical Trials Regulation is an improvement to the Clinical Trials Directive, although outstanding concerns remain. A major barrier to clinical research in the UK is the delay and duplication in obtaining research permissions from each NHS Trust involved in a trial.
- The Academy welcomes the establishment of the Health Research Authority. Although too early to judge success, we are supportive of the HRA's initial plans.
- We welcome the debate on, and efforts to improve, clinical trials transparency. Inevitably the results of clinical and health research are influenced by chance and other sources of variation. If only research with extreme, or favourable, results reach the public domain, a biased conclusion regarding interventions will be drawn. Transparency about the methods and results of all research is the best guard against such biased conclusions.
- The existence, methods and results of clinical and health research involving patients whether positive or negative should be made swiftly available for patient, social and scientific benefit. Many mechanisms to promote transparency, including registries, are best tackled in a coordinated and consistent manner at an international level involving the wide range of stakeholders.
- The Academy believes that the results of clinical and health research should be placed in the public domain through peer-reviewed media such as scientific journals. Validated research summary reports and clinical study reports without patient level data should be posted on a public web-based database, after regulatory approval and where relevant. Further consideration should be given to mechanisms to allow access to more detailed data given the need to protect patient confidentiality and to ensure that data is intelligible, assessable, reliable and usable.
- The Academy would be happy to give oral evidence to the Committee.

Introduction

1. The independent Academy of Medical Sciences promotes advances in medical sciences and campaigns to ensure that these are converted into health benefits for society. Our elected Fellowship includes some of the UK's foremost experts in medical science some of whom provided advice on this response (see Appendix 1).
2. Clinical and health research improves the health and wealth of the UK.¹ Recently the UK's strength in health research has been threatened. Our global market share of patients in pharmaceutical trials has fallen from 6% to 1.4% and there has been a similar experience in academic trials.² Central to this decline has been inappropriate regulation that prevents many clinical trials starting quickly and causes unnecessary costs. A proportionate and appropriate system of regulation and governance is essential to improving patient and public health by supporting UK clinical trials and attracting clinical trials from abroad. The Academy has played

¹ Academy of Medical Sciences (2010). *Biomedical research – platform for increasing health and wealth in the UK* <http://www.acmedsci.ac.uk/p48prid84.html>

² NESTA (2011) *All together now: improving cross sector collaboration in the UK biomedical industry.* http://www.nesta.org.uk/library/documents/Report_67_Biomed_web.pdf

a leading role in streamlining research regulation through our reports and consultation responses.³

The Clinical Trials Regulation (CTR) and the main barriers to conducting clinical trials in the UK and EU

Strengths of the proposals for the CTR

3. The Academy believes that the proposals for the new CTR are an improvement on the current Clinical Trials Directive (CTD). Particularly welcome are:
 - Greater proportionality and greater scope for risk adaptation.
 - Formal introduction of co-sponsorship to help partnerships between universities and hospitals, between EU countries, and within the UK.
 - Ambitious timelines to speed up the approval process that should be retained and encompass UK-specific assessments.
 - The use of a Regulation rather than a Directive that will reduce differing national interpretations.
 - Single submission via an EU portal that will facilitate multi-national trials.
4. We welcome the Medicine and Healthcare products Regulatory Agency's (MHRA's) engagement with stakeholders and the establishment of a reference group on which the Academy is represented.
5. Despite the above improvements a number of concerns remain:

Clarity and clarification

6. Five areas that require further clarification are:
 - How European institutions will create and implement the IT systems required to establish a single application portal and single application dossier. The publication of plans to deliver these systems would provide reassurance.
 - How personal data will be protected in the new public database and EU portal; and further information on the timing of the disclosure of such data.
 - Whether the US National Institute of Health (NIH) register clinicaltrials.gov will be included among the World Health Organization (WHO) accredited primary registries on which clinical trials are required to be registered. [Clinicaltrials.gov](http://clinicaltrials.gov) is the main registry used worldwide by sponsors but is not listed as a WHO primary register. We are keen to avoid unnecessary proliferation of registries, see paragraphs 36 and 44.
 - An assessment of whether allowing sponsors to choose the National Competent Authority (NCA) to which they apply means that stronger NCAs, such as the MHRA, receive many more applications. This could lead to excessive burdens on some NCAs that might impede their ability to regulate research nationally.
 - That insurance arrangements for multi-state trials (while welcome) will not be too cumbersome.
7. Although legally and internally consistent, some of the definitions in the CTR are different from those used by scientists. For example, the term 'low intervention trials' is not widely

³ Further information is available from: <http://www.acmedsci.ac.uk/index.php?pid=47&prid=88>
<http://www.acmedsci.ac.uk/index.php?pid=47&prid=118> <http://www.acmedsci.ac.uk/p100puid220.html>
<http://www.acmedsci.ac.uk/p100puid176.html> and <http://www.acmedsci.ac.uk/p100puid256.html>

recognised scientifically. Confusion around terminology may lead to conservative interpretations of the CTR that could inhibit research. We therefore strongly encourage clearer guidance and communication with stakeholders and an accepted glossary of terms.

Proportionality and established treatments

8. While measures to increase the proportionality of the CTR are welcome, we are keen that this will be reflected in practice. For example, measures to introduce proportionality should ensure that trials testing established treatments with good safety profiles for novel uses should be considered low risk if the case for this is made. Where the safety profile of an intervention is very well known, adding burdens of monitoring does not benefit public health.

Increased focus on trial conduct and oversight

9. The CTR should focus more on the facilitation of overall trial conduct and oversight, including:
 - More efficient approaches to trial conduct and monitoring in non-commercial settings that focus less on approaches derived from the International Conference on Harmonisation guidelines for Good Clinical Practice ('ICH-GCP'). The interpretation and implementation of ICH-GCP in practice has focused on specific aspects of its wording rather than its overarching intended objectives. This has resulted in rigid procedures that have been unduly prescriptive and obstructive. We welcome the HRA's recent statement that GCP training for researchers should be appropriate and proportionate to the type of research undertaken.⁴
 - The requirement for prior interview for consent that would pose a challenge to some studies where the only contact with participants is by post or electronically. A solution might be to change the text from 'prior interview' to 'prior dialogue' as this would allow greater choice in the method of communication.

Streamlined research generates results and data for further analysis

10. As discussed in a later section, we welcome the debate on, and efforts to improve, transparency around the existence, methods and results of clinical trials. It is important that the resource requirements of any new systems in the CTR to improve transparency are proportionate.

Additional barriers to clinical trials

11. The Academy's 2011 report on the regulation and governance of health research identified delay and duplication inherent in obtaining research permissions from each NHS Trust involved in a trial as the greatest barrier to health research in England (see also paragraph 16).⁵ Largely this barrier remains, however, we welcome recent steps by the National Institute for Health Research (NIHR) to incentivise reductions in the timeline. This includes the introduction of benchmarks for the approval and delivery of clinical trials linked to NIHR's funding of NHS organisations.
12. Other barriers include a lack of understanding about the complex regulatory and governance framework and lack of a 'one stop shop' or single portal for application and guidance.

⁴ HRA (2012). Training requirements for researchers. <http://www.hra.nhs.uk/hra-news-and-announcements/training-requirements-for-researchers/>

⁵ Academy of Medical Sciences (2011). *A new pathway for the regulation and governance of health research*. <http://www.acmedsci.ac.uk/p47prid88.html>

The role of the Health Research Authority (HRA) in relation to clinical trials

13. We support the initial plans of the HRA, although it is too early to judge whether it will be successful. The HRA is currently being established in primary legislation in the draft Care and Support Bill that has provided an opportunity to see how the HRA compares to our vision of a single regulator.^{6,7}

14. We welcome the HRA's focus on promoting the co-ordination and standardisation of the regulation and governance pathway of health and social care research in the UK and, as with the CTR, in seeking to ensure that such regulation is proportionate. This should help to reduce bureaucracy.

15. The HRA and MHRA have recently announced that they will not continue development and launch of e-submissions at this time, which formed a core component of the HRA's vision of a single unified process for applications.⁸ This vision was also articulated in our report. Further clarity is needed on how the HRA will coordinate the activities of review bodies, with sufficient authority and levers to provide a single route for all approvals and permissions.

16. Our vision for the HRA included the creation of a National Research Governance Service within the HRA that would support NHS Trusts and researchers by undertaking all **study-wide NHS research governance checks** just once. This was to ensure common standards and a consistent interpretation of the requirements. This recommendation was not taken forward and the Care and Support Bill does not explicitly mention the HRA's role in facilitating NHS research governance.⁹

17. We welcomed the HRA's recent announcement of a feasibility project that will explore whether it can support NHS Trusts by providing them with a simplified, streamlined and quality assured assessment for all research in the NHS.¹⁰ If successfully implemented, this would address the major barrier to research identified in our report.

18. The HRA should have a role in **developing metrics and indicators** for the regulation and governance pathway as a whole, and monitoring these to ensure that improvements are being made. It will be important to ensure that the timeline is not being manipulated (e.g. by 'stopping the clock' more often) and that the introduction of new benchmarks for Trust's research performance does not discourage them from undertaking certain types of research (e.g. more complex trials or those on rare diseases). Reliable metrics are extremely important both in terms of providing feedback on the success of initiatives but also in communicating success internationally to companies and researchers seeking locations for clinical trials.

19. In fulfilling its roles and functions, the HRA needs to **engage with a wide range of stakeholders**. The HRA has been in dialogue with patients and their representatives since its

⁶ Academy of Medical Sciences (2013). *Response to the joint scrutiny committee inquiry on the draft care and support bill*. <http://www.acmedsci.ac.uk/p100puid264.html>

⁷ Academy of Medical Sciences (2012). *Response to the Department of Health consultation on the draft Care and Support Bill*. <http://www.acmedsci.ac.uk/p100puid256.html>

⁸ Further information on this topic can be found at: <http://www.hra.nhs.uk/hra-news-and-announcements/future-of-iras/>

⁹ Academy of Medical Sciences (2013). *Response to the joint scrutiny committee inquiry into the draft Care and Support Bill*. <http://www.acmedsci.ac.uk/p100puid264.html>

¹⁰ HRA (2012). *HRA given go-ahead for feasibility study: HRA assessment for approval of research in the NHS*. <http://www.hra.nhs.uk/hra-news-and-announcements/hra-given-go-ahead-for-feasibility-study-hra-assessment-for-approval-of-research-in-the-nhs/>

establishment and we welcome the establishment of the HRA's Collaboration and Development group, on which the Academy is represented.

20. The recent transfer of responsibility for the research use of **confidential patient information** to the HRA provides a good opportunity to reduce complexity in this area of regulation and governance that has led to conflicting interpretations of it by researchers, Trusts, patients and other stakeholders.

21. We welcome the HRA's announcement of plans to follow up the commitments that researchers make to research ethics committees relating to the registration and **publication of trials** (see below).

Clinical trials transparency and disclosure of data

The importance of openness

22. The Academy strongly supports efforts to increase transparency around the existence, methods and results of clinical and health research. There is an excellent case for making the findings of research that involves patients available, because:

- Individuals often contribute to research for altruistic reasons and expect the results to be accessible by all.
- Failure to do so may mean that patients are unnecessarily put at risk in studies when results are already known.
- Under-reporting of research can lead to avoidable harm to patients and can waste limited healthcare and research resources.¹¹
- Greater access to appropriately controlled data for valid scientific inquiry offers significant scientific benefits and helps ensure scientific validity, particularly for large studies where replication is more difficult.
- It helps to develop hypotheses and improves trust in clinical and health research.

23. Transparency is an important issue for all those who conduct, fund, participate in and utilise the results of clinical trials in industry, academia, the NHS, charities and elsewhere. Solutions will therefore require the involvement of a wide range of stakeholders. The increasing number of cross-sectoral collaborations between these groups means that responsibility for transparency is increasingly shared.

24. Single studies rarely provide definitive evidence to answer important clinical questions.¹² Looking at a series of studies helps to address the effect of chance and other variation in results. It is usually necessary to combine results of studies to obtain reliable answers. If only research with extreme, or favourable, results reach the public domain, a biased conclusion regarding interventions will be drawn. Transparency about the methods and results of all research is the best guard against such biased conclusions.

25. Much discussion about transparency to date has focused on clinical trials to develop pharmaceuticals. However, clinical and health research is also conducted in other areas where transparency is important such as those involving surgery; devices; psychological, educational or organisational interventions; and understanding the causes and mechanisms of disease.

¹¹ Chalmers I & Glasziou P (2009). *Avoidable waste in the production and reporting of research evidence*. *Lancet* 374, 86-89.

¹² Ioannidis JPA (2005). *Why Most Published Research Findings Are False*. *PLoS Med* **2(8)**, e124. doi:10.1371/journal.pmed.0020124

26. The wide range of types and size of clinical and health research means that developing appropriate and generalisable guidelines and regulations will require considerable thought.

Clarity around transparency

27. Transparency in clinical and health research can cover many different sorts of activity some of which are undertaken at the present time and some of which are not, these include:

- public registration of trials, including their methods and protocols.
- public posting of progress of trials and summaries of results.
- publication of trials in journals.
- public posting of clinical study reports.
- providing access to individual patient level data.

28. Clarity about which aspect of transparency is being discussed is important as each presents different issues. It can also be helpful to distinguish between data, information and knowledge as is described in the recent Royal Society report '*Science as an open enterprise*'.¹³

29. Currently sponsors of clinical trials involving pharmaceuticals in the UK are expected to provide the MHRA and the relevant ethics committee with a report 12 months from the end of a trial.¹⁴ Funders often require the wider publication of trial results as part of their terms and conditions, and research ethics committees ask how researchers plan to publish their data and results before approving projects. Many medical journals endorse the CONSORT statement that encourages transparent reporting and describes ways in which this can be achieved.¹⁵ The European Union Drug Regulatory Authorities Clinical Trials (EudraCT) database of all recent EU clinical trials of investigational medicinal products does not collect the results of clinical trials and there is no single place where clinical trial results are published. However, we are aware of plans to collect results and make them publicly available.¹⁶

Models for transparency

30. The Academy believes that clinical and health research should be presented in a form that is intelligible, assessable, reliable and usable.¹⁷ The gold standard mechanism to achieve this goal is peer-review, which often takes place through journals. The results of clinical and health research should be placed in the public domain through peer-reviewed media such as scientific journals. Validated research summary reports and clinical study reports with patient level data removed should be posted on a public web-based database, after regulatory approval and where relevant. The resource implications of this proposal are considered in paragraph 33. Further consideration should be given to mechanisms to allow access to more detailed data to address issues such as patient confidentiality, particularly in small studies or for studies of rare diseases, and to ensure that data is intelligible, assessable, reliable and usable.

¹³ Royal Society (2012). *Science as an open enterprise*. <http://royalsociety.org/policy/projects/science-public-enterprise/report/>

¹⁴ Association of Medical Research Charities (2013). *Registration of clinical trials*. <http://www.amrc.org.uk/home/>

¹⁵ Further information about CONSORT is available from: <http://www.consort-statement.org/>

¹⁶ Association of Medical Research Charities (2013). *Registration of clinical trials*. <http://www.amrc.org.uk/home/>

¹⁷ Royal Society (2012). *Science as an open enterprise*. <http://royalsociety.org/policy/projects/science-public-enterprise/report/>

31. Careful consideration should be given to the storage and management of more detailed data from clinical and health research to tackle issues such as applications from countries that do not have as robust regulatory and governance frameworks as the UK.

32. As discussed in paragraph 24, when important issues of treatment or outcome effect have been studied in several trials, reliable systematic reviews are the preferred method for presenting summary data. Results from a single study may be misleading. This should be considered when thinking about open access to data of individual trials.

Resource requirements

33. Any initiatives or regulation around transparency should be proportionate and seek to maximise net patient and social benefit. One important consideration is the resources required to achieve the different sorts of transparency discussed earlier. This will need to be balanced against the benefits that greater transparency could bring, for example by preventing research in areas shown to be unproductive. Thought needs to be given about who should pay for creating and maintaining the requisite infrastructure and for any costs to researchers for uploading data. This is a particular challenge for non-commercial funders that often have less resources than industry. The issue of resource requirements for transparency are considered in the Royal Society's report on '*Science as an open enterprise*'.¹⁸

Roles and responsibilities for clinical trials transparency

34. GSK recently committed to a system of transparency where clinical study reports, are made publicly available through their clinical trials register.¹⁹ In a separate initiative, GSK will also provide a system to request access to anonymised patient level data for further research, with requests reviewed by a committee that GSK has announced will be composed of independent experts. GSK hopes that this will be a first step to a model whereby researchers can access trial data from multiple sponsors from industry, academia and charities to conduct further research. This initiative has been welcomed by many, although some have argued that responsibility for providing access to clinical trial data that has been authorised for marketing should be independent from the sponsor. The regulator might fulfil this role as this might engender greater public trust, although EU/UK regulators might not have the full dataset and this would only cover trials submitted as part of the market authorisation dossier. Furthermore, the UK regulator is only responsible for some types of medical intervention that might be the subject of clinical trials, such as drugs, but not others, such as changes to health education.

35. The European Medicines Agency's (EMA's) commitment to make clinical research data more available is welcome and we are keen to participate in the multi-stakeholder conversation about how this might be achieved.²⁰ We also welcome the BMJ's recent commitment to only publish trials where there is access to data on 'reasonable request'.²¹

The role of registries

36. Appropriately accredited public trials registries offer a useful mechanism for monitoring and encouraging transparency around clinical trials. There is a legal responsibility for all trials applying

¹⁸ Royal Society (2012). *Science as an open enterprise*. <http://royalsociety.org/policy/projects/science-public-enterprise/report/>

¹⁹ Further information on GSK's announcement can be found at: <http://www.gsk.com/media/press-releases/2013/GSK-announces-support-forAll-Trials-campaign-for-clinical-data-transparency.html>

²⁰ EMA (2012). *Access to clinical trials data and transparency workshop report*. EMA, London.

²¹ Godlee F (2012). Clinical trial data for all drugs in current use. <http://www.bmj.com/content/345/bmj.e7304>

for clinical trial authorisation to be registered on the private EudraCT clinical trials database.²² We are aware of a number of different registries in different countries and different fields so are keen that these initiatives are coordinated and coalesce to avoid duplication of effort and to increase simplicity (see paragraphs 6 and 44).²³ Patient friendly information should be available for all trials that are open for recruitment as is currently the case for all cancer trials recruiting people in the UK through Cancer Help, and via the UK Clinical Trials Gateway.^{24,25} Evaluative tools such the services provided by the company Research Fish and Research Council UK's Gateway to Research can also help monitoring.^{26,27}

Negative results

37. While the results of much clinical and health research with positive results are currently available, the results of much research with negative results or research that closed early are not.²⁸ This has major consequences for unbiased assessment of the totality of evidence on a clinical or public health question. Non-publication can result from factors such as:

- competition for space in journals.
- lack of capacity or willingness by researchers in industry and public service to spend time preparing such research for publication.

38. The Academy is a supporter of Universities UK's Research Integrity Concordat that commits to ensuring rigour, transparency and open communication when reporting research data, including the sharing of negative results.²⁹ The publication of negative results can help:

- ensure that time and resources are not spent pursuing unproductive areas of research.
- identify alternative uses for drugs or highlight patterns in responders and non-responders that might indicate sub-populations where the drug might be more effective.

39. A non-journal based portal with peer-review to ensure quality might help facilitate the publication of negative results. We are also aware of, and welcome, journals dedicated to publication of negative findings, such as the Journal of Negative Results in Biomedicine, or commitments by journals to publish negative results, such as from PLOS ONE.^{30,31}

Ensuring timely publication

40. Publication of clinical and health research in journals should happen as swiftly as practically possible once studies are complete and the results validated. However, we believe that setting a single deadline for publication of results of all clinical and health research in journals would not be helpful because:

- Researchers require time to rigorously analyse their findings.

²² Association of Medical Research Charities (2013). *Registration of clinical trials*.

<http://www.amrc.org.uk/home/>

²³ Examples of registers include: Clinical Trials.gov: <http://www.clinicaltrials.gov/> EudraCT: <https://eudract.ema.europa.eu/> and Current Controlled Trials: <http://www.controlled-trials.com/>

²⁴ Further information is available from: <http://www.cancerresearchuk.org/cancer-help/>

²⁵ Further information on the UK Clinical Trials Gateway is available from:

<http://www.ukctg.nihr.ac.uk/default.aspx>

²⁶ Further information on Research Fish is available from: <https://www.researchfish.com/>

²⁷ Further information on RCUK's Gateway to Research is available from:

<http://www.rcuk.ac.uk/research/Pages/gtr.aspx>

²⁸ For the purposes of this response the term 'negative results' refer to those studies where there is no evidence of the intended effect but are nevertheless scientifically useful.

²⁹ Universities UK *et al* (2012). The concordat to strengthen research integrity.

<http://www.hefce.ac.uk/whatwedo/rsrch/rinfrastruct/concordat/>

³⁰ Further information is available from: <http://www.jnrbm.com/>

³¹ Further details of PLOS ONE is available from: <http://www.plosone.org/>

- A single study may generate several papers that each may take time to prepare.
- Different journals have different times for peer-review.
- A paper may not be accepted by the first journal to which it is submitted.
- Researchers should have some initial degree of exclusivity to results otherwise there will be significantly less incentive to conduct important studies as the reward will be accrued by others.

41. As discussed in the previous section, we welcome the HRA's plans for research ethics committees to follow up publication plans with researchers and hope these will be proportionate.

42. We are aware of calls for retrospective registration and reporting of the full methods and results of all trials.³² Resources could be a key constraint in this regard and are considered further in paragraph 32. The Academy believes that the focus should be on developing mechanisms to ensure rapid prospective posting and publication of current and future trials as this can be practically addressed more swiftly.

Tackling clinical trials transparency and data disclosure internationally

43. As a result of globalisation clinical trials are increasingly conducted both within and between more countries than ever before. Transparency therefore needs to be tackled at the international level. This would:

- improve coordination
- increase simplicity
- reduce duplication
- help ensure that the UK remains scientifically competitive

44. We are aware that national and regional regulators, such as the MHRA and US Food and Drugs Administration (FDA), are already in regular communication on the matter of clinical trials transparency. Moreover, the Academy is discussing joint work on this issue with the US Institute of Medicine (IOM), our sister academy in the USA. There is an opportunity for the UK to take an important role in this area through engagement with others at an international, particularly European, level. However, we also understand that there are already many international measures that require the registration of trials and posting of results. It is therefore important to avoid duplication, particularly with UK specific solutions, see paragraphs 6 and 36.

This response was prepared by Christian Markus Hüber (Medical Science Policy Intern) and Laurie Smith (Medical Science Policy Manager). A draft was considered by Council and the final draft was signed off on their behalf by the President.

Declaration of interests

Many of the Academy's Fellows and experts who contributed to this response are involved directly or indirectly with academia, life sciences industries and the NHS. Further details are available upon request.

³² Further information is available from: <http://www.alltrials.net/>

The Academy of Medical Sciences

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The Academy seeks to play a pivotal role in determining the future of medical science in the UK, and the benefits that society will enjoy in years to come. We champion the UK's strengths in medical science, promote careers and capacity building, encourage the implementation of new ideas and solutions – often through novel partnerships – and help to remove barriers to progress.

February 2013

Annex 1 Contributing experts

We are grateful to the following individuals for their inputs into this response:

- Professor Sir John Bell FRS HonFREng FMedSci, Regius Professor of Medicine, University of Oxford
- Professor Dame Valerie Beral DBE FRS FMedSci, Head of the Cancer Epidemiology Unit, University of Oxford
- Professor Sir Alasdair Breckenridge CBE FRSE FMedSci
- Professor Sir Iain Chalmers FMedSci, Co-ordinator, James Lind Initiative
- Professor Sir Rory Collins FMedSci, Professor of Medicine and Epidemiology and Co-Director of the University of Oxford's Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), University of Oxford
- Professor Janet Darbyshire CBE FMedSci, Emeritus Professor of Epidemiology, University College London
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- Professor Stephen Evans, London School of Hygiene and Tropical Medicine
- Professor Lesley Fallowfield FMedSci, Director of SHORE-C and Professor of Psycho-Oncology, University of Sussex
- Professor Gary Ford, Jacobson Chair of Clinical Pharmacology, Newcastle University
- Professor Michael Parker, Professor of Bioethics and Director of the Ethox Centre, University of Oxford
- Professor Sir Michael Rawlins FMedSci, Chairman, National Institute of Clinical and Health Excellence
- Professor Geneva Richardson CBE FBA, The Dickson Pool School of Law, King's College London
- Professor Caroline Savage FMedSci, Vice-President and Head of the Experimental Medicine Unit, GSK
- Professor Robert Souhami CBE FMedSci, Foreign Secretary, Academy of Medical Sciences
- Professor Sir John Tooke PMedSci, President, Academy of Medical Sciences
- Professor Patrick Vallance FMedSci, President, Pharmaceuticals R&D, GSK
- Professor Sir Simon Wessely FMedSci, Vice-Dean and Professor of Psychological Medicine, Institute of Psychiatry, King's College London

Written evidence submitted by King's Health Partners' (CT33)

Question 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?

1. Many of the changes from the CTD proposed in the text are welcomed; in particular, the acceptance of co-sponsorship, the national indemnity scheme and some of the risk adapted modifications. On balance, we welcome the replacement of the CTD with a Regulation as it will remove much of the disparity introduced by Member State interpretation of the requirements of the Directive. However we have practical concerns about how the transition will work which may need to be addressed, in the following areas. Key considerations from KHP:
 - i. The Directive and Regulation are to run in parallel for three years. It is unclear how this will work. Sponsors will be keen to know which will take precedence during this period.
 - ii. It is unclear how the ICH requirement will work. There is no mention of repealing the GCP Directive (2005/28EC) but the Regulation cites ICH GCP with a cryptic caveat "...provided there is no other specific guidance issued by the Commission and that those guidelines are without prejudice to this Regulation." (Recitals; Clause 29; p 19)
 - iii. It is unclear whether the parallel period starts in 2014 or 2016. In the Explanatory Memorandum 3.13; p11 it states that: "...the regulatory framework at EU level will be complemented by national laws." It gives an example but a more comprehensive list of where this will apply would be useful. If national laws permit member states to variously tighten and relax the impact of the Regulation we may not be much better off than with the CTD.
 - iv. Proposed reporting times - times for declaring start and end of trials are short and potentially onerous.
 - v. Safety reporting requirements for Sponsors - there are requirements for Sponsors to make periodic reports to MA holders for IMPs. This will be difficult and resource intensive for non-commercial Sponsors.
 - vi. Co-Sponsorship – The proposal to permit co-sponsorship is welcomed. To date most member states have not permitted co-Sponsorship. In the UK non-commercial Sponsors have successfully engaged in co-Sponsorship arrangements which allow sponsor obligations to be distributed between institutions. KHP routinely co-sponsors within the partner institutions and with third parties and welcomes the potential ability to co-Sponsor with institutions in other member states.
 - vii. Risk Adapted modifications – The proportional approach to approvals and requirements for low risk trials is welcome. However, we have concerns that compiling the evidence (as currently required) to establish the risk of a given trial may prove onerous for the non-commercial sector. Consideration should be given to simplifying this process as it currently discourages researchers from attempting to have their studies classified as low risk.
 - viii. In type A trials, we believe consideration should be given to adopting a system where no adverse event reporting beyond that normally occurring in routine clinical practice should be required – ie investigator sites and not sponsors should be responsible for submitting reports via Member States' national pharmacovigilance reporting systems (In the UK this is the 'Yellow Card' scheme <https://yellowcard.mhra.gov.uk/hcp-form/reporterdetails/>) and recording the event in the study CRF for the purpose of Data Monitoring Committee (safety committee) review, if one is established. Beyond this, any requirement to report adverse events centrally which do not meet 'Yellow Card' reporting requirements would be at the discretion of the Trial Steering Committee/Chief Investigator and would depend on

the purpose of the trial. The ‘Yellow Card’ system is already in place and clinicians are fully aware of their responsibilities with regard to ‘Yellow Card’ reporting. Currently, all SAE reports for low risk trials are collected centrally at sponsor offices and are filed there, typically with no SUSAR’s being identified at all, creating a cumbersome paper trail for no discernible purpose simply because the regulations require that the Sponsor, rather than the study site investigator, report SUSAR’s. Although this may be appropriate in Type B and Type C studies, it serves no useful purpose in Type A studies. Allowing studies teams to specify in protocols that ‘Yellow Card’ reporting is all that is required is meaningful to site clinicians and simple to implement without the need for study specific documentation and procedures and central resource to track and monitor such events, which is particularly important in large, multicenter, pragmatic trials in routine clinical practice. However, the current model of specifying in the protocol which events do not need reporting is confusing for investigators and results in over-reporting.

- ix. We support the view of other academic organisations that more emphasis should be placed on the use of DMC’s and the benefits of DMC monitoring rather than collecting centrally individual SAE reports within sponsor organisations, where the IMP used has been on the market for a considerable time. Permission to use Yellow Card reporting should be an option on the Type A notification system, and possibly for some Type B studies, with the MHRA requesting additional reporting only in those trials where there is felt to be a specific concern.
- x. Portal and Database –a single comprehensive database, accessed via a portal would be expected to save administrative effort and to present a solution to many of the publication/transparency considerations. It is to be hoped that a suitable robust platform can be developed and implemented in time for the implementation of the Regulation.
- xi. Indemnity/insurance - the proposal to require member states to set up a national indemnification mechanism is welcome. We believe that it will provide a level of confidence for trial subjects regardless of whether the Sponsor is a commercial or non-commercial organization and will make multistate trials much easier to set up and potentially less costly for the non-commercial sector.
- xii. While obtaining insurance in the UK has not presented difficulties, non-commercial organisations have reported difficulties in obtaining insurance in a number of EU member states (e.g. France). This has largely arisen in multi-state trials where a participating member state does not accept existing insurance and demands that local insurance is secured. In some instances the barriers of cost and resource in obtaining this have led to the termination of clinical trials. Publishing an annual national/EU report on the incidence of trial related litigation would help balance the often exaggerated concerns of non-commercial sponsors of the risks of trials, given the relative attention given to the very few where serious adverse events occur at rates beyond those of routine care.

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

- 2. The majority of clinical researchers and R&D staff in KHP have very little awareness of the HRA aside from the fact it exists. One or two members of staff who are involved in national level with professional networks understand that the HRA is an “authority in waiting” it is understood that NRES and several associated functions have moved to fall within HRA remit and that HRA is conducting scoping activities to reshape the NHS R&D/REC interface.

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

3. There is extensive evidence in the public domain to show that pharmaceutical companies withhold clinical trial data. KHP is in no doubt about the veracity of this evidence and is aware of a number of specific pharmaceutical trials which have failed to publish the results in full (approximately 33% in a small subset of studies in a specific disease area reviewed, which is in line with published estimates.¹
4. There are two stages of trials where failure to publish has been raised as a concern. The first is where pharmaceutical companies conduct trials which are essentially 'invisible' to the public domain and this is likely to be during the early development phase of new drugs, when novel molecules are being tested in healthy volunteers. These are the studies more likely to cite commercial sensitivity and it would be suggested that any willingness to allow such studies to conceal their results should be strictly restricted to the time until the drug is licensed. At that stage, all studies pre-licensing should be published in full and the recent GSK announcement to this effect is to be welcomed (see <http://www.gsk.com/media/press-releases/2013/GSK-announces-support-forAll-Trials-campaign-for-clinical-data-transparency.html>). Once studies reach the stage of being conducted in NHS patients, it is unlikely they will be 'invisible' in the public domain. Academic investigators will have recruited patients to the studies and will make reference to those studies in papers and reviews relating to the disease area. However it is not uncommon for the 'results' of such studies to merely take the form of a press release, with limited data regarding the methodology, outcome measures, analysis methods, confidence intervals and so forth. The practice of medicine would be greatly improved by mandating that such data be made available in full, through publication in peer reviewed medical journals or full online reports..
5. The impact on public health is considerable. Unpublished evidence, if available, may prevent unnecessary trials being undertaken and act to obstruct meaningful meta-analysis resulting both in expensive treatments being prescribed when they are not needed and effective treatments being denied to patients even though the evidence exists, simply because it cannot be reviewed properly. KHP feels that swift action should be taken to ensure that pharmaceutical trial data is made available in full for all licensed medicines, regardless of whether the trials conducted relate to the licensed disease area or another.

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

6. Occurrence of trials: The International Committee of Journal Editors (ICJE) statement on trial registration has had a significant and welcome improvement to trial reporting (e.g. [EudraCT/clinicaltrials.gov/ISRCTN](http://eudraCT/clinicaltrials.gov/ISRCTN)) for both medicinal and non-medicinal trials but the issue of unregistered trials being published remains. Without enforcement the voluntary requirement to register trials rests with the sponsor.
7. Results of trials: Historically authors and publishers have refrained from publishing trial data with negative/abandoned/uninteresting results (both academic and pharmaceutical led trials) for very different reasons. More recently, increased awareness has highlighted the importance of publishing neutral/negative results. Further work now needs to ensure that all clinical trials and their primary results (in full) are made available routinely at the end of any trial, not limited to CTIMPs subject to regulations (i.e. surgical techniques, devices, psychological therapies, educational programmes or non-CTIMP medicinal trials). Ensuring all clinical trials are open to full public scrutiny cannot fall to the Competent Authority (CA) alone since only a subset of trials i.e CTIMPs and some device trials are subject to CA approval (MHRA in the UK). In general, it is the funder of an academic trial who ensures publication, as it is often made a condition of the funding award (eg NIHR HTA programme

¹ <http://www.bmj.com/content/346/bmj.f105#aff-1>

where it is overwhelmingly successful – see <http://www.bmj.com/content/346/bmj.f105#aff-1>) and while this is effective it is not the solution. ‘Own account’ or unfunded clinical trials also complete and fail to publish.

8. Responsibility to ensure both registration and publication of all trials: The simplest solution would be for the relevant ethics committee to mandate that trial teams produce evidence that they have registered their trial on a public database prior to their trial starting, since all trials (regardless of intervention) require ethical approval. If this became a routine condition of approval for all trials, it would keep any additional administrative burden to a minimum and would not be overly complex to administer, while still ensuring all trials from PhD projects through to large multinational trials, in all interventions from CTIMPs to educational programs, are registered. It is important that the solution resolves this for all clinical trials and not just a subset. Were it mandatory, to register it would be a relatively simple process to require the investigator to submit a copy of the primary publication (ideally in a peer reviewed journal within one or two years of the ‘last patient last visit’) to the ethics committee as the final step in the process. Where this is not possible investigators should continue to provide annual progress reports to the ethics committees, explaining delays to analysis/publication of results. By having access to full information about trials and their statuses, ethics committees are well placed to communicate and escalate any concerns to both Sponsors/investigators about publishing delays. In academic trials this would ensure unpublished trials come to the attention of the university administration or NHS R&D office routinely . For CTIMPs (most pharmaceutical trials), submission of the ‘end of trial’ declaration to either ethics or the MHRA could be permitted only after final publication. This would mean annual fees to the MHRA would be payable until publication and would continue indefinitely if the trial fails to publish. Provision could be made for specific studies to be exempt from the need to publish, if this is agreed with the CA, but this should only be for drugs in development. Once licensed, all retrospective trial data should be immediately published, in line with the GSK commitment made on February 5th (see <http://www.gsk.com/media/press-releases/2013/GSK-announces-support-forAll-Trials-campaign-for-clinical-data-transparency.html>). Importantly, the ethics committees for such trials would consider the trial ‘open’ unless the MHRA/CA confirms the exemption to the requirement for immediate publication. The ethics committees therefore will also have a record of all trials where the results will not be published until the IMP is licensed.

Question 5. Can lessons about transparency and disclosure of clinical (trial) data be learned from other countries?

9. KHP does not have any detailed information about systems in place in other countries, in order to provide a view

Declaration of interests:

Professor Andrew Pickles, Director, King’s Clinical Trials Unit, Department of Biostatistics, Institute of Psychiatry, King’s College London
No interests to declare

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February 2013

CONSULTATION FEEDBACK FORM

Consultation:	Commons Select Committee - Clinical Trials
Reply date:	Friday 22 nd February, 2013

Name	Designation and Cancer Site	Comment
Dr Richard Adams	Consultant Clinical Oncologist, Colorectal Cancer National Specialist Advisory Group	1 - I have discussed these at NCRI level and am happy with the concept of simplification of trial approval which is currently excessively burdensome and prolonged.
Dr Martin Rolles	Consultant Clinical Oncologist, Head & Neck Cancer National Specialist Advisory Group	<p>1 - This is a relatively small cancer subspecialty, compared to lung, breast, prostate, colorectal etc. Research, and research budgets simply do not exist on the same scale for H&N as for the big 4.</p> <p>3 - H&N has been comparatively untroubled by pharma with regard to drug trials. Apart from influential trials of Cetuximab (Bonner JCO 2005) and Docetaxel (Posner NEJM 2007) most of the drive in H&N research has been in surgery or technical radiotherapy, or radiotherapy plus generic chemotherapy, where (hopefully) there is little commercial incentive to conceal data. H&N, with its exacting anatomical problems has to an extent driven the development of technical radiotherapy. Historically, trials have tended to be small, often inadequate and underpowered.</p> <p>3 or 4 - Over the last few years the H&N body in the UK has started to run some highly relevant multicentre trials in all modalities, and there are a number of new NCRN-badged trials opening or in set-up.</p> <p>3 or 4 - There are important questions to answer about HPV p16+ H&N cancer and its treatment and there is significant interest in trials of various types related to aspects of this disease.</p> <p>5 - There is interest in the use of Nimorazole, an old antimicrobial with radiosensitising effects, used as standard with radiotherapy in Denmark and Scandinavia instead of chemoradiotherapy, but until recently almost impossible to obtain anywhere else.</p> <p>There are a few phase 2 biological trials, which should fall under the full data disclosure philosophy if they are to be permitted to run in the UK. Many of these fall roughly into the category of "throw expensive new molecule at lots of different tumours and see where it sticks" with parallel studies in different tumour subtypes.</p>

Name	Cancer National Specialist Advisory Group	Comment
Professor Peter Barrett-Lee	Consultant Clinical Oncologist, Breast Cancer National Specialist Advisory Group	<p>1 - They will help but the single EU PORTAL needs to be done well to avoid becoming another obstructing step in the process.</p> <p>2 - Not even sure we have this in Wales.</p> <p>3 - Widely said that they do but it is hard to know what they withhold if we don't know about it. There is evidence that a well known flu drug is not as good as it seems from undisclosed data.</p> <p>4 - It should be a requirement of all government/charity funded trials in the UK to be fully disclosed and published and this is audited. (it is a requirement of HTA funded trials and most are published.)</p> <p>5 - Not sure they are any better than us. Maybe Scandinavia is better.</p>
Dr Louise Hanna	Consultant Clinical Oncologist, Gynaecological Cancer National Specialist Advisory Group	<p>1 – Yes</p> <p>2 - I believe it has brought together the roles of the NPSA and the REC. I am unsure if it has been effective.</p> <p>3 - I am aware of drug companies being fined for withholding information. This can only be detrimental to public health.</p> <p>4 - Could make it a legal requirement to publish trial results. The investigators should be responsible though ultimately the sponsors.</p> <p>5 - I am not familiar enough with the systems in other countries to comment.</p>

Written evidence submitted by BioMed Central and Current Controlled Trials (CT35)

Background and competing interests

1. BioMed Central is an STM (Science, Technology and Medicine) publisher which has pioneered the open access publishing model. All peer-reviewed research articles published by BioMed Central are made immediately and freely accessible online, and are licensed to allow redistribution and reuse. BioMed Central is part of Springer Science+Business Media, a leading global publisher in the STM sector. All BioMed Central's medical journals require prospective registration of clinical trials as a condition of publication.

2. Since its launch in 2000, BioMed Central has demonstrated that commercially viable business models exist which allow scientific publishers to make the peer-reviewed research articles they publish immediately and freely available online in their official form, with costs typically covered via a publication fee.

3. BioMed Central's journal portfolio includes the journal *Trials* [<http://www.trialsjournal.com>], which is an open access, peer-reviewed journal that encompasses all aspects of the performance and findings of randomised controlled trials. *Trials* publishes articles on general trial methodology as well as protocols, commentaries and results and strongly supports publication of all trial results, regardless of the outcome of the trial.

4. Current Controlled Trials, part of BioMed Central Group, administers the ISRCTN register of clinical trials [<http://www.controlled-trials.com/isrctn/>]. The ISRCTN register allows users to search, register and share information about clinical trials. Access to all the information on this website is free; there are fees for the registration services offered by Current Controlled Trials.

5. The focus of this submission is on Terms of Reference numbers 3, 4 and 5. References are provided in square brackets [] throughout the text.

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

6. There is much published evidence on the unavailability of clinical trial data leading to negative effects on public health, which we will not repeat detail. Reporting bias in medical research has been identified in around 50 different medical interventions [<http://www.trialsjournal.com/content/11/1/37>] and there are many examples of its negative impacts on public health. Reporting bias tends to favour positive results of trials, which support the effectiveness of the intervention (such as a drug or device) being tested, meaning treatment decisions are frequently being made by doctors who have incomplete information on the benefits and harms of medications. A particularly high profile case includes the widely prescribed antidepressant drug reboxetine [<http://www.bmj.com/content/341/bmj.c4737>] which was found to be ineffective or potentially harmful when unpublished data were analysed. There are many other serious examples, which are documented in the article by Peter C Gøtzsche published in the journal *Trials* [<http://www.trialsjournal.com/content/12/1/249>]. We encourage the Committee to consider the examples of harms to patients described in this article.

7. It is widely accepted in the scientific community that results which do not support the hypothesis or healthcare intervention being studied – negative results – are of vital importance. Many peer-reviewed journals in clinical medicine, from a number of publishers, strongly encourage publication of negative results including *Trials*, *BMJ Open*, *BMC Research Notes*, and *PLOS One*. And at least one journal makes publication of negative results its mission, *Journal of Negative Results in Biomedicine*, published by BioMed Central. However, despite many opportunities for investigators to publish all trial results in journals, and ethical (in the UK/EU) requirements to publicly register the existence of clinical trials at their inception, relying on ethical policies of journals, editorial organisations, and research funding agencies has so far been insufficient to address the problems of bias in clinical evidence. Despite prospective registration of clinical trials being required by major medical journals since 2004, evidence continues to emerge that adherence to policies for registration of trials

[<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0025258>] and reporting of results [<http://www.bmj.com/content/344/bmj.d7292>] is worryingly low.

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

8. The initiative by the European Medicines Agency, to require sharing of raw data supporting all drug and device license applications by pharmaceutical companies in the EU from January 2014 [<http://www.bmj.com/content/345/bmj.e8423>], should be applauded. However, in the UK, there is no legislation requiring the public registration of trials or the public disclosure of results of trials.

9. Around early 2000, two major initiatives were launched in response to a general need for more transparency. (i) A group of UK based medical research organisations pushed for the creation of a public listing of clinical trials, which led to the creation of the UK based Current Controlled Trials website and its trials database the ISRCTN register [http://www.controlled-trials.com/mrct/meeting_ukcc_29jul98.asp]. (ii) US patient groups demanded better access to ongoing clinical trials in dangerous and life threatening disease areas such as cancer and HIV and this led to federal legislation and the creation of the ClinicalTrials.gov website [<http://clinicaltrials.gov/ct2/about-site/background>].

10. Two other types of stakeholders were instrumental in making sure that clinical trials were more open to scrutiny:

- (i) A number of medical journals editors declared that they would not consider the publication of the papers about clinical trials if specific details about those trials had not been publicly disclosed well before enrolment started [<http://www.icmje.org/update.html>]. (ii) The World Health Organization (WHO) described the public listing of clinical trials as a scientific, ethical and moral responsibility and set about defining standards and capacity building methodologies [http://www.who.int/ictrp/trial_reg/en/index.html]. This led to creating a public platform that brings together all vetted international, regional and national registers [<http://apps.who.int/trialsearch/>].

11. Increases in the numbers of registers worldwide divides opinion. For some, the multiplication of registers is seen as a waste of resources and efforts, leading to duplication of information with different levels of completeness and quality which makes global analyses on clinical evidence very difficult if not impossible. For others this should be seen as a positive step and a proof of increased awareness, regulations and protection of trial participants, and the acknowledgement of different geopolitical remits and language needs. A realistic view might well be that of the WHO which advocates a harmonised – rather than uniformed – approach.

12. ClinicalTrials.gov backed up by federal legislation and a substantial budget has grown to become the largest source of trial information in the world. Additional legislation in 2007 required that all trials be listed before enrolment starts and furthermore that basic results of all those trials should also be reported within well defined time frames [<http://clinicaltrials.gov/ct2/about-site/results>]. Germany is to follow suit [http://www.gesetze-im-internet.de/englisch_amg/englisch_amg.html#p0930].

13. An additional step towards increased transparency was the decision to make some sections of the confidential regulatory database EudraCT open to the public via the EU-CTR register [<https://www.clinicaltrialsregister.eu/>]. EudraCT will also add results and the way the information is required is very much along the lines developed by ClinicalTrials.gov [http://ec.europa.eu/health/files/eudralex/vol-10/2012_302-03/2012_302-03_en.pdf].

14. In the UK, a number of organisations including the Department of Health [http://www.crncc.nihr.ac.uk/about_us/processes/portfolio/isrctn_index/], the Medical Research

[http://www.mrc.ac.uk/ResearchPortfolio/About/index.htm#P187_19342] Council and the Wellcome Trust [<http://www.wellcome.ac.uk/Funding/Biomedical-science/Application-information/WTX022708.htm>] support prospective registration of clinical trials. An effort has been made to simplify steps when seeking all required approvals for a trial by designing the Integrated Research Application System (IRAS) which provides researchers with a 'one-stop shop' displaying all the relevant forms (including the clinical trial authorization to be submitted to the Medicines and Healthcare products Regulatory Authority (MHRA) then passed onto the EudraCT database and ultimately EU-CTR). But using IRAS is not compulsory [<https://www.myresearchproject.org.uk/Help/UsingIRAS.aspx>].

15. The Association of Medical Research Charities has advocated the need for a plain English summary for all scientific outputs in a recent report [http://www.amrc.org.uk/our-members_patients-participate].

16. As increased participation in trials remains very much supported by the UK government [http://cdn.hm-treasury.gov.uk/2011budget_growth.pdf], 2010 saw the launch of the UK Clinical Trials Gateway (UKCTG) which gives a overview of the trials that have enrolled or are enrolling UK participants, in a single environment [<http://www.ukctg.nihr.ac.uk/default.aspx>]. The UKCTG has two challenges: coverage (using other data sources apart from the ISRCTN database and ClinicalTrials.gov data might be required) and accessibility (clinical trial descriptions are often not in plain English).

17. As of 2013, there is still no legal requirement to publicly register clinical trials in the UK. Existing efforts to ensure trial registration have focused on ethical aspects and researchers' motivations to publish in good journals but does not have the power to ensure all trials are registered and their results reported. Others have gone further and called for a global network to enable universal trial registration and data transparency [<http://www.trialsjournal.com/content/11/1/64>].

18. Requiring registration of trials and reporting of results is less complicated to implement than the sharing of raw data but is equally important. Raw data is important for researchers, such as systematic reviewers, wishing to build on or validate previous research. However, other important stakeholders such as patients, research funding agencies, ethics committees and journal editors, would greatly benefit from human readable (understandable) summary information about all trials. Furthermore, there are fewer considerations for patient privacy – a barrier to full public disclosure of clinical data – when sharing summary information about trials, compared to sharing raw data. The public registration and reporting of results of all trials is the aim of the AllTrials initiative [<http://www.alltrials.net/>], which is supported by BioMed Central and Current Controlled Trials.

19. Furthermore, registration of all trials and reporting of all results, if made law, could be achieved through incremental developments to existing tools for public disclosure of information about trials. The ISRCTN register already accepts trial registrations globally of all trial designs and at any stage of the trial. And at Current Controlled Trials we are investigating the feasibility of providing a results reporting service within the ISRCTN database. As a commercial organisation which operates a trial registration service with a strong UK focus we clearly have an interest in stronger requirements to register trials. However, the ISRCTN database is just one of many trial registers operating in the EU and we regularly collaborate with other registers in the WHO network for mutual benefit.

20. Services for trial registration and reporting of results are already widely available, and so these activities are supported by the publishing industry and other organisations which provide trial registration services. Responsibility, however, for registration of trials and reporting of results is ultimately that of the investigators and their sponsors or employers. Trial sponsors and investigators have a responsibility to patients recruited to trials – and been exposed to unknown benefits and harms of treatments – to disclose results, so research is not repeated unnecessarily. Trial registration also helps reduce wasteful duplication of research as it creates a public record of a trial, reducing the

potential for patients to be recruited to redundant trials and put at unnecessary risk. Evidence of adherence to legislation could be provided by provision of a unique trial identifier from an approved trial register, such as an ISRCTN number, and an equivalent or updated identifier for the reporting of results. These publishing services largely exist already, and could partner with Government bodies to ensure implementation is effective and adherence simple to ascertain.

21. Increased transparency in clinical trials could also be achieved by: (i) Leveraging increased support for open access to publicly funded scientific research in the UK, and extend this to all clinical trials, regardless of the source of funding. (ii) Health research funding bodies encouraging researchers to provide high quality information publicly about trials they fund, in plain English, with funding retained in the future if this criterion is not met. (iii) Encourage publishers and journals to demand proof of prospective registration (this may even go as far as a commitment to data sharing). (iv) Engage with patient groups to understand what participants need to read and understand about trials before contacting their doctor and/or a researcher directly. (v) Develop consensus guidelines regarding basic results posting that do not, critically, jeopardize peer-reviewed journal publication in the future. (vi) Legislate in a way that takes into account the views of all parties: industry (intellectual property), research communities (help them design better studies and meet their recruitment targets), prospective participants (easy to understand information).

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

22. There has been growing awareness of the need for transparency under the aegis of the WHO. But transparency and access comes at a cost and funding is a constant concern. Trial registration services are often funded through research or governmental grants, the availability of which may change over time. The ISRCTN register is ensured to be sustainable through fees which are levied for each trial which is accepted for public registration in the database. This model of charging “authors” is increasingly common with the growth of open access journals and publishers which operate a model of charging authors of accepted papers. It is employed by BioMed Central, parent company of Current Controlled Trials, and is also known as “gold” open access which already has the support of the UK Government for financially sustainable approaches to open access scientific publishing.

23. The UK was a pioneer regarding transparency for clinical trials but over the years we may have lost some momentum. Legislation has been key to increasing trial registration in the USA and Germany and initiatives such as the UK Clinical Trials Gateway (UKCTG) are an opportunity to build up on past efforts.

24. ClinicalTrials.gov is very open about the challenges represented by results reporting. Although the focus is on reporting numeric data, data quality is highly variable and the uptake is slow [<http://www.nejm.org/doi/full/10.1056/NEJMSa1012065>]. Complimentary initiatives to legislation could improve matters. These include reporting standards agreed by relevant stakeholders for the reporting of summary trial results. Reporting guidelines for complete reports of clinical trials are already widely adopted by journals – in the CONSORT statement and checklist [<http://www.trialsjournal.com/content/11/1/32>].

25. Although the volume and quality of information that is publicly available has evolved dramatically over the past decade, expectations about coverage, completeness and usability still need to be managed. More efforts will be needed in defining, applying and enforcing standards.

February 2013

Joint written evidence submitted by Healthy Skepticism UK (HSUK) and Health Action International (HAI) (CT36)

1. Healthy Skepticism UK and Health Action International (HAI) Europe value this opportunity to provide evidence why access to clinical trial results are of great importance to patients for the effective and safe use of medicines. For that reason, this response will focus only on the evidence in support of access to data and the practical means by which data disclosure can be introduced to facilitate the practice of evidence-based medicine and rational healthcare decisions.

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

2.1 The HRA is a very young organisation and our knowledge of it is limited to that which can be obtained from their publications. HSUK and HAI Europe strongly support the last point of HRA's vision statement: 'clinical trials get registered and research results get published'. In HRA's first annual report, it is stated that HRA has 'carried out a process review of the entire research project journey: from initial idea, development, funding, approval, conduct, compliance, inspection, publication and translation' (1), although there is no mention of the review findings. Therefore, we are unable to judge how effective HRA has been in achieving its aims.

2.2 The HRA seem to focus their efforts on the ethical involvement of patients in studies from the outset, analysing important issues such as the risk/benefit balance of participation, as well as communication and understanding between participants and researchers. HSUK and HAI Europe would argue that in order for studies to be ethical, the participants must be assured that the information obtained from their involvement will be used for the purpose outlined and furthers insight into treatments, whether viable or not. We would welcome more obvious work into this area.

3.1 What evidence is there that pharmaceutical companies withhold clinical trial data?

3.1.1 Clinical trial data can be withheld in many different ways. Besides the obvious withholding of information, as will be demonstrated below with the example of Oseltamivir, there are also more subtle and/or indirect means of restricting access to information. Examples of these are outlined clearly by the Cochrane handbook and reproduced below (2):

- Publication bias: The publication or non-publication of research findings, depending on the nature and direction of the results.
- Time lag bias: The rapid or delayed publication of research findings, depending on the nature and direction of the results.
- Multiple (duplicate) publication bias: The multiple or singular publication of research findings, depending on the nature and direction of the results.
- Location bias: The publication of research findings in journals with different ease of access or levels of indexing in standard databases, depending on the nature and direction of results.
- Citation bias: The citation or non-citation of research findings, depending on the nature and direction of the results.
- Language bias: The publication of research findings in a particular language, depending on the nature and direction of the results.

- Outcome reporting bias: The selective reporting of some outcomes but not others, depending on the nature and direction of the results.

3.1.2 The current medical research model encourages the dissemination of study results through publication in peer-reviewed journals – the gold standard of information accessibility in academia. However, the seven sources of bias outlined in the Cochrane handbook demonstrate that the information that is published in academic literature can not only misrepresent the actual results or conclusions of that study, but also skew the larger body of evidence. Scargle illustrates this point in his paper ‘Publication Bias: The “File-Drawer” Problem in Scientific Inference’ by stating that ‘apparently significant, but actually spurious, results can arise from publication bias, with only a modest number of unpublished studies’.

(3)

3.1.3 Studies have investigated the phenomenon of publication bias and demonstrated that data is not published and therefore not accessible. Moreover, summaries and analyses of clinical trial data may be published in peer reviewed journals, but regardless of whether an article is published, much of the raw data is currently never made public. Scherer et al. (4) found that ‘only about half of all studies first presented as abstracts were published in full following presentation at meetings or publication as a summary report’ whilst Song et al. (5) furthered this by concluding that ‘positive trial data is twice as likely as negative trial data to be published’.

3.1.4 Examples of specific medicines demonstrate the above points:

3.1.4.1 Oseltamivir or Tamiflu, was purchased for thousands of pounds by the UK government amid concerns about its effectiveness at easing influenza symptoms. The therapy was marketed by Roche in 2005 as being able to provide a ‘67 percent reduction in secondary complications such as bronchitis, pneumonia and sinusitis in otherwise healthy individuals’ (6). Numerous requests for the raw data substantiating these claims from entities including the Cochrane review and the UK government, have been met with the answer ‘The files appear to have been discarded’ from the study authors and the statement “Following discussions with our medical teams both in the UK and Basel, unfortunately we are unable to send you the data requested as a similar meta-analysis is currently commencing with which there are concerns your request may conflict” from Roche (7). Despite the company’s promise to publish the raw data in 2009, it is still unclear whether it has been made publicly available. Godlee of the British Medical Journal writes that ‘there are at least 123 trials of oseltamivir and that most (60%) of the patient data from Roche’s phase III completed treatment trials remain unpublished’ (8). The sheer quantity of unpublished data illustrates the size of the problem of publication bias. Nonetheless, Oseltamivir is still used by thousands of patients in spite of the fact there is no publically available conclusive evidence of its efficacy.

3.1.4.2 Rosiglitazone is another example of a drug that demonstrates publication bias. First used in 1999 and originally developed to treat diabetes, Rosiglitazone, has since been shown to have serious adverse effects on the heart. In 2004, the manufacturer, GlaxoSmithKline, was obligated to publish all of the trial results by a court of law. Data from 35 of the 42 studies had remained unpublished until then (9).

3.2 What impact does this have on public health?

3.2.1 The current situation of limited access to a fraction of trials results, coupled with widespread promotional messages, ultimately drives prescribers and consumers to make choices based on inaccurate or unbalanced information. Poorly informed decisions lead to the increased risk of otherwise preventable adverse reactions and to the waste of public resources on inappropriate or unnecessary medicines. Worse

yet, poorly informed treatment decisions lead to increased hospitalisation and the concomitant costs involved or even in death.

3.2.2 Without complete access to research results, further investigations into medicines of genuine therapeutic advance may be neglected. Greater trials data disclosure could ease unnecessary bottlenecks in research & development and reduce wasteful repetition of trials – all of which potentially delay the development of life-saving medicines.(17)

3.2.3 Trial data secrecy is an abuse of participants' trust that the risk they've taken contributes to medical advances. 'Most trial participants give consent to the risks involved in an experimental study under the assumption that they are making a contribution to science. If that study remains unpublished, their contribution is for nought' (4). Trials to investigate public health advances depend on patients, and if their contribution is kept secret, then patients' trust in trials and willingness to participate may one day be lost.

3.2.4 The increasing tendency to outsource clinical trials to low and middle income countries exacerbates the potential for vulnerable populations to be inadequately informed and protected. Cases documented by Nina Lakhani in the Independent demonstrate that trial participants from these countries (e.g., India) may not be empowered to give informed consent. (18)

3.2.4.1 Participants profiled by Lakhani were reported to be included in clinical studies despite their prior exposure to environmental toxins, making it nearly impossible to dissociate the effects of the trial medicine with those of the patients' toxic exposure. Lakhani has stated that these trial medicines have since been approved to be marketed in Europe.

3.2.4.2 Unethical clinical testing is by definition unscientific medical research. Full access to the raw data at the patient level would enable regulatory authorities and public watchdogs to identify whether a medicine has been tested in unethical circumstances, for instance, when a medicine had been tested on vulnerable populations and if the participating patients had previous harmful exposures.

3.2.5 By withholding information, including the original methodology and raw data, the possibility to re-analyse study results is undermined. Several drug disasters illustrate why all results should be publicly available and trials should be followed up in the longer term. In one example, it took nearly one year to make the link between rare and unusual limb defects reported in children and the medicine Thalidomide. In a second example, evidence of adverse events such as heart attacks resulting after using the medicine Rofecoxib, Vioxx, was not reported in its entirety in peer-reviewed publications, according to a timeline by National Public Radio (NPR). NPR reports that research published in the Lancet estimates that "...88,000 Americans had heart attacks from taking Vioxx, and 38,000 of them died" (19). Access to all study data enabled timely, retroactive research that can establish links between therapies and adverse effects, and ultimately save lives.

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

4.1 There are two natural time points at which the disclosure of trials information could be introduced and effectively enforced, while limiting the administrative burden on trial sponsors and authorities.

4.2 Time point one: A study investigator or sponsor submits an application to the relevant body for approval to conduct a trial in the UK.

4.2.1 First, an accurate and complete record (i.e. list) of all clinical trials submitted for approval should be maintained on a publicly accessible website. Clinical trials registration is a prime example of such record keeping in which basic details of the study are recorded and made publicly accessible. Registration must

be done at the point of application for approval (i.e. prior to decision) and before the first patient is recruited to participate in the trial.

4.2.2 Second, trial sponsors should submit a list of all known clinical trials already undertaken on the product to be tested and the clinical trial protocol for the study in question. This information can greatly reduce the number of so-called 'missing trials' whose occurrence has not been properly documented and whose study structure and results can not be independently analysed.

4.2.3 The EU Database foreseen in the EU Clinical Trials Regulation proposal is one potential EU-wide registry in which the above information could be submitted and published. The current proposal foresees that all data and information submitted by the applicant in the process of seeking approval to conduct a clinical trial would be contained in the EU Database, which is to be maintained by the European Commission. (10) Therefore, the disclosure of these additional documents would seem unlikely to impose a serious additional administrative burden, as a public submission portal is already foreseen in European legislation.

4.2.4 The EU Database would only be an effective registry if the information above is correctly and accurately recorded and published openly and in a timely manner in respect of the principles in EU Regulation (EC) 1049/2001 on Access to Documents.(11) Evidence shows that even mandatory trial registration may not always be respected.(12) Therefore, the monitoring and enforcement of registration is an essential element of any trials register (see point 5).

4.2.5 Approval bodies should only review the trial application after the above criteria have been fulfilled and the relevant documents are publicly available to download from the EU Database. Approval bodies should also pro-actively publish on their website(s) the criteria by which trial applications will be evaluated.

4.3 Time point 2: Companies submit evidence from clinical trials in support of their market authorization applications to UK or European regulators. If authorised, the product may be marketed for the approved indication.

4.3.1 First, applicants should submit proof of trial registration in primary or partnered registry of the international clinical trials registry platform of the World Health Organization (13) for all evidence supporting its product. Regulators should only review applications that contain evidence from registered trials.

4.3.2 Second, applicants should submit a list of all known clinical trials already undertaken on the product. Products seeking market approval in Europe or the UK may not be the same as those tested in trials in the UK, therefore a list of all known clinical trials on a given product should be submitted at both time points (i.e. approval to test, approval to market). This requirement is a step towards ensuring the proper documentation of all trials conducted globally.

4.3.3 Third, applicants should submit both clinical study reports from trials supporting their application and the corresponding raw, anonymised data at the patient level to the regulators.

4.3.4 All the above information should be proactively disclosed by the regulators on established, publicly-accessible websites they maintain. For example, technical adaptations to existing registries, such as the EU Clinical Trials Register, could enable the online publication of these documents.

4.3.5 Following the recommendations of the European Ombudsman (14), and in line with the EU Regulation on Access to Documents, the European Medicines Agency currently releases clinical study reports on request (15) and is in the process of developing a proactive publication policy for these and other documents (16). Yet, these trials only represent a fraction of all clinical trials taking place, some of

which may not be used in a market authorisation application in the EU and therefore will not be in the Agency's possession. Therefore, it is crucial that disclosure requirements be applied at both the point of approval to start a trial and the approval to market a medicine.

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

5.1 Robust disclosure policies fall by the way-side without monitoring and enforcement mechanisms. In 2008, the Food and Drug Administration Amendments Acts (FDAAA) introduced mandatory rules whereby any drug that is already licensed by the FDA must publish the results of all their studies within one year of completion. A detailed study (12) of 738 trials that were subject to this legislation found that only 22% produced results within one year, the missing 78% of studies were conducted on drugs in use on humans and not produced within the time scale for open scrutiny. It was however an increase on those who were not subjected to the legislation, of which 10% produced their results within one year. Considering these results, fines or another means of liability for missing or incomplete registrations may be a useful penalty mechanism to ensure compliance.

This submission was compiled by:

Healthy Skepticism UK (HSUK) aims to improve health by reducing harm from inappropriate, misleading or unethical marketing of health products or services, especially misleading pharmaceutical promotion in the UK. In addition, we aim to support evidence-based health care, provided according to need, to optimal health outcomes in the UK. Both aims are equally important as misleading pharmaceutical promotion and non-evidence based-medicine can harm health and waste limited resources. www.healthyskepticismuk.com

Declaration of interests: HSUK is a network of concerned and motivated health professionals and other interested individuals who work together to improve the health of the UK population. HSUK does not accept funding from the pharmaceutical industry.

Health Action International (HAI) is working towards a world where all people, especially those who are poor or marginalised, are able to exercise their human right to health. Our goal is to achieve universal and equitable access to affordable essential medicines of assured quality and to ensure that those medicines are used rationally to promote the highest standards of health throughout the world. www.haieurope.org

Declaration of interests: HAI is an independent global network of health, consumer and development organisations working to increase access to essential medicines and improve their rational use. HAI receives funding from public entities including the UK Department for International Development and the EU Health programme, as well as from non-profit, private foundations. A complete statement of HAI's income sources can be found online at: <http://haieurope.org/wp-content/uploads/2012/08/List-of-donors-2006-2011.pdf> HAI does not accept funding from the pharmaceutical industry.

February 2013

References

1. HRA annual report 2011-2012.

<http://www.official-documents.gov.uk/document/hc1213/hc03/0312/0312.pdf>

2. Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.
3. Scargle, J. Publication Bias: The “File-Drawer” Problem in Scientific Inference. *Journal of Scientific Exploration*, Vol. 14, No. 1, pp. 91–106, 2000
4. Scherer RW, Langenberg P, von Elm E. Full publication of results initially presented in abstracts. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: MR000005. DOI: 10.1002/14651858.MR000005.pub3
5. Song, F, S Parekh, L Hooper, Y K Loke, J Ryder, A J Sutton, C Hing, C S Kwok, C Pang, and I Harvey. “Dissemination and Publication of Research Findings: An Updated Review of Related Biases.” *Health Technology Assessment (Winchester, England)* 14, no. 8 (February 2010): iii, ix–xi, 1–193. doi:10.3310/hta14080.
6. http://www. Roche.com/media/media_releases/med-cor-2005-11-07.htm
7. Cohen, D. Complications. Tracking down the data on Oseltamivir. *BMJ* 2009;339:b5387
8. Godlee, F. Open letter to Roche about Oseltamivir trial data. *BMJ* 2012;345:e7305
9. Jefferson, T. Ensuring safe and effective drugs, who can do what it takes? *BMJ* 2011;342:c7258
10. Article 78(1) of the European Commission’s EU Clinical Trials Regulation proposal. [See link to proposal: http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf](http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf)
11. Namely, the exceptions to disclosure found in Article 4 of the EU Access to Documents Regulation and including the narrow interpretation of the concept of commercial confidentiality and overriding public interest exception. [See link to EU Access to Documents Regulation: http://www.europarl.europa.eu/register/pdf/r1049_en.pdf](http://www.europarl.europa.eu/register/pdf/r1049_en.pdf)
12. Prayle, A. Hurley, M. Smyth, A. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study *BMJ* 2011;344:d7373 doi: 10.1136/bmj.d7373
13. See the WHO website: <http://www.who.int/ictip/en/>
14. See the European Ombudsman decision in complaint 2560/2007/BEH against the European Medicines Agency for failing to disclose clinical study reports and protocols: <http://www.ombudsman.europa.eu/en/cases/decision.faces/en/5459/html.bookmark>
15. See article *The first two years of the European Medicines Agency’s access to documents policy: Secret no longer* published in *Arch Intern Med* in December 2012
16. See web link to EMA *Workshop on access to clinical-trial data and transparency kicks off process towards proactive publication of data* in November 2012 : http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/11/news_detail_0_01662.jsp&mid=WC0b01ac058004d5c1
17. Health Action International (HAI) Europe and the Trans-Atlantic Consumer Dialogue (TACD). *Time for the EU to lead on innovation*. Policy paper. 2012. http://haieurope.org/wp-content/uploads/2012/04/HAI-Europe_TACD-EU-Innovation-Paper.pdf
18. Lakhani N. the Independent. *From tragedy to travesty: Drugs tested on survivors of Bhopal*. 2011. <http://www.independent.co.uk/news/world/asia/from-tragedy-to-travesty-drugs-tested-on-survivors-of-bhopal-6262412.html>
19. See *Timeline: The Rise and Fall of Vioxx* on National Public Radio website in November 2007. <http://www.npr.org/templates/story/story.php?storyId=5470430>

Written evidence submitted by UKCRC Registered Clinical Trials Units Network (CT37)

The UK Clinical Research Collaborations Registered Clinical Trials Units Network consulted its members for feedback on the questions raised.

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?

Overall, it is felt that the European Commission's proposed Clinical Trial Regulation includes some important improvements, such as a single submission point for the EU clinical trial authorisation, the proposed co-sponsorship arrangements, greater flexibility for consent in clinical trials in emergency situations and measures to decrease trial indemnity costs within the EU. Our membership strongly endorses the points raised by Professor Sir Rory Collins of Oxford Clinical Trial Service Unit & Epidemiological Services Unit in his letter to Vice President Maroš Šefčovič on 24 October 2012 [appended]. Additional concerns are set out below:

- i. Members felt that although the new regulations afford more flexibility, greater clarity is needed in obtaining consent in emergency situations including situations, for example, where the clinical condition of the patient makes it an emergency but also situations where the health service may be in an emergency state for example, during a pandemic. There is also inadequate provision for consent via postal based trials.
- ii. The definition of 'low intervention' trials would be better defined as 'low risk' and should be extended to trials testing established treatments with good safety profiles for novel uses that are not standard practice for example, aspirin in cancer prevention. The current definition of 'low intervention' trials is felt to be too restrictive and could potentially be interpreted as more restrictive than the current risk adaptations permitted within the UK under the Medicines for Human Use (Clinical Trials) Regulations which are documented in the MRC/DH/MHRA Joint Project document for Risk Adapted Approaches to the Management of CTIMPs. Article 2(3) of the new proposal defines these as trials on an authorised medicine used *in accordance* with the authorisation or in the context of a standard treatment, and that the additional intervention only poses a minimal additional risk. We propose that this definition is extended to include: trials of an existing drug (with a well documented side-effect profile) at a lower dose or for a longer duration, trials of an existing drug for a new condition (particularly where there is extensive class evidence of its safety profile), trials of food supplements or other products that can be sold without prescription.
- iii. Consideration is required for a risk based approach to pharmacovigilance once patients have stopped treatment and it is no longer necessary to actively monitor individual patients for treatment side effects (this includes the active monitoring of individual patients for SARs and SUSARs and also the development of an annual safety report). Under the current legislation and the proposals for the new Regulation in such circumstances this can lead to huge pharmacovigilance costs for trials that are following patients up for long periods of time, sometimes over many years. It is also pertinent to note that pharmaceutical companies do not routinely follow up participants long term and therefore long term effect can be missed. Follow up may involve postal follow-up, via

GPs or annual attendance at hospital and so does not necessarily involve the regular active monitoring of patients for pharmacovigilance purposes. One suggestion has been to amend the end of clinical trial definition. However, the other approach is to explore other methods of monitoring pharmacovigilance over these periods where the intervention is not being used. The European Commission's response to Professor Collins' letter stated that "Creating two divergent reporting systems would result in different levels of patient protection between clinical practice and in clinical trials." These differences already exist. Patient protection is greater in clinical trials than in clinical practice. Post marketing reporting of SUSARs is at a completely different level from SUSAR surveillance and reporting in clinical trials. The difference being the need to actively monitor SAEs and for each SAE, to consider whether or not it is a SUSAR only exists for clinical trials. The difference in these levels of protection already has enormous practical implications. As a result, decisions about the safety of drugs have to be made based on poor quality epidemiological data.

iv. The blanket reference to ICH-GCP within the new Regulation risks further embedding processes into practices that are not commensurate with the risks of the trial or treatment. The following examples demonstrate:

- "The rights, safety and well-being of the individual research subject should prevail over all other interests." This would mean that it is almost impossible to do a phase I or II clinical trial. It is felt that these rights should be preserved as far as possible, but the role of the ethics committee is to balance the risk to these against the potential of the research to save lives and improve the health of future generations.
- "Ensuring that the group of subjects participating in the trial represents the population to be treated" The issue about trial participants being representative might be acceptable for phase III trials but is unlikely to be helpful for phase I or II trials. It is also felt that even late phase trials do not need to be representative; what is important is that they are as generalisable as is reasonably possible, which is a completely different requirement. For example, it might be desirable to include larger numbers of less common types of participant to get more reliable estimates for such subgroups, in which case the trial would be deliberately less representative in order to be more generalisable. Additionally, the cost of including a very broad spectrum of patients (who may eventually receive the treatment) may delay introduction of a beneficial treatment in the vast majority of patients.

The MRC/DH/MHRA Joint Project document mentioned previously sets out standards for risk adaptation that are permitted within the current legislation. This is helping to reverse the trend in excessive bureaucracy and over-interpretation of Directive 2001/20/EC and 2005/28/EC which is currently seen in the conduct of clinical trials, but can only go so far.

In Summary, whilst the proposal offers the promise of a more facilitatory environment for trials, unless the concerns identified are addressed, there is risk that the current obstacles will become a greater impediment to clinical research.

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

- v. Whilst the Network welcomes the spirit of the HRA, there is yet to be a demonstrable impact in practice on the operations of clinical trials units. The impression is that a pragmatic approach is being undertaken to adapt procedures to facilitate high quality clinical research.

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

- vi. There are a number of systematic reviews published which show that there is a significant difference in the proportion of trials published with pharma involvement that show a positive finding compared to those trials published with no pharma involvement. This has been taken to be evidence that pharma must be avoiding publishing negative studies. However there is little distinction made between early and late phase trials in these discussions and it is possible that more phase 3 trials are positive if there is a better decision making process made at phase 2. However if those early phase trials are not published then this still distorts the picture of what products are successful when we come to have an overview of the evidence in a systematic review.
- vii. We recommend that this scrutiny of evidence should not be restricted to pharmaceutical companies, but should include all clinical trials (for example, devices, surgery, talking therapies and complex interventions).

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

- viii. Full prospective registration of trials in a publicly accessible database should be mandatory before recruitment of the first patient. There would then be a public record of the study, what participants will be recruited, what interventions compared, and what outcomes collected. This is the essential first step in making trials more open to scrutiny. This would make an impact if this was a condition for ethics approval rather than registration prior to ethics submission in case approval is denied. Prospective publication of the trial protocol, preferably in an open access journal should also be strongly encouraged. Protocols can change during the course of a trial and ideally reasons for protocol changes should also be registered.
- ix. There should be commitment to publishing the full findings of trials, whether positive or negative, wherever possible with open access.
- x. Strong concerns were expressed about the possible introduction of requirements that complete individual patient data be made publicly available, without access control, at the end of a clinical trial, as a means to achieving greater transparency. Consideration should be given to: potential compromise of patient confidentiality in small trials where such details might allow the identification of particular individuals; potential for data dredging and inappropriate re-analysis; risk of exploitation (including selective analysis and reporting) by commercial parties for publicity purposes. While we are committed to the principles of data sharing (and this is a requirement of funding for many non-commercial trials), we feel it is essential to control access to data via an explicit data sharing agreement, to ensure that the data are shared for a set purpose, that the specified purpose is in line with the original informed consent provided, and that there is an agreement in place that the secondary user does not try to link the clinical trial data to

other data sets in such a way that might result in the identification of individuals, compromising confidentiality.

- xi.** Good clinical practice in Phase III academic trials already have robust systems for external scrutiny through the Independent Data Monitoring Committees (IDMC) and independent members of the Trial Steering Committees. These could easily be strengthened and made more transparent through minor modifications to the IDMC and TSC charters, by requiring that both committees sign off the main trial publication prior to submission. This would provide assurance that the protocol and statistical analysis plan had been followed, or if not that deviations were explained in the report and that the paper was a true reflection of what happened in the course of the trial and of the data. Making sure this was in place would be a responsibility of the Sponsor. Whether these governance structures could be adapted to work for commercial trials would require some thought, but of course they already have IDMCs.

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

- xii.** It is felt that this is a global issue, one which has not been resolved by any one country, not least because evidence doesn't stop at our country's borders.

Responding CTUS:

- Barts CTU
- Cardiff Haematology CTU
- CRCTU, Birmingham
- CRUK/UCL Cancer Trials Centre
- Institute of Cancer Research Clinical Trials & Statistics Unit
- Kings CTU
- Leeds CTRU
- Liverpool Trials Collaborative
- London School of Hygiene and Tropical Medicine CTU
- Medical Research Council CTU
- Newcastle CTU
- Nottingham CTU
- Oxford CTSU
- South East Wales Trials Unit
- Wales Cancer CTU

February 2013

Written evidence submitted by the UK Research Integrity Office (CT38)

1. **Scope of submission:** The UK Research Integrity Office (UKRIO) is submitting evidence on two particular questions:
 - Question 3: What evidence is there that pharmaceutical companies withhold clinical trial data and what impact does this have on public health?
 - Question 4: How could the occurrence and results of clinical trials be made more open to scrutiny? Who should be responsible?
2. **Question 3: What evidence is there that pharmaceutical companies withhold clinical trial data and what impact does this have on public health?**
3. There is a very substantial body of evidence that many clinical trials, about half, are not published. This evidence is well summarised in Ben Goldacre's book (1) and a recent editorial in the BMJ (2). UKRIO has always stressed – through its practical advisory service, its education and training, and its publications - that all research should be conducted to the highest standards of honesty, accuracy, integrity and accountability. We would expect research organisations to share our ambition to uphold high standards and we find the examples of bad behaviour in *Bad Pharma* all the more disappointing. These are neither historical problems nor isolated examples. Far more should have been done to address the non-publication of clinical trials and the selective reporting of data and results. Regulatory, professional, funding and other organisations now have an opportunity to take a clear stand on these issues and bring about real change.
4. It is important to note that it is not only the results of clinical trials that are not published but also the results of all scientific studies. This is an important problem for all of science because it means that conclusions are being reached on only part of the evidence - and almost certainly a biased part.
5. There is evidence, presented in the BMJ editorial, (2) that trials funded by pharmaceutical companies are less likely than trials funded by, for example, Government to be published, but, as we have said, it is a substantial problem for most research, although it is interesting to note that the UK Health Technology Assessment programme (HTA) has very high rates of publication. This may be related to its policy of withholding part of the funding until the work is published and also of producing its own reports rather than requiring publication in peer-reviewed journals. (2)
6. The emphasis in the current debate is on the publication of analysed results but equally important is the publication of the full (raw) data of the trial or study. It has not been normal in science to publish full data, but the arrival of the internet has made it possible to publish full data sets. Research funders are now beginning to require this, partly to allow full examination of studies but more to allow reuse of the data, which can bring substantial scientific, social, and economic benefits. A systematic review of trials of a drug that uses individual patient data will be much superior to a systematic review that uses only summary

data. So it is important to push not just for the publication of results but for the publication of full anonymised data.

7. We have known for a long time that trials funded by pharmaceutical companies are more likely to have results favourable to the company than publicly funded trials. (3 4) We know too that studies with negative results are less likely to be published than studies with positive results and that studies with positive results are likely to be published more than once.
8. The consequence of trials not being published combined with a bias in those that are published is that patients and clinicians are misinformed about the balance of benefit and harm that might be expected from a drug. The usual distortion is that drugs will seem to be more effective and less harmful than they are in reality. The difference between the evidence and the actuality may in some cases be substantial.
9. The strongest evidence we have on this difference is with antidepressants, which are prescribed on a massive scale in Britain. As Ben Goldacre describes in his book, systematic reviews of some antidepressants that use all trials reveal that they have little or no effectiveness and substantial side effects. (1)
10. Because many factors go into the prescribing of drugs it is hard to know how much harm to public health results from the distorted information. It may well be that drugs are overprescribed: benefits may be less and harms greater than expected.
11. **Question 4: How could the occurrence and results of clinical trials be made more open to scrutiny? Who should be responsible?**
12. It seems relatively uncontroversial to insist that the results and full data of all trials and, indeed, all scientific studies, particularly those funded with public money, should be published. Publication does not have to be in journals, and as publication of full data becomes the norm it will make more sense to publish on large databases rather than in journals. Indeed, current publishing practices mean that trials are often published in journals that allow access only to those with subscriptions or who pay. Pharmaceutical companies are keen to have their most positive results published in high profile journals that reach many prescribing doctors and carry great prestige. We have growing evidence that exciting results published in high profile journals are more likely to be misleading than the results published in less prestigious journals. (5 6) This is a further source of bias in prescribing information for clinicians, who receive much of the information from these journals.
13. We support the registering of all trials on publicly available databases, and we support the move to publish the protocols of all trials. There is considerable evidence showing important changes between protocols and published studies, and some of these changes are designed to make drugs being trialled appear to be more effective than they actually are. (7). Clinical trial registration has a critical role to play. It is the start of a process that should ensure publication of trial results, and in a complete and unbiased way. Currently trial registration is an incomplete process and inconsistently enforced. If a more uniform approach to trial progress tracking could be achieved and those failing to deliver could be subject to some form of penalty, then we might make progress.

14. Many parties - authors, employers, funders, ethics committees, regulators - might potentially play a role in ensuring that all trials and studies are published, but there is clearly a danger that something that is everybody's responsibility becomes nobody's responsibility. We suggest that the prime responsibility should lie with the funders of the research, and they should develop and implement processes for ensuring that they: register all studies that they fund; follow up the studies; and insist that they are published. The mechanism for achieving the latter could be withholding the last part of the funding until publication has taken place, following the example of the HTA.
15. Although prime responsibility should rest with funders, there needs to be regulatory oversight. As the main concern is with drug trials and because much research is international, the European Medicines Agency is probably best to provide that oversight. It should almost certainly work with the US Food and Drug Administration (and other international drug regulatory bodies) to fulfil this oversight role. Any requirement to publish a clinical trial within a certain period following its completion would be worthless unless it was actively enforced. A new rule on its own would not be enough; its implementation would need to be monitored and action taken against those who choose not to comply.
16. In addition to these statutory roles it will be useful to write into codes of scientific conduct and employment contracts the duty to publish the results of all scientific studies. Publishing within 12 months of the completion of a study might be the aim but could be quite tough to achieve in practice, as the publication processes of some journals are slow. Setting a deadline of publication within 18 months of study completion may be more realistic.
17. Ethics committees might also develop mechanisms to ensure that all the research studies they approve are published, though they would need to be better resourced in order to carry out such a role without their other work suffering. Decisions would need to be made on a case-by-case basis and all research should be scrutinised in this way, whether it originated from a commercial organisation or elsewhere. Some argue that ethics committees should be able to refuse to approve research projects proposed by researchers who have not published results from earlier studies or trials.
18. In UKRIO's experience, policies, systems and even contracts are not sufficient on their own to effect real change. If left unsupported they can lead to a 'tick box' exercise, rather than becoming an integral part of the research practices of an organisation. Instead, they must be:
 - supported with appropriate resources, training, dissemination activities and sources of help;
 - monitored for effectiveness and periodically reviewed, informed by feedback from researchers, participants and others;
 - promoted by senior research and managerial staff in institutions, encouraging researchers to engage critically with standards for good practice in the publication and dissemination of research and with other issues of research integrity.
19. **Declaration of Interests:** This submission draws upon the views of the Trustees, Advisory Board and staff of UKRIO. These include persons who have: undertaken medical/ scientific

research, including clinical trials; worked as editors of academic journals which publish medical/ scientific research, including clinical trials; and/or held senior roles in institutions such as universities which undertake medical/ scientific research, including clinical trials.

20. UKRIO is funded by subscriptions from UK public sector or charitable research organisations, including over 30 universities. It has received funding from bodies that fund or undertake medical/ scientific research, including clinical trials. None of the bodies which fund or support UKRIO had any input into the content of this submission.
21. UKRIO has never received any funding from private sector organisations which conduct pharmaceutical/medical research or clinical trials. During our first phase, which ran from 2006 until mid-December 2010, UKRIO received £10,000 in funding from the Association of the British Pharmaceutical Industry (ABPI).
22. UKRIO is a signatory of the All Trials petition for the publication of clinical trials results. Further information on the petition can be found at www.alltrials.net.
23. **About the UK Research Integrity Office:** The UK Research Integrity Office (UKRIO) is an independent charity, offering support to the public, researchers and organisations to further good practice in academic, scientific and medical research. We promote integrity and high ethical standards in research, as well as robust and fair methods to address poor practice and misconduct. We pursue these aims through our publications on research practice, the support and services we provide to organisations, our education and training activities, and by providing expert guidance in response to requests for assistance.
24. Since 2006, UKRIO has provided independent, expert and confidential support across all disciplines of research, from the arts and humanities to the life sciences. We help all involved in research: researchers, research organisations and members of the public, including patients and research participants. UKRIO covers all research sectors: higher education, the NHS, private sector organisations and charities - wherever the research affects the public good. No other organisation in the UK has comparable expertise in providing such support in the field of research integrity. We welcome enquiries on any issues relating to the conduct of research, whether promoting good research practice, seeking help with a particular research project or investigating cases of alleged fraud and misconduct.
25. We are not a regulatory body and have no formal legal powers. UKRIO fills gaps between jurisdictions, where no overall regulation might apply, and helps to direct researchers, organisations and the public to regulatory bodies when issues fall within their jurisdiction. We help institutions achieve high standards when they have to manage challenges to research integrity and support individuals faced with bad practice. Our advice and guidance emphasises the good practice that runs across all research disciplines and all regulatory remits. In this way our role complements that of regulatory bodies for research and supports the work of Government and research funders.

February 2013

References

1. Goldacre B. *Bad Pharma*. Fourth Estate, 2012.

2. Chalmers I, Glasziou P, Godlee F. All trials must be registered and the results published. *BMJ* : British Medical Journal. 2013 Jan;346. Available from: <http://dx.doi.org/10.1136/bmj.f105>.
3. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ*. 2003 May;326(7400):1167–1170. Available from: <http://dx.doi.org/10.1136/bmj.326.7400.1167>.
4. Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L. Industry sponsorship and research outcome. *Cochrane database of systematic reviews (Online)*. 1996;12. Available from: <http://dx.doi.org/10.1002/14651858.MR000033.pub2>.
5. Young NS, Ioannidis JPA, Al-Ubaydli O. Why Current Publication Practices May Distort Science. *PLoS Med*. 2008 Oct;5(10):e201+. Available from: <http://dx.doi.org/10.1371/journal.pmed.0050201>.
6. Ioannidis JA. Contradicted and Initially Stronger Effects in Highly Cited Clinical Research. *JAMA*. 2005;294(2):218-228. doi:10.1001/jama.294.2.218.
7. Lundh A, Krogsboll L, Gotzsche P. Sponsors' participation in conduct and reporting of industry trials: a descriptive study. *Trials*. 2012 Aug;13(1):146+. Available from: <http://dx.doi.org/10.1186/1745-6215-13-146>.

Written evidence submitted by Ethical Medicines Industry Group (EMIG) (CT39)

Summary

This submission is based on a paper submitted by EMIG to the EMA as part of the on-going work to determine a holistic approach to the release of clinical trial data that meets the needs and addresses the concerns of all stakeholders.

With regard to Marketing Authorisation Applications (MAA) EMIG supports the principle of the intent to publish clinical research data once a regulatory opinion has been given on a MAA (or variation thereof). There are however significant issues that need to be addressed in order for this process to be holistic and robust. These are;

- To ensure the integrity of “raw” data re-analyses, there should be a “gate-keeper” function and requests for data release should be accompanied by a clear prospective “project plan”.
- A critical issue is how this would operate and be funded.
- Plans must be implemented to mitigate the risk of unfair competition for products which rely on data protection.
- Consideration could be given to extending and standardising the time for data protection of SPCs, potentially through an ICH mechanism.
- The incentives to innovate must be maintained, but with due consideration given to fair competition and overall medicines affordability.

EMIG welcomes the opportunity to engage constructively with the Science and Technology Select Committee, the MHRA, EMA and other organisations to design, implement and manage a “clinical research data release” system that meets the needs of all stakeholders in healthcare, most important of which are patients.

Introduction

- 1.1** The Ethical Medicines Industry Group (EMIG) welcomes this opportunity to submit to the Science and Technology Committee inquiry into Clinical Trials. This paper was authored by Dr Mark Edwards, EMIG R&D Director, with significant input from the EMIG membership, who collectively represent multinational and specialty pharmaceutical companies, and organisations with specific legal and biostatistical expertise.
- 1.2** EMIG is the biopharmaceutical trade association that represents the interests of over 200 companies and organisations, mostly SMEs, based in the UK. Our members range from start-ups, whose prime focus is often research and development (R&D), to highly developed businesses delivering essential products to patients and health services in the UK and internationally. Whilst providing important medicines to patients, the small and mid-sized life sciences industry is also a significant contributor to the UK economy. In the UK, SMEs constitute approximately 90% of the total number of biopharmaceutical companies and it is estimated that 80% of innovation is derived from these small companies. EMIG member companies employ approximately 20,000 people in the UK and have a combined annual turnover of £4bn.
- 1.3** This paper aims to articulate a holistic perspective on the issue of data release from clinical trials. It aims to be constructive, fair and balanced, in order to facilitate a progressive dialogue.

- 1.4 EMIG would be delighted to give oral evidence to the Select Committee if it would be valuable or if any of the points in this submission require further detail.

The European Commission's proposed revisions to the Clinical Trials Directive

- 2.1 EMIG is a member of the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), which represents small to medium-sized companies and associations operating in Europe. As a member, EMIG supports EUCOPE's position in response to the European Commission's Clinical Trials Directive¹. The Commission's proposal foresees a new assessment process for clinical trials which would provide for less reporting, lower insurance costs and shorter timelines. This approach is broadly welcomed. We believe that the new regulation will help to speed up the approval process and increase the number of clinical trials conducted in the EU, whilst at the same time ensuring patient safety.
- 2.2 Whilst welcoming the proposed revisions, EMIG believes there are points requiring further clarification, namely:
- a) The protection of commercially confidential data in the new database;
 - b) The inclusion of ethical aspects in the assessment procedure;
 - c) The consideration of the specifics of clinical trials in rare and ultra-rare diseases when applying the provisions of the Regulation;
 - d) The informed consent requirement in emergency situations;
 - e) Establishment of one language for the application dossier for the complete procedure.

Transparency and disclosure of clinical data

The EMIG "base case"

- 3.1 First and foremost in setting the regulatory framework for clinical trials are patients. Patients who volunteer to take part in clinical research, where the risk/benefit of an experimental medicine or the effectiveness of an approved product may not be established and doing so is therefore the primary objective of the study, or programme of studies must be respected and protected. Patients with serious, life-shortening or terminal diseases also frequently take part in clinical research with the knowledge that they may not directly derive long-term benefit from their participation, but do so out of a sense of altruism. They may, for example, have themselves derived quality- and/or quantity-of-life benefits from medicines that previous patient volunteers helped to research. In turn, they may now wish to play their part to help future patients to benefit from advances in medicines. Being able to understand what conclusions were made from their participation in clinical research, to share learnings with other patients, and to know that other researchers would be able to progress research further as a consequence of their participation, are all important issues for patient volunteers.

¹ EUCOPE's submission to the European Commission's proposed revisions to the Clinical Trials Directive is included in the annex of EMIG's submission.

- 3.2 In the UK, the Faculty of Pharmaceutical Physicians has publicly advocated full publication of study results for some time.² Contained in this document are two explicit statements regarding the publication and sharing of the results of clinical research;

“Publication

There should be openness and honesty in sharing the results of research. It is unethical to withhold the publication of any results of research on any pharmaceutical product whether the results are positive, negative or inconclusive.

Sharing Findings

All studies should be performed to increase knowledge in some useful way, and there should be openness and honesty in the sharing of this knowledge with the wider world. Study findings need to be communicated, whatever the outcome, for the benefit of the community at large. The sponsor should have a clear policy regarding study publication which should be agreed with the clinical researcher prior to study initiation, and neither the sponsor nor the researcher should seek to prevent publication or the admission of trial results within the public domain. Communications on clinical studies must be a correct objective representation of all the findings, allowing others, in their turn, to give well-balanced risk-to-benefit advice to patients and their families. It is especially important that negative results or adverse safety data are communicated to regulators and clinicians in a timely manner where this information may affect prescribing practices and the protection of patients.”

- 3.3 **EMIG fully endorses these statements and believes that all sponsors of all types of clinical research have a fundamental duty to patient volunteers to ensure that the results and conclusions from all clinical research (including post-marketing studies in industry) in which they have participated should be made publicly available in the form of Sections 1-15 of ICH-3 compliant Clinical Study Reports (CSRs)³.**
- 3.4 We believe that the EMA proposals demonstrate a step-change further to the above, inasmuch its intent is to publish “raw” clinical research datasets, which, *inter alia*, will therefore contain patient-level data. We do not believe this is problematic as long as the process for data release is designed, implemented and managed carefully (see below). **We would like to see the Science and Technology Select Committee join with organisations like EMIG to ensure the proposals can be implemented in a way that can offer real benefits to patients and introduce a new openness in the clinical trial environment.**
- 3.5 Notwithstanding our belief that the EMA could have explained the rationale for its intent to release clinical trial data much more clearly than it chose to do, we understand that this is predicated fundamentally by the growing expectation within the EU Commission over the last few years, that all EU public organisations will move from a default position of privacy, to one of openness. Accordingly, the EMA is mandated to move from, "why *should* we support open access?" to "why *shouldn't* we support open access?" **The key reason however, where open access should not be supported by the regulators, is where the needs of transparency are outweighed by important, but temporary, confidentiality aspects that**

²<http://www.fpm.org.uk/policypublications/guidingprinciples>.

³ Full ICH-3 compliant CSRs contain a listing of the patient-level data, and includes all of the Case Record Forms (CRFs), in section 16. This also contains items such as all Investigator/co Investigator CVs (data protection) and copies of all papers referenced in the report (copyright). Hence our proposal to release sections 1-15 only.

would impair the ability to continue objectively to research the intervention under study.

- 3.6** In terms of the topic under discussion here therefore, it must be up to the data's sponsor organisation to articulate the objective scenarios where release of clinical research data would be to the detriment of the continuity of ongoing research and to gain timely agreement on that with the EMA. In this instance, EMIG regards a "refusal to play ball" as not credible, which should understandably be overruled. Otherwise, anyone can make the 'detriment' argument and "because it is confidential it is not open to scrutiny".
- 3.7** **However, we would like the Science and Technology Committee to join with us to request clarity and confirmation from the EMA as soon as possible with regard to precisely what data is intended to be released.** There is a considerable lack of understanding on this in organisations, which is a barrier to building a collective and progressive agreement on the way forward. There must, however, be a clear distinction drawn between data from clinical trials and other data such as highly commercially sensitive analytical or manufacturing methods that form a critical part of the Common Technical Document (CTD), that should not be released.
- 3.8** Our current understanding is that it is only the clinical research components of a regulatory submission that will be released. The non-clinical aspects e.g. structural, chemistry, manufacturing and control data are commercially sensitive and therefore are not for consideration.
- 3.9** However, even within this there needs to be a distinction made between "results" and "raw" data. With the former, we believe all companies should be encouraged to state that they will release all primary and secondary parameters and safety data, as well as protocol details, selection parameters, demographics and analysis plans in a specific minimum timeframe. The release of raw data-sets represents an entirely different scenario and needs special consideration (see below).
- 3.1.1** Overall, we believe that measures which will increase transparency in clinical research could prove to be valuable in driving better-designed and more cost-effective clinical development programmes. For example, it could enable clinical trial programmes to be designed more quickly and targeted more effectively to the likely responsive patient populations, thereby complementing the increasing focus on personalised medicine. It could also correspondingly reduce the number of unnecessary clinical development programmes, with benefits to patient safety and R&D portfolio budget management. Furthermore, clinical trial planning would be improved through wider access to data on variability of data and effect sizes, which would enable more informed sample size calculations to be conducted. Patient safety would also benefit from the enhanced ability of researchers to access full data-sets to assess safety signals. It is recognised that such independent analyses, but often using less robust information, occur now. Sub-optimal analyses can only inevitably lead to sub-optimal conclusions and sometimes these will be dangerous to public health. Routine controlled access to fuller data-sets will help avoid these disasters. For HTA purposes, the existence of full study results or study data would improve the quality of evidence synthesis reviews through the provision of more complete data. This should result in more accurate inputs to health economic models thereby enhancing assessment of cost-effectiveness of products.

3.1.2 Accordingly, we support fully the *principle* of the EMA’s intent to publish clinical research data once it has issued an opinion (negative or positive) on a drug’s marketing authorisation application, or subsequent variations.

3.1.3 However, there exists a number of legitimate concerns for industry, which largely centre on the “why”, “who” and “when” aspects of such data release. These are elaborated below, together with potential solutions. Our principal request is that a robust “gate-keeping” process is developed and implemented to ensure that the release of clinical research data and in particular, “raw” data-sets, is done in a manner that safeguards its integrity and acknowledges the concerns below. We assert that it is to no one’s benefit, and in particular, regulatory authorities, to support uncontrolled “fishing” expeditions for data by any type of organisation (public, private or charitable). This is not about data release *per se*, but rather the separate concerns about selective reanalysis.

3.1.4 Making an analogy therefore, to the pharmaceutical formulation of many medicines that has helped thousands of patients over the years, we believe that it will be the “controlled release” of clinical research data that is key to meet the needs and aspirations of all stakeholders.

Concerns and ideas for solutions

4.1 Whilst all sponsors of clinical research should be open to sharing publicly all of the information used to design, execute and report it, in terms of that proposed for release by the EMA, EMIG believes data-sharing needs to be carried out with all due attention paid to the method of release. For example, full open access could be envisaged for data where key parameters have been analysed. Safety data specifically should also follow this route. As mentioned above, ideally all companies should be willing to do this, and this shouldn’t require EMA “management”.

4.2 However, where raw data-sets are being considered for release, this must follow a controlled process, with well-constructed, prospective requests made by an ‘applicant’ to a future ‘gatekeeper’ authority. *Inter alia*, these requests need to articulate clearly the hypothesis to be tested and its analysis plans. In turn, there may be a role for the company and the EMA to review these reanalyses together, subsequently to reassess the validity and benefit / risk of a product as a result.

4.3 In simple terms, having a well-meaning, but less than regulatory-standard re-analysis of benefit/risk performed, could compromise or even seriously risk patient safety. A fully open uncontrolled “free for all” access to data also risks the dangers of “cherry-picking” parts of the full dataset, which could give rise to erroneous conclusions and consequently to not evaluating the “whole” and putting the new results in their correct context.

4.4 In addition, we are concerned that should selective data re-analyses be allowed in an uncontrolled manner, there is a serious risk of undermining the careful prior work of and conclusions on benefit/risk made by the regulatory agencies. These reviews are hugely thorough in terms of the time taken carefully to review submission dossiers and the number of highly detailed questions for clarification that are sent to the sponsor as a consequence. Every bit of the regulatory review process is designed to ensure the very best understanding of a new product’s benefit/risk, which of course is fundamental to safeguard patients. *A priori*

therefore, this must not be put at risk by making allowance for open selective data re-analyses.

- 4.5 To mitigate these risks, EMIG therefore proposes that a robust, but straightforward “application” process is put in place for those wishing to access data. Similar to the process recently launched by GSK, data could be made available to requesters, following receipt of a prospective research proposal and analysis plan. This would need to include an independent peer-review via a central mechanism in order to decide if the data should be released. The obvious body to manage this is the EMA. However, we would question whether the EMA currently has the resource and the funding to do this? If not, what would the EMA’s “designate” body look like? How would this be funded? **Funding therefore is a critical issue**, not least because the small and mid-sized company sector i.e. the very sector that the European Commission seeks specifically to support in terms of its growth and sustainability, does not have the resources to fund such an undertaking. Additionally, the management of a large data repository would be very expensive and would need to be done properly.
- 4.6 One idea might be to look at the organisational principles of the Innovative Medicines Initiative (IMI), to assess the feasibility of a public-private partnership to establish an independent and collectively-funded third party to perform peer-review, and perhaps adjudicate disputes e.g. should secondary analyses suggest different results from an original clinical study report (CSR)?
- 4.7 A second concern surrounds the potential “commercial sensitivity” of clinical research data. At face value, if the intent is to publish *only* that part of a regulatory submission that relates to the clinical research i.e. the design methodologies, raw data and results, and NOT also other pre-clinical structural and formulation data which could be highly commercially sensitive, it is difficult to see what is truly commercially sensitive. Indeed, as highlighted above, there are potentially significant gains to be had by enabling access to more anonymised datasets.
- 4.8 Perhaps therefore the issue here is not so much the clinical data *per se*, but *how* it could be used by competitors in certain circumstances. For instance, not all products are covered by patents and instead, rely on data protection laws. The EMA has said that it will not allow submissions within the EU from anyone other than the Marketing Authorisation Holder (MAH), using data released after an initial application, but there is nothing to stop a generics company or anyone else from compiling an application package and submitting it in other territories. Without mitigation, this could have completely unintended consequences for EU patients; a scenario could be envisaged where EU submissions occur only *after* applications have been made in all of the other regions. This would achieve the unwanted outcome of putting EU citizens at the back of the queue for some new medicines.
- 4.9 Taking this one stage further, some have suggested that the only answer to the requirement for hard endpoint/outcome AND head-to-head superiority before the approval of drugs and full disclosure of all assets afterwards, is a radical overhaul of the patent system. Could this be a step too far? It is possible. But, what, in a new environment of open access to all clinical research data, could be done to achieve a balance that maintains fairly the incentives for inventors and their funders to continue to invest and innovate in the development of new health technologies; the rights of generic manufacturers to compete and national public health needs for cheaper medicines to achieve affordable overall medicines budgets?

4.1.1 Suggestions include -

- For products covered by data protection rules, the international regulatory authority community collaborates to put in place additional checks and audits world-wide to ensure that submissions comprise only studies conducted by the originator companies.
- To extend the duration of the Supplementary Patent Certificate (SPC) so that the overall data protection is always 20 years.
- An ICH Working Group is convened to address holistically the issue of data exclusivity.

4.1.2. Importantly, this issue should not detract from the fundamental aims of achieving greater openness for clinical research data. Yet it is a key “covariable” for which a solution is needed in order to achieve full consensus among all stakeholders, and therefore progress for all. **EMIG therefore requests that the Science and Technology Select Committee works with organisations such as the EMA to influence this happening.**

February 2013

Appendix: EUCOPE submission

EUCOPE Position

on the Proposal for a Regulation on clinical trials on medicinal products for human use (COM 2012 369) and repealing Directive 2001/20/EC published by the Commission on 17 July 2012

Summary

The Commission proposal foresees a new assessment process for clinical trials. This provides for less reporting, lower insurance costs and shorter timelines. **EUCOPE generally welcomes this approach.** We are convinced that the new regulation will help to speed up the approval process and - equally important - will increase the number of clinical trials conducted in the EU while at the same time ensuring patient safety.

Points that require further clarification are:

1. **the protection of commercially confidential data in the new database;**
2. **the inclusion of ethical aspects in the assessment procedure;**
3. **that the specifics of clinical trials in rare and ultra-rare diseases are sufficiently considered when applying the provisions of the Regulation;**
4. **the informed consent requirement in emergency situations;**
5. **establishment of one language for the application dossier for the complete procedure.**

EUCOPE particularly welcomes:

1. the introduction of a **single EU portal** for the submission of data relating to clinical trials which is held by the European Commission and free of charge for sponsors;
2. the **two-part assessment** procedure, distinguishing aspects where Member States cooperate and aspects where each Member State acts individually;
3. the **integration of the ethic evaluation** in the assessment procedure. However, it **might be helpful to clarify** that ethical aspects and the decision of Ethics Committees are part of the assessment

procedure in order to prevent duplication of assessments, compliance with timelines and the harmonization of documents (Annex I). **Member States are free to choose the persons and the entity to review ethical documents set out in Annex I;**

4. the adoption of the **tacit approval** and the **withdrawal** concept which will ensure compliance with the timelines;
5. the **risk-based approach** distinguishing between low-interventional clinical trials, general clinical trials and clinical trials with an advanced therapy investigational medicinal product. This distinction takes effect on the timelines, the reporting and the insurance requirements.

However, we see a need for amendments with regard to the following aspects:

A. Protection of commercially confidential data in the new EU database (Art. 78 COM proposal)

Article 78 provides for the establishment of an EU database to enable the co-operation between Member State authorities which shall be publicly available unless the data is considered to be commercially confidential information (Art. 78(3)).

As data needed for the approval of a clinical trial often contains a significant amount of know-how and personal information it:

1. needs to be **clearly defined what constitutes “commercially confidential information”** and
2. that **intellectual property is considered automatically as commercially confidential and**
3. a **consultation of the sponsor** should be implemented

1. Intellectual property of the sponsor

The **protection of** personal data for individual privacy, **intellectual property**, and commercially sensitive information is a **core principle** of EU and Member State legislation and is binding in particular for the European Commission when access to document legislation is concerned. Article 4(2) of Regulation 1049/2001 regarding public access to European Parliament, Council and Commission documents stipulates that “the institutions shall refuse access to a document where disclosure would undermine the protection of commercial interests of a natural or legal person, **including intellectual property**...” This clarification urgently needs to be included in the new clinical trial legislation as the Commission as the holder of the database should respect the intellectual property of sponsors as foreseen for example in Regulation 1049/2001 (see above).

Also, it should be borne in mind that the Commission only recently explicitly stated “that keeping **valuable information secret is often the only or the most effective way that companies have to protect their intellectual property**” (*Public consultation on the protection of business and research know-how* http://ec.europa.eu/internal_market/consultations/2012/trade-secrets_en.htm).

Therefore, the existing Article 78(3) of the Proposal should be amended as follows:

“...confidentiality is justified on any of the following grounds:

– ...

– protecting commercially confidential information, including intellectual property;”

2. Definition of the term “commercially confidential information”

The general concept of transparency of information is fully supported by EUCOPE. However, it needs to be considered **that even today a vast amount of information about clinical trials is publicly available** on the EU Clinical Trials Register website (www.clinicaltrialsregister.eu – see attached screenshots). The published data fields are the following:

- Identification of the clinical trial and the sponsor;
- Identification of the medicinal product;
- Identification of the indication under study;
- General descriptive information on the clinical trial and the patient population included:
 - major objective, principal inclusion and exclusion criteria of the clinical trial,
 - phase of the clinical trial and design (e.g. randomised, controlled),
 - comparators (medicines/other treatments) if this is part of the clinical trial,
 - number of patients anticipated in the clinical trial, age range(s) and gender.

(Communication from the Commission regarding the guideline on the data fields contained in the clinical trials database (2008/C 168/02))

This level of transparency is secured under the existing legal framework. The concept of transparency is generally welcomed by research-driven mid-sized pharmaceutical companies. The Commission’s view that the public **needs access to additional information beyond what is already available (see examples attached)** is comprehensible but needs to be debated on substance in the European Parliament and in the Council. It needs to be borne in mind that know-how and valuable confidential intellectual property especially regarding the manufacturing, certain technological approaches and certain data in the development of an innovative medicinal product are of crucial value. The European Court of Justice has stated in Case C 453/03 (ABNA) that the publication of detailed product data is against the principle of proportionality as far as the authorities dispose of such data. Therefore, such publication may not be justified by the objective of protecting public health. **Without any protection of this value innovation might be impeded significantly. Clinical trials would even more than today be conducted in third countries in order to safeguard the innovation and the intellectual property.** This would contradict the main objective of the proposal.

In order to provide for legal clarity and predictability for patients, industry and public bodies a definition would be advisable. **EUCOPE suggests including the following definition** into Article 2(31) – (new) of the Proposal:

“Commercially confidential information is considered to be any information, including know how, trade secrets and information which is not in the public domain or publicly available and where

disclosure could undermine or damage the economic interest or competitive position of the proprietor of such information. Information contained in the investigational medicinal product dossier (IMPD) pertaining to the pharmaceutical and non-clinical pharmaco-toxicological testing results and detailed clinical development plan other than the summary of the approved clinical trial protocol shall be considered as commercially confidential information.”

Whereas the EU largely safeguards that detailed regulatory data cannot be used by competitors before the data exclusivity period has expired, competitors could use this data in third countries with a less strict or even not existing data exclusivity regime.

3. Consultation of the sponsor

The concept of transparency regarding clinical trial data as put in practice today is welcomed by EUCOPE. This concept could be further discussed in case the protection of **commercially confidential information is secured by a consultation of the proprietor of the information / the sponsor**. Only the consultation of the sponsor safeguards that his know-how especially regarding the manufacturing and certain technological approaches in the development is protected. **The Commission alone cannot assess this.** Therefore, the consultation of the sponsor is mandatory.

The involvement and consultation of the proprietor of the information before dissemination is also foreseen by law in access to documents legislation. All EU institutions must consult third parties according to Article 4(4) of Regulation (EC) No. 1049/2001 (http://www.europarl.europa.eu/register/pdf/r1049_en.pdf) before the information can be disclosed in order to assess whether the content is commercially confidential. The same degree of involvement is foreseen in EU competition law. **This procedure must urgently be followed especially when sensitive clinical data is concerned.**

Therefore, the existing Article 78(3) of the Proposal should be amended as follows:

“The EU database shall be publicly accessible unless, for all or parts of the data and information contained therein, confidentiality is justified on any of the following grounds:

[...]

“The Commission shall consult the sponsor with a view to assess whether the request of information contains commercially confidential information before making it publicly available. The information can be made publicly available if the sponsor does not object in writing within 30 days after the Commission has notified to the sponsor that it intends to disclose this information. The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to specify this procedure.”

This would avoid disputes from the beginning and be in line with the approaches of the EU institutions in the legislation regarding access to documents and EU competition law.

B. Ethic evaluation in the assessment procedure

The current proposal does not explicitly refer to the involvement of ethics committees in the assessment procedure. This led to occasional assumptions that ethical aspects are generally not to be involved in future assessments of clinical trials. This, however, is a misconception. **EUCOPE would like to underline that aspects clearly related to ethical matters are referred to in Recital 63 and Article 44. Ethical aspects are part of the assessment procedure in Article 7 since they are mentioned in Annex 1 of the Proposal.** Yet the inclusion of ethical review is not explicitly mentioned. **To resolve all doubts and give clarity, EUCOPE strongly suggests supplementing Article 9 of the proposed regulation by a paragraph 4 as follows:**

“All ethical aspects are subject to this regulation and shall be assessed by an independent body chosen at the national level.”

C. Clinical trials in rare and ultra-rare diseases

It is important that the future Regulation takes into account **the therapeutic developments as well as the latest EU policies on rare and ultra-rare diseases** (*inter alia* laid down in Council Recommendation of 8 June 2009 on an action in the field of rare diseases). Rare and ultra rare-diseases are a serious threat to the health of EU citizens as they are life-threatening or chronically debilitating. Despite their rarity, there are many different types of rare and ultra-rare diseases that affect millions of people. For this purpose, it has to be clarified that the specifics of clinical trials in these diseases are sufficiently considered when applying the provisions of the Regulation. Clinical trials in these diseases must be judged for statistical relevance with methodology that takes appropriate account of the patient population and potentially low levels of diagnosis. Therefore EUCOPE suggests including a **new Recital 23** into the text of the Regulation:

“Whereas most clinical trials are intended for the evaluation of therapies for larger patient populations, this Regulation shall not discriminate against persons suffering from rare diseases and ultra-rare diseases and shall take into account the specificities of conditions with low patient populations when assessing a trial.”

D. Clinical trials in emergency situations

Article 32(1)(e) of the Proposal provides that in emergency situations informed consent may be obtained after the start of the clinical trial, provided that the clinical trial poses a risk to, and imposes a minimal burden on, the subject. **However, since an emergency situation requires a sudden life-threatening or other sudden serious medical condition, it would be very difficult for a physician to assess the actual risk the clinical trial poses on the patient.** Whether this risk is minimal or above minimal could be hard to predict and therefore, it has to be feared that physicians will rather refrain from including the patient into a clinical trial than facing a potential dispute about the involved risk. **This might lead to a situation where patients are denied the only available form of treatment for a serious disease.** Therefore, Article 32(1)(e) should be amended in the following way:

“the clinical trial poses a ~~minimal~~ **tolerable** risk to, and imposes a ~~minimal~~ **tolerable** burden, on the subject.”

E. Language requirements

The Proposal states that it should be left to Member States to establish the language requirements for the application dossier but that Member States should consider accepting a commonly understood language in the medical field as the language for the documentation not destined to the subject (Article 26). It should be clarified that once a Member State has accepted an application dossier in a certain language **all other communication not destined to the subject shall be in this language as well**. This would facilitate the administrative work of the sponsor and the investigator and would also considerably lower the costs for translations. Consequently, Article 26 first sentence should be amended as follows:

“The language of the application dossier, or parts thereof, *as well as of the further communication not destined to the subject* shall be determined by the Member State concerned.”

Written evidence submitted by Dr Mark Edwards FRCA FSB (CT40)

Introduction

- 1.1 As a staunch advocate for the UK life sciences, these are my personal views on the work of the Health Research Authority (HRA) and what it could achieve for the UK with appropriate resource.
- 1.2 Since its inception, the HRA has presented itself as a dynamic champion of change, with a determination to review every aspect of clinical trial regulation, to remove processes that do not work or really make sense, and to develop and implement revised procedures that do.
- 1.3 **I believe the HRA has the potential to evolve as *the* single, hugely credible, unifying port of entry to do clinical research in the UK.** While recognising that it must be able to walk before it can run, its scope of influence is potentially enormous. It also has the *right* people in place to achieve this vision, most notably Janet Wisely, who, with a common-sense approach, is an inspirational leader of the first order.

The HRA approvals process

- 2.1 Via the National Research Ethics Service (NRES), the HRA has established a process that works well for the ethics approval of clinical trials and I rarely now hear about this being an issue for companies. Similarly, the process for obtaining MHRA approval for clinical trials seems to work well overall.
- 2.2 So, the remaining challenge for the HRA in the “approvals” space is to achieve a **single NHS Research & Development (R&D) approval for multicentre trials**. This is a huge challenge, but one that, if successful, could alone make a significant impact on the attractiveness of the UK as a place to do clinical research i.e. for the UK to be able to offer industry the “holy trinity” of a single approval for ethics, regulatory and NHS R&D matters.
- 2.3 Personally, having worked with the Office for Strategic Co-ordination of Health Research (OSCHR) and then the National Institute of Health Research (NIHR) to help establish the Translational Research Partnerships (TRPs), which are predicated on the fact that a commercial partner can access all of a TRP’s clinical academic expertise through a single contractual signature, I believe the achievement of a single NHS R&D approval for clinical trials is completely doable. It does however, require a collective mind-set to be established in which people understand the importance of “waking up and smelling the coffee”. In this instance this means the development of a common understanding that collaboration between Trusts will achieve more than each Trust continuing to operate in its own silo. **One idea for the HRA might be to bring together selected Trust CEOs (and their R&D office personnel) who have demonstrated a willingness to “do things differently” to develop a framework for a single NHS R&D sign-off.**
- 2.4 This now brings me to the overall "time, cost, quality, reliability" (TCQR) quartet that are the primary industry considerations for placement of certainly later phase clinical trials. The HRA

has to date, quite rightly, focussed on improvements to the “time” element. The single NHS R&D approval is a key component of this.

- 2.5** The *costs* of doing clinical research in the UK present a mixed bag of opinion from industry. Most agree that paying a reasonable premium for clinical research in the UK is acceptable, as long as time, reliability and quality factors are addressed such that the “end product” justifies the premium price. The key bugbears seem to be 1) instances where the UK is cited to be a “high end” outlier compared to other countries and where no explanation for the exorbitant costs are supplied and 2) a general concern that overhead charges are just too high and cannot be justified. Companies end up feeling ripped off. At the very least, there should be **efforts made to standardise overhead costs across the NHS and provide greater transparency as to how they are derived**. The HRA could play a pivotal role in achieving this. Indeed, a parallel could be drawn here with the way in which Trusts have Health Resource Groups (HRG) under Payment By Results (PBR) whereby they group procedures into HRGs and cost them accordingly. This leads to a consistent charge across the NHS.
- 2.6** This leaves *quality* and *reliability* factors. I do not sense that lack of *quality* in UK clinical research is routinely a major issue with companies. *Reliability* issues are, however, a concern. Some companies have told me that this is indeed their most significant issue with clinical research in the UK i.e. “they do not deliver what they said they would deliver”. Most late phase clinical research is conducted on a global scale, which, within industry requires a great deal of planning to allocate the right degree of resource (and associated costs and budgetary management) to the various countries where the research has been placed. Under-delivery therefore, not only delays the timelines for delivery of the research results (and therefore potentially the approval of a new medicine), but can also increase overall development costs by forcing companies to revise their clinical operations strategies in “mid-flow”. Such over-promising and under-delivering is therefore a serious issue for any territory which hopes to attract commercial R&D investment. **Maybe there is a role for the HRA here, which in the first instance could be to understand its root cause?**
- 2.7** What is certain however is that for the HRA to be successful in improving all TCQR factors, it needs the wider and more open engagement of industry to share its experiences. These need to include helping the HRA and its networks to understand how the UK is benchmarked against other countries in these key parameters. In turn, this requires industry to provide truly comparable data i.e. data from like-for-like studies are needed. **The UK offices of the large global contract research organisations (CROs) may be in one of the best positions to help here and I would recommend discussions between them and the HRA are commenced soonest.**

Recommendations for future areas of focus

- 3.1** Looking further to the future of possibilities for the HRA, I now suggest a few areas for consideration where I sense it could have a greater role to play, or at the very least needs to keep an eye on. They are based on what I perceive is the HRA’s ability to act as an “honest broker” and to adapt to changing circumstances i.e. to ensure that health research regulation

keeps pace with evolving science and safeguards patients, but in a manner that enables the UK to be world-leading;

- **Patients and adherence with medicines;** helping industry engage constructively with patients/patient groups to enable it to play a full part in the clinical research patient engagement, involvement and participation agendas (it should be remembered that industry scientists and physicians probably know the in's and out's of their medicines in development better than anyone else). In turn, this "better engagement" would play its part to assist the enormous issue we have with medicines adherence. We are aware that this is a "hot topic" within Dept. Health under the Medicines Optimisation agenda led by Dr Keith Ridge (Chief Pharmaceutical Officer) and Clare Howard (Deputy Chief Pharmaceutical Officer). This requires pan-stakeholder action and the HRA may be well-placed to play its part.
- **Adaptive licensing;** a great chance for the UK to be world-leading should pilot projects be successful. The emphasis that this will have on effectiveness data collection puts the UK at a potential advantage over elsewhere because of the relative maturity of health informatics systems here. What role could the HRA play to ensure an appropriate level of regulation for adaptive licensing projects?
- **Stratified medicine;** the Technology Strategy Board has issued a "roadmap" for stratified medicine which appears, rightly, to be embrace policy, as well as scientific issues. This will build on the UK's translational research expertise and will have emergent health research regulation considerations.
- **Open access;** helping all stakeholders to understand that, with the right processes in place, it's "OK" to share your toys, because you'll get access to a whole load more for the benefit of all.

Conclusion

- 4.1** I wish the HRA sustained success, influence and growth. I call on the Government to ensure that it receives the right level of resource to achieve its full potential as a key driver of clinical research investment into the UK.

February 2013

Written evidence submitted by NICE (CT41)

Introduction

1. We would like to thank the Committee for the opportunity to contribute to this inquiry. In this memorandum we have addressed those matters raised by the committee that relate directly to the work of NICE.
2. The National Institute for Health and Clinical Excellence (NICE) is the independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health, and from April 2013 our remit will expand to provide a similar service to the social care sector. NICE guidance supports health and social care professionals and others to make sure that the care they provide is of the best possible quality and offers the best value for money.
3. The issue of disclosure of clinical trial data and NICE's work has been raised in a number of other settings, including with the House of Commons Health Select Committee¹ and in published correspondence between NICE's chairman Sir Mike Rawlins and Dr Fiona Godlee, editor in chief, BMJ².
4. The issue of public disclosure of clinical trial data is relevant to all our guidance that offers advice to the NHS on clinical practice, but is especially important in two programmes: technology appraisals, which make recommendations to the NHS on the clinical and cost-effectiveness of new and existing medicines and other technologies; and clinical guidelines, which provide advice on clinical- and cost-effective approaches to the management of patients with specific conditions.

The NICE technology appraisal process

5. When NICE appraises technologies such as drugs and medical devices, we ask the manufacturer to provide us with any data, including any unpublished studies they may have, which relate to the appraisal³. We also carry out our own review of the published evidence, including for example examining the European Medical Agency's European Public Assessment Reports to help secure the information we need.
6. In the case of pharmaceuticals, the medical director of the company is required to confirm that, to their knowledge, the company has provided us with all the relevant information they hold, but as we have no means of independently corroborating this it is impossible for us to know, absolutely, that we have all the unpublished information that might be available. However, we would not continue an appraisal knowing that data likely to be material to the outcome of the appraisal existed but had not been made available.

The NICE clinical guideline development process

¹ www.publications.parliament.uk/pa/cm201213/cmselect/cmhealth/782/78202.htm

² www.bmj.com/tamiflu/nice

³ See section 4.2, *Guide to the methods of technology appraisal*, available at www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf

7. NICE's clinical guidelines are different from NICE technology appraisals in that they provide recommendations across the care pathway for a disease or condition, rather than specifically on a technology or group of technologies.
8. This broader approach means that we do not have the ability to contact every manufacturer of every drug available for a specific condition, so we rely heavily on published evidence. The issue of publication bias, and the non-reporting of negative results, has an additional impact for our clinical guidelines because we would not wish to recommend treatments that are ineffective, instead support the use of those that are clinically and cost effective. If the evidence of lack of effectiveness isn't published, it makes these 'do not do' recommendations⁴ impossible to compile.
9. This has not been a general problem in guidelines we have published, but it can occasionally make the development of a guideline more challenging. For example, in 2005 we published a guideline on depression in children and young people. In order to produce recommendations on the use of selective serotonin reuptake inhibitors (SSRIs) in childhood depression we wrote to the manufacturers requesting information. We were unable to obtain sufficient information from them on studies that had been carried out, and it was only when the Medicines and Healthcare products Regulatory Agency (MHRA) Commission on Human Medicines published the results of all of the clinical trials they knew about, we were able to develop recommendations on the appropriate use of SSRIs in children. A Lancet article⁵ describes this in more detail.

Questions posed by the committee

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?

11. We believe the revisions acknowledge that there have been problems with the directive and its implementation, and are therefore a genuine attempt by the commission to address many of the problems. The Academy of Medical Sciences report *A new pathway for the regulation and governance of health research*⁶ provides a comprehensive summary of the issues.

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

12. The Health Research Authority (HRA) was only established in December 2011 and as such it is too early to judge its effectiveness. However, we have begun to develop a good relationship with the HRA and we believe it is making good progress, particularly in the areas of merging research ethics approvals and addressing issues around research governance.

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

13. There have been well-publicised examples of where clinical trial data has not been published which has led to adverse consequences for patients and for health systems resources. We

⁴ www.nice.org.uk/usingguidance/donotdorecommendations/index.jsp

⁵ The Lancet - 24 April 2004 (Vol. 363, Issue 9418, Pages 1341-1345) available at [www.thelancet.com/journals/lancet/article/PIIS0140-6736\(04\)16043-1/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(04)16043-1/fulltext)

⁶ www.acmedsci.ac.uk/p47prid88.html

strongly believe that companies should make all the data they have available so that those organisations and individuals with responsibility for developing recommendations, and making treatment decisions, have all the necessary information to hand to help them do so safely and efficiently.

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

14. This is a complex issue and there may not be a simple solution. It is our view that legislation is not the answer, not least because clinical research and drug development is an international endeavour and regulation as a result would need to apply consistently across jurisdictions.
15. We would prefer to see a solution that is based on research ethics approvals. For example ethics committees could refuse permission for further research, and research funders refuse further funding, if the principal investigator has not published results from previous trials. Regulatory authorities could insist on all trials (even if the results are negative) with a drug for any indication, if it has any type of marketing authorisation, being published and publically available within 12 months of completion.

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

16. As we have described above; clinical research is a global endeavour and we don't know of any other country that has found a suitable solution to this problem.

February 2013

Written evidence submitted by Roche (CT42)

1. Introduction

1.1 Roche is a leading manufacturer of innovative medicines in a range of therapeutic areas, including cancer, rheumatoid arthritis and infectious diseases, such as hepatitis C and influenza. Many of our treatments have changed the standard of care in difficult to treat conditions, extending and enhancing the lives of millions of patients.

1.2 We operate two autonomous research units, as well as 150 research partnerships all over the world, to foster diversity of research and translate science into medicines. In 2012 we invested nearly 8.5 billion Swiss Francs in research and we now have 72 new molecular entities in clinical development. Last year there were 2,280 clinical trials in operation involving Roche medicines, involving 35,720 healthcare centres across the world. In total, 326,642 patients were involved in these trials.

1.3 Clinical trials are critical for determining the safety and efficacy of new medicines and the clinical value of diagnostic tests. They also provide important information on the cost effectiveness of a treatment or diagnostic test and how a treatment improves quality of life. This information is shared with regulatory authorities and payers in order to gain marketing approval and, ultimately, reimbursement. Roche also publishes the results of our clinical trials through numerous channels, such as peer reviewed journals and online, as we recognise that healthcare professionals, researchers, patients and the public are also interested in knowing about potential new therapies.

1.4 We therefore have a good deal of expertise in the issues associated with conducting clinical research, including ways in which data and findings can be published. As such, we welcome the Committee's inquiry and this opportunity to contribute evidence. As previously outlined in a letter to the Chair, we would be happy to provide oral evidence. Given the recent publicity relating to our decision around disclosure of patient-level clinical trials data on oseltamivir (Tamiflu), we have also extended an offer to the Committee to share in detail Roche's data on this medicine, as well as to answer any specific questions the Committee may have regarding the data and to discuss the reasons for the approach we have taken.

2. 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?

2.1 As one of Europe's largest sponsors of clinical trials we see the changes being introduced through the new clinical trials regulation as positive. A single portal for a submission, with harmonised decision-making is a major simplification and the proposal to introduce a timeline for the ethical committee approvals is most welcome.

2.2 The main barriers to conducting clinical trials in the UK are not the same as across the EU. From our experience in conducting significant numbers of trials throughout Europe it is clear that the clinical trials environment varies hugely between EU member states. Different countries interpret and implement international regulatory requirements in different ways, some with a much less legalistic approach than others. The UK has taken an excessively rigid approach, and conducting clinical trials in the UK is becoming increasingly costly and bureaucratic.

2.3 Barriers and enablers to conducting clinical trials in the UK can be categorised as follows:

- **Cost:** the cost of conducting clinical trials in the UK can be much higher than in other countries. The reason for this appears to be twofold. The UK has a particularly intensive approach to implementing regulation compared to other countries, and the NHS does not see clinical trials as part of its day to day operation, but instead a marginal activity which is priced accordingly. Whilst standard of care interventions (such as the set number of scans a patient with a particular condition would normally receive) are charged at standard tariff

prices, any additional activity required to meet rigorous clinical trial standards tends to be priced much higher – often up to 100% higher.

- **Time:** establishing trials in the UK and getting levels of recruitment up is often a more time consuming process than in other EU countries. Local inconsistency is the main source of delay. Each NHS organisation interprets compliance with regulations differently, and this manifests itself in wide variations in local processes to gain approval. Furthermore, the wide-ranging remits of organisations such as ethics committees can lead to many clinical trials being delayed. There is a perception that the relatively slow recruitment to trials in the UK is indicative of how trials are perceived in the NHS, and this makes arguing the case for centring trials in the UK a more challenging one.
- **Quality:** whilst the quality assurance standards in the UK are extremely comprehensive, the NHS is inherently a risk-averse environment and this filters down to individual provider units such as radiotherapy and pharmacy. This risk-aversion will increasingly have an opportunity cost in terms of being able to host the most advanced, high quality clinical trials. In addition, because the NHS is often a ‘low and slow’ adopter of innovative new medicines, the standard of care is not always of the same quality as in comparable EU health economies, and this makes the NHS a less attractive clinical trials environment. Similarly, there is lower motivation to undertake trials in an environment where the population is unlikely to benefit from the outcome.

These views are not held by Roche alone, and were confirmed by the Academy of Medical Sciences in their 2011 report *A new pathway for the regulation and governance of health research*, which concluded that ‘a complex and bureaucratic regulatory environment is stifling health research in the UK.’

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

3.1 The HRA has been given a significant and appropriate role in protecting patients and the public in health research. However, there are concerns that it has not been given the resources to achieve its role effectively and therefore may be at risk of either scaling back its remit or slowing down its work and the research and trials that rely upon it. The HRA should be appropriately funded or given access to alternative funding routes.

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

4.1 Bringing a new medicine to market involves conducting extensive clinical trials, often involving thousands of patients. Pharmaceutical companies therefore generate a huge amount of data on a particular medicine. This data is gathered to meet the requirements of Health Authorities globally, including the provision of patient-level data to the US Food and Drug Administration (FDA), and support them in reviewing the safety and clinical effectiveness of a medicine. Much of these data will also be reported in peer-reviewed publications and many manufacturers publish summaries of all their trials, both positive and negative.

Publication of trial data

4.2 Since 2007 Roche, along with other pharmaceutical companies, committed to disclose protocols of trials and the subsequent trial results in a public registry (ClinicalTrials.gov) and have published these on our own registry (Roche-trials.com) since 2005. In addition, any medicine for which marketing authorisation is sought is subject to full disclosure to regulatory authorities around the world, in accordance with local regulations. The vast majority of health authorities request specific and extensive information on a medicine when reviewing its approval. The EMA bases its approval of a medicinal product or a new indication on clinical study reports and can also include full data listings of anonymised data and aggregated summary data. Once approved, safety data is supplied on an

ongoing basis and in annual summary reports (periodic safety update reports). The US FDA also receives the same data as the EU, but in addition receives the electronic patient-level data files, which it has the capacity to reanalyse.

Tamiflu

4.3 Roche has recently been the subject of concerns raised about transparency of clinical trial data following our inability to agree with a group of academic reviewers the release of patient-level clinical trials data on Tamiflu. We stand behind the robustness and integrity of our data supporting the efficacy and safety of Tamiflu, which has been shared with all relevant regulators according to their requirements and guidelines. When considering the case of Tamiflu, it is important to note that:

- Tamiflu has been reviewed and approved by regulatory authorities in over 80 countries and over 95 million patients have received this medicine since it was first licensed and made available.
- Clinical trials and real-life experience from flu pandemics have shown that Tamiflu is effective in reducing the severity and duration of symptoms in those infected with flu and decreases the risk of developing the illness if there is contact with an infected individual.
- Various analyses of Tamiflu show a benefit in reducing the duration of symptoms, fever and time to return to normal sleep, health and activities, as well as reducing occurrence of lower respiratory tract complications (including bronchitis) requiring antibiotics in infected patients.
- Tamiflu is recommended as a flu antiviral by public health bodies worldwide including the US Centers for Disease Control & Prevention (CDC), the European Centre for Disease Prevention & Control (ECDC) and the World Health Organization (WHO)
- The US FDA has just extended the license for Tamiflu, now approving its use in children two weeks of age and over. This recent approval further substantiates the safety and efficacy of Tamiflu.

4.4 Over the past 15 years Roche has been the sponsor for 81 trials into Tamiflu. Of these, 1 was terminated before any patients were enrolled, and 74 are now completed. Of the 74 completed Roche sponsored trials, 71 (or 96%) are in the public domain either as a primary publication or secondary publication or on Rochetrial.com. Arrangements are underway for the three sponsored studies which are completed but not yet in the public domain to be posted.

4.5 Roche receives requests regarding the release of clinical trial data from academic and independent institutions worldwide. As part of this, we request an analysis plan and signed confidentiality agreement. Given some of the complexities inherent in making available patient-level data which was generated many years ago on the basis of consent forms which were never intended to enable such access. In addition the merit for any request should be assessed to ensure that the pre-planned analyses are based on clearly defined scientific and clinically relevant questions.

4.6 In relation to an initial request from the Cochrane Acute Respiratory Infections Group for access to data on Tamiflu, we provided large volumes of information in 2009 which we believe was sufficient to answer their questions. The reviewers questioned and did not sign a confidentiality agreement. In circumstances where concerns are raised about the detail of a confidentiality agreement, it is usual to investigate alternative arrangements that protect patient confidentiality, commercial sensitivities and provides them with the reassurance they require. In this instance, no such discussion was had, a mutually acceptable position was not reached and therefore patient-level data was not released to the review group.

4.7 Roche has subsequently shared Tamiflu data with another academic group under the scope of an agreement covering these necessary issues.

4.8 We maintain the highest ethical standards in the conduct of our clinical trials and transparency of our interactions with all external parties for all of our medicines. We recognise, however, that

following the debate about Tamiflu, there is legitimate policy interest in our data. Roche is confident in the data supporting Tamiflu and that and this is why we have offered to share in detail Roche's data on Tamiflu with the Committee, answer any specific questions it may have and discuss the reasons for the approach we have taken.

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

5.1 The medicines licensing system was established for very good reasons. It is vital that new treatments are assessed to ensure that the benefits to patients outweigh any potential risks for the condition in question. For this reason, and in order to maintain public confidence in medicines, the relevant licensing authorities need to remain the gatekeeper for drug approval. Provision and review of patient data should be conducted in a legitimate, independent and appropriately resourced environment to avoid the risk of offering false hope to patients or, conversely, giving rise to public health scares and consequences. Accordingly, the complete liberalisation of access to all data on medicines, without sensible assessment mechanisms in place, would not be without difficulties. Inappropriate data analysis and interpretation can lead to inconsistent messages regarding a given medicine and how best it should be used, and there are examples, such as the scares around MMR vaccines, that highlight the importance of handling data in a responsible way.

5.2 That being said, there is also legitimate interest from healthcare professionals, researchers, patients and the public into issues relating to the efficacy and safety of medicines, as well as in understanding what new therapies are in development. Accordingly, we recognise the importance of transparency and we support efforts to enable greater transparency of clinical trial results. We also understand that pharmaceutical companies have an important role to play in both facilitating and supporting this.

Role of pharmaceutical companies in supporting transparency

5.3 It is important to note that the demands for access to patient level data have increased significantly in recent years. Unfortunately many of the trials of today's medicines were conducted many years ago when the imperative for transparency of patient-level data was somewhat less. As a result, they were not always conducted in a way which supported easy disclosure of patient-level data and, in some circumstances, the wording of the patient consent forms makes this very difficult to achieve. We believe this challenge lies at the heart of much of the current debate about the transparency of trials and is something that we are committed to addressing.

5.4 We support moves to increase transparency and believe that these are best achieved on a cross-industry basis. In doing so, it will be important to consider how transparency can be improved:

- Prospectively, ensuring that clinical trial conduct and patient consent is delivered in such a way which maximises the transparency about medicines of the future
- Retrospectively, ensuring that more data are available on medicines in standard use today for which trials were conducted some years ago.

5.5 This is why we, along with many other stakeholders, offer our support to the European Medicines Agency (EMA) in their commitment to the proactive publication of data from all clinical trials supporting the authorisation of medicines. As a member of one of the EMA advisory groups, we are keen to see the results of deliberations on how proactive publication of data can be taken forward. We understand that a draft EMA policy will be available in June 2013 allowing us to prepare for the full implementation of the policy which will come into place on 1 January 2014.

5.6 Additionally, Roche is developing a policy and a process to make patient level data available: either to external researchers where a confidentiality agreement is in place and the scientific validity of the request has been reviewed by an independent third party, or for the scientifically valid request to be analysed by a third party. It is our intention to make this raw data available, but to be rigorous

about the scientific standards of the requests and the quality of the analysis. We believe this to be in the interest of the trial participants and the patients and prescribers who use the medications.

Additional scrutiny of Tamiflu

5.7 In the specific case of Tamiflu, and in addition to the offer we have extended to the Committee to review and discuss the data we hold, we are taking steps to facilitate further independent review. We are seeking to establish an independent multi-party advisory board comprising expert clinicians, academics and independent institutions to look at the data on Tamiflu, identify any medically relevant unanswered questions and agree on a statistical analysis plan to address these. Given the Cochrane Acute Respiratory Infections Group's interest in Tamiflu, it may wish to be part of this advisory board.

Real world data

5.8 Roche believes, when considering the overall benefit-risk of a medicine, all available data should be taken into account. This includes both formal clinical trial data as well as 'real world' data generated during a medicine's routine clinical usage. This approach offers important insights into how a medicine can be used to maximum effect, supports evaluations of cost effectiveness, informs pricing and enables authorities to ensure that treatment is delivering value for money.

5.9 There are already good examples of real world surveillance of drug efficacy, although more can and should be done. For example, the WHO conducts detailed global surveillance of influenza resistance to anti-virals such as Tamiflu. Clinical trials and real life experience from the 2009/10 flu pandemic have shown that Tamiflu is effective in reducing the severity and duration of symptoms in those infected with flu and decreases the risk of developing the illness if there is contact with an infected individual.

5.10 Equally, efforts are underway to collect data on the usage, efficacy and safety of anticancer medicines in routine NHS use, through the development of the Systemic Anti- Cancer Therapy (SACT) database, which will collect data on every cancer patient who receives cancer drug therapy in England.

5.11 We would welcome the Committee's recommendations on how best the collection and use of real world data can be improved as part of wider efforts to enhance the transparency of data.

6. Lessons from other countries

6.1 We provide health authorities around the world with all the data they request when assessing the benefits and risks of our medicines. However different national licensing authorities take different approaches to assessing and analysing data.

The vast majority of health authorities request specific and extensive information on a medicine when considering whether to grant marketing authorisation. The U.S. Food & Drug Administration (FDA) specifically requests anonymised patient datasets whereas the European Medicines Agency (EMA) does not. The FDA re-programmes and reanalyses the data in order to verify the analysis performed by the company. The EMA rather interrogates the sponsor and requests additional analysis or reanalysis from the company directly.

6.2 There are benefits and drawbacks to both this approach and that adopted by the EMA. The more information that is supplied to regulatory bodies, then the greater the cost that is associated with analysis and securing approval. Ultimately these costs will need to be borne either directly (through additional funding to the regulator) or indirectly (through higher medicines costs) by the taxpayer. It is for policymakers to determine whether or not this additional cost is justified by the benefits which may be incurred by submission of anonymised patient-level data.

Written evidence submitted by PatientsLikeMe UK (CT43)

Submitted by: Paul Wicks, PhD., Managing Director. Dr Wicks is a neuropsychologist (Institute of Psychiatry, King's College London) specializing in the conduct of clinical research using the Internet. He worked as a researcher for six years investigating cognitive aspects of motor neuron disease and later Parkinson's at King's College Hospital. For the past decade he has been involved in using the Internet to improve clinical trials, develop new measures of disease, and accelerate the pace of clinical research.

Disclosures: Paul Wicks is an employee of PatientsLikeMe and owns stock / stock options in the company. The PatientsLikeMe R&D team has received research support from Abbott, Acorda, the AKU Society, AstraZeneca, Avanir, Biogen, Genzyme, Johnson & Johnson, Merck, NIH, Novartis, Robert Wood Johnson Foundation, Sanofi, and UCB. PW sits on the advisory board of Current Controlled Trials for Biomed Central and is an associate editor at the Journal of Medical Internet Research.

Summary

1. A clinical trial is one of the most expensive, complicated, but scientifically robust tools available to medicine.
2. When the data arising from this exercise are compressed into a poster, conference presentation, or journal article, a great deal of information is lost that could benefit patients, clinicians, and researchers.
3. Specifically, the presentation only of averages and summary tables (rather than raw data) makes it difficult for future researchers to conduct meta-analyses i.e. to combine and summarize many studies to reach a more robust finding than could be reached by any one finding alone.
4. A mandatory open registry of machine-readable trial data could be constructed which would permit those who make healthcare decisions based on evidence to make better decisions.
5. Software developers could build applications that help patients to more easily interpret such data and make better shared decisions about their care with their doctors
6. Such an undertaking might initially be considered burdensome or expensive but may represent a useful mechanism to make better decisions about the most effective treatments available given constrained resources in the healthcare system
7. A level playing field for the presentation of evidence generated by clinical trials should reward those with the most effective products and so stimulate innovation.

Introduction

8. The Science and Technology Committee of the House of asked "How could the occurrence and results of clinical trials be made more open to scrutiny? Who should be responsible?"
9. In times of austerity we need to spend what resources we have on the best treatment options, but the status quo clouds and obfuscates data through publishing mechanisms rendered obsolete by the Internet.
10. PatientsLikeMe is an online patient network that allows those with long-term conditions to record and share their health data, connect with their peers, contribute to research, and identify clinical

trials for which they might be eligible. Over the past 7 years we have conducted studies investigating attitudes to trial participation.

11. We find that patients take part in clinical trials out of altruism, to help researchers make a better life for the next generation of patients to come. If we fail to make maximum use of the value generated by trials, we violate that social contract.
12. We believe that a repository of machine-readable clinical trial data, accessible to all free of charge, would be of major benefit to patients, researchers, health services, and government.
13. Through PatientsLikeMe we have demonstrated that with the right information visualizations, explanation, and importantly, the support of their peers, patients with no formal medical training can easily understand many of the important aspects of clinical data. After all, they are the ones living with disease and taking their treatments day after day.
14. Such systems lie within relatively easy reach, but as we have seen with ClinicalTrials.gov, successful implementation can only be driven by legislation.

Background:

15. PatientsLikeMe UK is a wholly-owned European subsidiary of PatientsLikeMe, a company that provides a data platform for the exchange of information between users living with chronic illness. PatientsLikeMe provides a number of resources to its user base of nearly 200,000 patients, including an interface for the retrieval of clinical trials from www.clinicaltrials.gov.
16. PatientsLikeMe permits patients with long-term illnesses such as multiple sclerosis, epilepsy, or depression to complete validated patient-reported outcome measures alongside symptoms (e.g. pain, insomnia, fatigue), lab tests (e.g. white blood cell count, lung function), and treatments (including drugs, surgery, or behavioral modifications).
17. Members are able to share their experience of treatments and rate their perceived efficacy, tolerability, burden, side effects, adherence issues, and out-of-pocket costs, along with the opportunity to provide tips and advice to other patients who may be considering taking the treatment. The aim is not to provide medical advice per se, but rather to share the experience of what it is like to live well with illness.
18. This data has the limitation of not being collected as part of a double-blind randomized placebo-controlled clinical trial, the gold standard for evidence based medicine. Rather, the data provided on PatientsLikeMe reflects “real world evidence” from patients taking the treatment but assigned in a non-random way. Therefore the impressions voiced by patients are subject to bias such as the placebo effect, recall bias, or awareness only of perceptible side effects such as light-headedness but not imperceptible benefits such as stroke prevention.
19. Despite this, studies from our platform benefit from coming directly from the voice of the patient, being conducted rapidly, and investigating areas that would not normally receive research funding. To date we have published over 30 peer-reviewed scientific studies in clinical trial design, off-label drug prescribing, the development of new patient reported outcome measures, and barriers to medication adherence. We have conducted an observational study approaching the level of a clinical trial over the Internet to investigate the effects of lithium carbonate on motor neuron disease.

Problem:

20. Today, data collected in clinical trials benefits from being collected by physicians in a structured and carefully controlled manner. However, once a trial is completed, the data are locked away from public view. Dissemination channels have advantages and disadvantages:
21. Posters or oral presentations at conferences:
 - ✓ Rapid sharing of information with practitioners and researchers in the field
 - ✓ Presentations typically contain findings “hot off the press” including efficacy analyses and safety data and keep the scientific field informed of study progress
 - X Results are summarized as a brief abstract (a multi-center trial of thousands of patients might be summarized in 250 words) or in briefly presented slides
 - X While abstracts themselves may have been peer-reviewed before acceptance these are very concise and the final content will not have been peer-reviewed before being presentation
 - X There is very limited availability of the findings outside conference attendees
22. As a published journal article in the peer-reviewed literature
 - ✓ Peer-review helps to ensure quality of science
 - ✓ Creates a citable document-of-record for future reference
 - ✓ Increasingly, modern journals such as “Biomed Central Trials” encourage the publication of trial protocols in advance of publishing the results which can then be cited to help ensure transparency and consistency throughout
 - X Peer reviewers and readers can only see what the study authors have presented, typically summaries or averages. It is not possible for reviewers to check the statistical analyses from the raw data to identify error or obfuscation.
 - X A single study is rarely enough to be conclusive. The best understanding comes from systematic meta-analysis of multiple studies conducted by different researchers – but data in a manuscript is rarely sufficient to allow meta-analysis
 - X Journal access is generally restricted to expensive subscriptions, presenting a barrier for non-academic clinicians, private providers, patients, and those attempting to access information from the developing world. Contrast with the “open access” movement, for example
 - X Negative studies are considerably harder to get published than positive studies, resulting in bias in the scientific literature

Opportunity:

23. As a consumer, Which? or Amazon can instantly compare the profile of washing machines stratified by customer satisfaction, drum capacity, colour, price, or manufacturer, but the same level of granularity and information quality does not exist for patients to evaluate their treatment options.
24. The government, academia, and the pharmaceutical industry invest billions of pounds in conducting trials and generating evidence, yet the value inherent in this data remains unstructured, unsearchable, incomparable, and hidden from view.
25. We believe that society would benefit significantly from the transition of trial results from inaccessible records of unstructured text, tables, and graphs of the average to an open repository of machine-readable data to permit ongoing research, re-analysis, scrutiny, and meta-analysis. If we can do it with a washing machine, why not medicine?

26. Demonstration of an interim step along the way can be seen in ClinicalTrials.gov's summary of trial data (enclosed). For instance, the record for NCT00355134, "Efficacy and Safety of Fingolimod (FTY720) in Patients With Relapsing-remitting Multiple Sclerosis (FREEDOMS II)" by Novartis® includes results from the completed study, publicly viewable online. Detailed data provided includes the number of participants recruited, their demographics, the number of patients lost to follow up, number of side effects reported, and the average group characteristics on the outcome measures of interest (which ultimately lead to the drug being approved as the first oral treatment for MS). This data was submitted by the manufacturer and is publicly viewable free of charge from the same record containing the trial protocol.
27. However, there is additional work to be done. Although open and well labeled, this report remains a document rather than a true dataset that could be re-analyzed by other researchers for purposes of assessing the natural history of MS, for instance. Whether the trial itself had been positive or negative, data from the placebo arm could contribute to a shared resource, which might allow future exploratory trials to be conducted without a placebo arm.
28. Additional benefits could be achieved by supporting such machine-readable data as part of structured informatics ontology such as ICF, ICD, SNOMED, and MEDDRA, such that data could be used across multiple diseases or allow more systematic interrogation of the data.
29. There is increasing recognition of the importance that patients become "engaged" with their own management, i.e. to take "actions (as) individuals... to obtain the greatest benefit from the health care services available to them". "Engagement" stands in contrast to medical paternalism and advocates that patients take responsibility for their own healthcare in partnership with their healthcare professionals, such as understanding their disease, connecting with other patients like them, being compliant with their medications, and taking a proactive role in living well with illness.
30. For instance, patient engagement advocates promote "shared decision making" whereby the best decision is reached by the patient discussing and having a shared understanding of the risks, benefits, and alternatives of different treatments with their physician. For instance, a patient might find there are a dozen different medications available for their condition. While their doctor should be up to date on the latest literature the sheer volume of scientific research makes this practically impossible, and the scientific literature is inaccessible to patients.
31. By ensuring that product manufacturers submit machine-readable data arising from their Phase III and IV trials in a standardized format, it should be relatively simple for scientists, NHS staff, or entrepreneurs to create software programs that continually compare and contrast products on their risks and benefits. Additional data sources such as electronic medical records, patient safety registries, or extension studies could continue to increase users' confidence levels by increasing the patient-exposure years reported through such a tool. Such a system could also permit patients who have taken (or considered) taking a given treatment to share their experiences from an anecdotal perspective, providing different levels of confidence for different classes of data provided.
32. Such a tool would also empower commissioners of NHS services to better make cost-effective decisions.
33. In addition to existing methods of dissemination (conferences and journal articles), archiving anonymised patient-level data in an open trials repository has the following advantages:

- ✓ Permits re-analysis to identify subgroups, responders, or meta-analysis
- ✓ Data can contribute to non-trial research such as natural history studies
- ✓ Lessons learnt in terms of outcome responsiveness or population recruitment could accelerate future studies
- ✓ Improve public confidence by assuring that doctors and researchers have full and unrestricted access to the data
- ✓ A brief lay summary aimed at patients with the condition could help educate non-

Threats & Criticism

34. A recent debate in the European Parliament's Environment and Health Committee on Clinical Trial Regulation (<http://tacd-ip.org/archives/865>, enclosed) details a number of objections put forward by opponents of trial transparency, which we will address.
35. Competition – In a world with open trial data and software solutions that help interpret this into information, manufacturers with a superior product should benefit by competing on efficacy and safety data, not marketing messages. While causing some short-term disruption to pharmaceutical manufacturers, open trial data will ultimately better reward innovative and more effective products. Embargo periods might also protect competition.
36. Administrative burden – Pharmaceutical companies have a robust and renowned capability to write regulatory filings in multiple territories with large volumes of documentation, isolate the prescribing habits of individual doctors from terabytes of data, identify fraudulent medicines in the farthest corner of the developing world, and to create high-quality scientific output en masse. They are therefore well equipped to deal with what is a comparatively small administrative burden.
37. Cost – It has been estimated that the cost of bringing a new treatment to market is between \$300m and \$1.2b, depending on the study. In part this is due to a system that silos data and prevents stakeholders from learning from past errors. Barriers to entry force new researchers to learn how different outcomes measures will perform, which trial centres have the best recruitment, and the magnitude of placebo effects. An evenly distributed and enacted requirement for open trial data should reduce costs for manufacturers in the long term.
38. Our proposal will not be without cost and will require incentives to be adopted. We recommend that experts be consulted to provide a robust estimate of the costs of an open trial data repository.
39. No real need of greater openness – We would refer readers to Dr Ben Goldacre's book "Bad Pharma" for a systematic argument against this notion.
40. Role of ethics committees and protection of human subjects - There are several potential approaches here, such as pseudo-anonymisation through adding random noise to the data. Ultimately no solution will be perfect and so we welcome proposals for legislation to further protect altruistic patients who share their data from risk or harms.
41. "Data is too complicated for the public to understand". – It should be noted that although the *primary* beneficiaries of open data will be other researchers, "the public" includes everybody, including those with scientific training necessary to correctly interpret scientific findings and patients themselves. Open and machine-readable trial data represents an opportunity for software developers to visualize and simplify the data into information, that is the entire point of information technology. Most people are not surveyors and yet Zoopla and MousePrice provide detailed information from the Land Registry to help them make better decisions about buying a

home. Most people are not nutritionists and yet food labelling allows them to make better decisions. Most people are not cartographers and yet Google Maps helps them to navigate more clearly. Free the data, and complexity will be resolved.

42. Convenience - It may not be convenient to give the public open access to data on clinical trials, but initiatives such as 311 in the United States and Data.gov have shown that there can be substantial benefits. Furthermore the risks of large expenditures on ineffective treatments would seem to outweigh these. The major hurdles to overcome are cultural, not technical.
43. Permit the data to be used only by “independent experts.” – Any restriction to open trial data would be harmful because “independent experts” do not exist. If a person has the experience and knowledge to design, run, or critique a trial, at some point they have likely worked for the pharmaceutical industry, received support from them, or are looking to do so in the future. There is no benefit in restricting the eyes that can access this data.
44. Potential for identification of participants with rare diseases – In our experience, patients with rare diseases are the ones most desperate to take part in research, and the siloed nature of the status quo makes participation difficult. For instance, recent reports (attached) in the Wall Street Journal of families with the rare disease Sanfilippo Syndrome show that parents resent having to take their children for multiple redundant blood draws and spinal taps in trials performed by different companies, when they have already provided similar data in other trials.
45. Consumer panic – Public trust in the pharmaceutical industry is low, and can only be strengthened by transparency, and although experts interpret data, it is ultimately patients who decide whether to ask their doctor for treatment, and once prescribed, whether or not to take it. Open data validated and certified by a trusted body such as NICE should reassure the public and rebuild trust in what is an innovative and important industry to the UK.
46. In conclusion we propose that the potential advantages of open, computable trial data far outweigh the disadvantages and will ultimately contribute to a continuously learning and improving healthcare system for the benefit of British citizens as well as industry and researchers.

February 2013

Written evidence submitted by PharmAware (CT44)

Introduction

PharmAware is a student-led network, part of Medsin-UK, which aims to raise awareness of the importance of evidence-based medicine and ethical interactions between health professionals and the pharmaceutical industry. The national committee is composed of four medical students and one medical law student. Our vision is a world in which people's health is improved, never jeopardised, by the pharmaceutical industry. We aim to achieve this through education, advocacy and action.

We welcome this inquiry as we feel it is both timely and important. We want to be able to make decisions about the people we treat in light of all the evidence and we want to be able to collaborate with the pharmaceutical industry. Yet that can only happen if we know we can trust the industry to report all clinical trial data.

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?

1.1 From its introduction, the initial European Clinical Trials Directive has been heavily criticised. The new provisions introduced by the European Commission are an improvement on the existing directive and remove some of the barriers to conducting clinical trials. However, the revisions do not cover consent in emergency situations and will stifle research into emergency care.

1.2 We feel that the EU clinical trial regulation has a number of problems pertaining to reporting and patient safety.

1.3 The regulation doesn't require trials to be justified following systemic review of previous trials in the same area. The CONSORT [1][2] statement for reporting clinical trials states that the trial results should be interpreted in light of all the previous evidence; systematic reviews of all the available evidence will also allow decisions to be made on treatment and further research. If we know a drug works or doesn't work, then we don't need to randomise patients to trials anymore, avoiding potential harm.

1.4 The regulation states, "Within one year from the end of a clinical trial, the sponsor shall submit to the EU database a summary of the results of the clinical trial". Instead of simply publishing summaries of clinical study reports, the full clinical study reports and raw data should be published. History has shown that publishing summaries is insufficient, Tamiflu being the most prominent example. The regulation also states "if it is not possible to submit a summary of the results within one year, the summary of results shall be submitted as soon as it is available". There should be no exception to this one-year rule. Delays in the publication of data in medicine have real-life effects, and missing data in medicine costs lives.

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

No comment on this matter.

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

3.1 The pharmaceutical industry has been responsible for great advances in medical science, which have saved millions of lives. There is no medicine without medicines. But these past successes cannot excuse withholding essential information in the present day. Daily, doctors

and patients must make decisions about prescribing with access to only a fraction of the available data. University teaching staff is teaching future doctors with incomplete knowledge about the drugs that they will need to understand and use in practice.

3.2 For decades, the pharmaceutical industry has been more likely to publish the results of clinical trials that show its products in a positive light [3]. Negative clinical trial data seems to disappear; it is never published and never seen by doctors and patients. This phenomenon is so widespread that it is known in epidemiology as “publication bias”. In addition to publication bias, positive results are more likely to be published rapidly, in English, more than once, and are more likely to be cited by others.

3.3 The current best estimate is that half of all the clinical trials that have been conducted and completed have never been published in academic journals; this information is hidden from doctors and patients. This figure comes from a systematic review conducted in 2010 by the NHS NIHR Health Technology Assessment programme [4]. This occurs in trials sponsored by the pharmaceutical industry and in publicly funded research.

3.4 In trials of statins, industry funded trials were twenty times more likely to give a positive result [5]. This was also shown to happen with antidepressants, proton pump inhibitors, antipsychotics, and vasodilator drugs [6]. It is estimated that only about half of research presented at academic conferences appears in the medical literature, the remainder disappears and isn't published [7]. This is a systemic problem that is well documented for research in infectious diseases [8], cancer [9] and psychiatry [10].

3.5 This problem of negative trial data has been studied so much it has even been demonstrated in the form of a randomised controlled trial [11]; researchers sent well-conducted randomised controlled trials that differed only in their outcome to two peer-reviewed journals and they found that positive outcome bias was present during the peer-review process. A manuscript with a positive result was more likely to be recommended for publication than was an otherwise identical no-difference manuscript.

3.6 This phenomenon of missing trial data is nothing more than scientific misconduct and it undermines the integrity of evidence-based medicine. Failure to publish this data actively breaches several articles of the Declaration of Helsinki [12], a set of ethical principles designed to oversee human experimentation. The Declaration expresses an expectation that every patient enrolled in a clinical trial should, at the end of the trial, be assured access to the best-proven therapy identified in the study.

3.7 The best-publicised example of the extent of missing trial data is the Tamiflu saga [8], which is on going. Tamiflu (oseltamivir) is a drug manufactured by the Swiss pharmaceutical company Roche, which was stockpiled in response to the H1N1 pandemic of 2009. Governments around the world, including our own, stockpiled Tamiflu on the basis that it can reduce the risk of complications from H1N1. Tamiflu has so far not been shown to prevent such complications.

3.8 Cochrane Collaboration researchers set out to test Roche's claim that Tamiflu prevented complications from influenza and reduced the number of people needing hospital treatment. The investigation has so far been hampered by Roche's refusal to provide all of its trial data for analysis. The team obtained some clinical study reports from the European Medicines Agency (EMA), but found inconsistencies with published reports and possible under-reporting of side effects. They have parts of 16 clinical study reports but there is estimated to be at least 123 trials on Tamiflu, possibly more. Oseltamivir has been a great commercial success for Roche. Billions of pounds of public money have been spent on it, and yet the evidence on its effectiveness and safety remains hidden from appropriate and necessary independent scrutiny. For all we know, it may be no better than paracetamol.

3.9 There have been previous attempts to fix the problem of missing data. The International Committee of Medical Journal Editors wrote a policy paper claiming that they would only publish trials that had pre-registration of trial protocols. In 2009 it was shown that only half of all trials published after this requirement had been announced had been properly registered, and a quarter had not been registered at all [13].

3.10 The Food and Drug Administration Amendment act 2007 required reporting of results one year after completion of a trial on clinicaltrials.gov [14]. An audit was conducted independently and published in the BMJ in 2012 [15]. Only one in five trials had met this reporting requirement. Despite this fact, no fine has ever been levied against any company or researcher for failing to post results.

3.11 The BMJ has been at the forefront of the push for access to clinical trial data regarding Tamiflu (www.bmj.com/tamiflu), and of the alltrials.net campaign. The BMJ decided from January 2013, that trials of drugs and medical devices would be considered for publication only if the authors commit to making the relevant anonymised patient level data available on reasonable request [16]. We can all learn from their example.

3.12 Dr Hans Georg Eichler from European Medicines Agency stated in November 2012 that there is no way back from unpublished data, and the European Medicines Agency's policy that will come into force in 2014 will define how data is going to be published. While this only applies to data submitted to the regulator for market approval, and is only proactive transparency, this is an amazing step forward. However, we do need proactive and retroactive transparency from EMA.

3.13 The focus of this question is pharmaceutical companies, however we should also say that the problem is multifaceted, and to lay blame solely with the pharmaceutical industry is shortsighted. Universities, academics, editors, regulators, ethics boards and doctors are all part of this flawed system of disseminating trial data.

3.14 We believe that there is another large barrier to access to missing clinical trial data. There is a document that contains a series of factually incorrect statements on important issues that have a significant impact on patient care, including medical education, and the availability of withheld data from clinical trials. The document is entitled "Guidance on Collaboration between healthcare professionals and the pharmaceutical industry [17]," produced by the Ethical Standards in Health and Life Sciences Group (ESHLSG) and endorsed by the great and good of healthcare in the United Kingdom, including the Department of Health, Welsh and Scottish governments, British Medical Association, several Royal Colleges and many others. This document is currently being scrutinized by the Bad Guidelines campaign [18], of which we are a part.

3.15 In this document, the ESHLSG pretend the problem of missing trial data doesn't exist. It claims that 'Information about industry-sponsored trials is publicly available'. This is untrue.

3.16 The document also claims that drugs company sales representatives 'can be a useful resource for healthcare professionals'. While this is not the focus of this inquiry, this statement, again, is a misleading. The best available evidence from 58 studies summarised in a recent academic review [19] shows that overall, doctors who see drug company sales representatives are worse prescribers, prescribing more and with higher prescribing costs. No research has ever shown that "drug reps" improve prescribing.

3.17 These inaccurate statements are concerning and undermine on-going efforts to gain access to unpublished data from clinical trials. Members of the ESHLSG are notable for their absence among the group of organisations that have endorsed the All Trials campaign [20]. It

is time that they joined GlaxoSmithKline, the Wellcome Trust, the Medical Research Council, the Cochrane Collaboration, more than eighty patient groups, professional organisations such as The Faculty of Intensive Care Medicine and tens of other organizations in showing real leadership and standing up for patients. These guidelines fly in the face of the best available evidence. We as part of the Bad Guidelines campaign have called on the organisations that have endorsed these guidelines to heed the evidence, reconsider their position and retract their support for this document.

3.18 So far, only the Lancet, one of the world's most prominent medical journals, have taken a stand and withdrawn their support for the ESHLSG guidelines [21]. Other organisations have only stated that the guidelines should be revised, they've refused to retract their support and refused to explain why they agreed to claims that are completely untrue. We urge the committee to investigate this thoroughly.

3.19 In order to make the best decisions on a particular treatment doctors and patients need all the information from all trials, of all drugs that are currently in use, or have ever been used. They also need to know the context in which trials occurred, in order to make a fair and unbiased decision on the appropriateness of the drug for the presenting patient. This is undoubtedly one of the biggest ethical problems facing modern medicine; what we need is transparency in results, publicly accessible clinical trial registers and publication of the negative results to ensure the best care for future generation.

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

4.1 The problem of missing clinical trial data is multi-faceted and requires a solution that addresses each stage at which information is lost. Industry, universities, academics, ethics committees and regulators are all responsible for the reporting of clinical trial data. Transparency is enforceable at all levels. We feel that full disclosure is a moral responsibility incumbent on all these organisations and individuals, but when data is clearly not being released there should be enforceable penalties at different levels, from fines levied on companies to journals refusing to publish affected studies.

4.2 Clinical trial data should be stored indefinitely, in searchable, accessible electronic formats such as a pdf. Scanned copies are not acceptable because they are not searchable, and are too lengthy to be analysed in a practical timeframe. The clinical trial data should be accessible to everyone; if we have many eyes looking at the data, we will be able to spot things that one individual cannot. For individuals accessing the data, it would be good practice to post a publicly accessible analysis protocol before accessing the data.

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

5.1 The best example that we are aware of is an initiative set up at Yale University. The Yale University Open Data Access (YODA) project was set up to develop, test and implement methods to disseminate research data as widely, comprehensively, responsibly and productively as possible [22]. The model is designed to provide analysis that will be scientifically rigorous, objective and fair. The YODA model is a good model to promote transparency.

References

[1]Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.

- [2] Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG, for the CONSORT Group. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trial. *BMJ* 2010;340:c869.
- [3] Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;326:1167-7
- [4] Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ, et al. Dissemination and publication of research findings: an updated review of related biases. *Health Technol Assess* 2010;14(8).
- [5] Bero L, Oostvogel F, Bacchetti P, Lee K. Factors Associated with Findings of Published Trials of Drug-Drug Comparisons: Why Some Statins Appear More Efficacious than Others. *PLoS Med* 2007; 4(6):e184.
- [6] Bourgeois FT, Murthy S, Mandl KD. Outcome Reporting Among Drug Trials Registered in ClinicalTrials.gov. *Annals of Internal Medicine* 2010; 153(3): 158-66
- [7] Scherer RW, Langenberg P, Von Elm E. Full publication of results initially presented in abstracts. *Cochrane Database Syst Rev* 2007; 2: MR000005
- [8] BMJ. Tamiflu Campaign. Available at: www.bmj.com/tamiflu
- [9] Ramsey S, Scoggins J. Commentary: Practising on the Tip of an Information Iceberg? Evidence of Underpublication of Registered Clinical Trials in Oncology. *The Oncologist* 2008;13:925-929
- [10] Turner EH, Matthews AM, Linardatos BS, Tell RA, Rosenthal R. Selective Publication of Antidepressant Trials and its influence on apparent efficacy. *N Engl J Med* 2008; 358:252-260
- [11] Emerson GB, Warne WJ, Wolf FM, Heckman JD, Brand RA, Leopold SS. Testing for the Presence of Positive Outcome Bias in Peer Review: A Randomized Controlled Trial. *Arch Intern Med* 2010; 170(21): 1934-9
- [12] WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Available online at: <http://www.wma.net/en/30publications/10policies/b3/>
- [13] Mathieu S, Boutron I, Moher D, Altman DG, Ravaud P. Comparison of Registered and Published Primary Outcomes in Randomized Controlled Trials. *JAMA* 2009; 2;302(9):977-84.
- [14] Food and Drug Administration. Food and Drug Administration Amendments Act (FDAAA) of 2007. Available at: <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentstotheFDCA/FoodandDrugAdministrationAmendmentsActof2007/default.htm> Accessed 21/2/13
- [15] Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. *BMJ* 2012;344:d7373
- [16] Godlee F, Groves T. The new BMJ policy on sharing data from drug and device trials. *BMJ* 2012;345:e7888
- [17] Ethical Standards in Health and Life Sciences Group. Guidance on collaboration between healthcare professionals and the pharmaceutical industry. Available at: <http://www.abpi.org.uk/our-work/library/guidelines/Documents/Guidance%20on%20collaboration.pdf>
- [18] Bad Guidelines. Available at www.badguidelines.org Accessed on 8/2/13
- [19] Spurling GK, Mansfield PR, Montgomery BD, Lexchin J, Doust J, et al. (2010) Information from Pharmaceutical Companies and the Quality, Quantity, and Cost of Physicians' Prescribing: A Systematic Review. *PLoS Med* 7(10): e1000352. doi:10.1371/journal.pmed.1000352
- [20] Alltrials.net Available at: www.alltrials.net
- [21] Horton R. Falling out with Pharma. *Lancet* 2013;381, Issue 9864, Page 358
- [22] Yale University Open Data Access Project. Available at: <http://medicine.yale.edu/core/projects/yodap/index.aspx>

Declaration of Interests:

Dr Ben Goldacre spoke among others at the conference “[We Have a Drug Problem](#)” in London on November 24th-25th which was part organized by PharmAware.

PharmAware are currently part of the Bad Guidelines campaign with Healthy Skepticism-UK, Conflict Free Conferences, MedAct and Dr Ben Goldacre.

Two members of the national committee are members of the non-governmental organisation Health Action International, An independent network working to improve access to, and the rational use of, essential medicines with evidence-based advocacy.

February 2013

Written evidence submitted by Cancer Research UK (CT45)

1. Every year around 300,000 people are diagnosed with cancer in the UK. Every year more than 150,000 people die from cancer. Cancer Research UK is the world's leading cancer charity dedicated to saving lives through research. Together with our partners and supporters, Cancer Research UK's vision is to bring forward the day when all cancers are cured. We support research into all aspects of cancer through the work of over 4,000 scientists, doctors and nurses. In 2011/12 we spent £332 million on research. The charity's pioneering work has been at the heart of the progress that has already seen survival rates in the UK double in the last forty years. We receive no government funding for our research.
2. Clinical studies are a vital strand of Cancer Research UK's work. We currently fund over 240 clinical studies in the UK; we are one of the largest funders of clinical research in Europe. In 2011/12 over 37,000 patients were recruited to clinical studies supported by CR-UK.
3. We take an active role in ensuring that regulation associated with clinical studies is proportionate to allow patients to participate and benefit from the results of clinical research. In February 2012, together with the Academy of Medical Sciences, Cancer Research UK brought together leading figures from across the health research sector to discuss the evolving regulatory landscape¹. Cancer Research UK has also led on coordinating a joint statement between academia and industry funders, to feed into revisions of the EU Clinical Trials Directive².

We would therefore welcome the opportunity to provide oral evidence to the committee.

4. Our key points are as follows:
 - Cancer Research UK is broadly supportive of the draft Clinical Trials Regulation and its aim to streamline and improve the regulatory environment for clinical trials of investigational medicinal products in Europe. We believe that certain aspects of the Regulation could be amended further in order to facilitate more effective running of clinical trials in the UK.
 - The Health Research Authority (HRA) has already demonstrated its competency in regulating research in the UK.
 - We are particularly pleased that in October 2012 the HRA announced a feasibility study to test the potential benefits of a simplified and streamlined HRA assessment for all research in the NHS. This feasibility study should remain a key focus for the HRA; as if successful it has the potential to significantly impact on the environment for running clinical studies in the UK.
 - Cancer Research UK welcomes efforts to improve transparency in research, especially the publication of negative data from all sectors involved in clinical studies.
 - We would support requirements for clinical studies to publish a summary of results within a year of when the data analysis is planned in their protocol, which is submitted as part of regulatory approval to set up a clinical study.
 - Solutions to increase transparency must be discussed and implemented at an international level in order to improve standards for studies and benefit patients. Without these key discussions it is possible that isolated action at either the UK or EU level could further discourage clinical research from being located in Europe, without benefitting patients.

¹Transforming the regulation and governance of health research in the UK. May 2012

http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@pol/documents/publication/cr_087422.pdf

² Proposal for an EU Regulation on Clinical Trials: A joint statement from non-commercial and commercial organisations, December 2012 <http://prodcontrib.cancerresearchuk.org/cancer-info/publicpolicy/workingwithgovernment/europe/ssLINK/CTRJOINTSTATEMENT>

5. We have used the term ‘clinical study’ when referring to all types of clinical research undertaken in the NHS in the UK. We use the specific term ‘clinical trial’ only when referring to a clinical trial of an investigational medicinal product, which is currently regulated by the EU Clinical Trials Directive. The term ‘clinical study’ encompasses ‘clinical trials’ and studies that look at other interventions such as screening tests.

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?

6. The EU Clinical Trials Directive 2001/20/EC (CTD) set out with the best intentions to improve the regulatory landscape and the quality and safety of clinical trials in Europe. However it has been widely acknowledged that the CTD contributed to the general trend of decreasing numbers of clinical trials in Europe without providing benefits to patients. Research conducted by Cancer Research UK at the time found that “CTD had resulted in a doubling of the cost of running non-commercial cancer clinical trials in the UK and a delay to the start of trials” and research staff were “unable or unwilling to open trials in non-UK centres because of the different interpretation of the CTD by member states.”³ Between 2003 (before the Directive) and 2007 (following the Directive) the time to set up a study increased by 65% and the staffing requirements increased by 75%.⁴
7. Cancer Research UK is broadly supportive of the draft Regulation adopted by the European Commission on 17 July 2012 and its aim to streamline and improve the regulatory environment for clinical trials of investigational medicinal products in Europe. Our assessment, based on consultation with our Clinical Trials Units, is as follows:
 - As a Regulation this legislation will achieve one of its principal goals in harmonising the regulatory system for clinical trials across Europe.
 - Provisions in the new Regulation will improve the set-up and running of multinational trials. For example, we welcome the legislation’s explicit introduction of co-sponsorship as well as the introduction of a single European portal for applications.
 - Cancer Research UK’s main concern is how the Regulation will work in practice. Provisions such as the single European application portal have the potential to greatly improve the application process and reduce trial set up times. However we have requested more information to understand how the new systems will operate and what resources will be allocated to it.
 - The Regulation has introduced a risk adapted approach. This means that the levels of monitoring and reporting associated with a trial are adapted to suit the level of knowledge about a medicine being tested. For example a medicine which is being used within its existing licence would require less assessment compared to a treatment being tried in man for the first time. We welcome this move as the previous ‘one size fits all’ approach meant that many academic trials had a disproportionate amount of regulatory oversight.
 - Set timelines for approvals have been introduced into the legislation which should provide a marked improvement over existing timelines in some member states.
8. We believe that certain aspects of the Regulation could be amended further in order to facilitate more effective running of clinical trials in the UK. We have put forward amendments to both the Medicines and Healthcare products Regulatory Agency (MHRA) and the European Parliament:

³ The impact of the ‘Clinical Trials’ directive on the cost and conduct of the non-commercial cancer trials in the UK. J Hearn and R Sullivan. *European Journal of Cancer* 43 (2007), 8-13.

⁴ *Ibid.*

- To reduce the scope of the Regulation so that clinical studies which require additional monitoring but do not pose any additional risk to patients would not fall under the Regulation.
 - To ensure that only medicinal products fall within the scope of the Regulation.
 - To clarify language around the terms clinical trial and clinical study.
 - To risk adapt the safety reporting mechanisms so that treatments which are considered standard use do not need to submit particular types of safety reporting.
9. The purpose of these amendments is to improve the efficiency of running clinical trials and make the Regulation proportionate to the type of work being conducted by academic researchers.
10. If clinical trials cannot take place due to excessive regulatory requirements then no patient benefit can be derived at all. Amendments to the proposed Regulation must be carefully considered to make sure they do not have the same unintended consequences.

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

11. Clinical studies do not solely involve the testing of a medicine; many studies involve testing new devices, non-medicinal products and surgical interventions. The Health Research Authority has responsibility for regulating and approving many elements of clinical studies, however many important regulatory requirements sit with other bodies such as the MHRA.
12. The Health Research Authority's role in relation to clinical studies is through the approval of the ethical aspects undertaken by National Research Ethics Service.
13. The Health Research Authority's current role in relation to clinical studies is through the approval of the ethical aspects undertaken by National Research Ethics Service. Since its formation in December 2011, the HRA has demonstrated its competency in regulating research in the UK. It has also shown that it is capable of leading a programme of work to streamline and improve regulation and governance of clinical research in the UK. We are particularly pleased that in October 2012 the HRA announced a feasibility study to test the potential benefits of a simplified and streamlined HRA assessment for all research in the NHS⁵. In our evidence to the Academy of Medical Sciences review of regulation and governance of health research in June 2010⁶ we outlined that the biggest barrier facing clinical studies in the UK was the layers of governance associated with seeking permission from NHS Trusts to run studies. Our main recommendation was to develop a streamlined process for these NHS permissions, to be implemented at a national level. We strongly believe that the feasibility study being run by the HRA is the biggest step towards achieving this recommendation, with the ultimate vision outlined as:
14. *'NHS organisations would be able to rely on the HRA assurance and devote their review to confirming their capacity and capability to host and deliver the research. RECs would be able to focus their expertise on projects raising ethical issues.'*
15. To our knowledge there has not yet been data published outlining the impact of the HRA, however we remain confident that its establishment has been an important breakthrough in the regulation of UK clinical research. Our priority is that the HRA is able to continue to focus on

⁵ <http://www.hra.nhs.uk/hra-news-and-announcements/hra-given-go-ahead-for-feasibility-study-hra-assessment-for-approval-of-research-in-the-nhs/>

⁶ Cancer Research UK submission to the Academy of Medical Sciences review of the regulation and governance of medical research. June 2010
http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@pol/documents/generalcontent/cr_053410.pdf

developing a streamlined assessment. The draft Care and Social Support Bill currently passing through pre-legislative scrutiny will grant the HRA statutory footing and allow it to continue to develop independently from Government, and push forward with its programme of work.

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

16. Cancer Research UK welcomes efforts to improve transparency in research, especially the publication of negative data from all sectors involved in clinical studies, and supports the AllTrials campaign.⁷
17. Over the past 10 years Cancer Research UK has financed and endorsed 298 trials of more established treatments (late phase trials) organised by hospital trusts or universities and now completed. Of these, 183 have reported results to date and the remaining 115 trials have yet to be fully analysed. One of the reasons for this is that a trial cannot generally report until a pre-defined time point has been reached or a specified number of events have occurred. See appendix for a case study.

Results of clinical studies

18. Transparency is an important principle in research studies, from basic research through to clinical studies regardless of whether supported by academia or industry. We welcome efforts to improve transparency in research, especially the publication of negative data from all sectors involved in clinical studies. For example, we are involved in initiatives that take on drugs to further their development and publication of previous trial data on these compounds would speed up progress and reduce unnecessary duplication of effort.
19. Cancer Research UK has policies in place to support transparency in research studies. We require that trials funded through our Clinical Trials Awards and Advisory Committee undertake clinical trial registration and we monitor when these trials publish their results. Cancer Research UK runs the CancerHelp UK clinical trials database which aims to list all cancer studies recruiting in the UK - not just those supported by Cancer Research UK.⁸
20. CancerHelp UK works with trial teams to produce summaries of studies to provide useful, easily understandable information for the public. This helps patients with cancer identify which studies they could potentially participate in as well as giving information on both positive and negative studies that have been completed. The database currently includes details of approximately 500 studies recruiting people in UK, and more than 400 summaries of study results. In 2012 we added 83 results summaries, including 25 from studies that had received funding from Cancer Research UK and 15 that were sponsored by pharmaceutical companies.
21. We would support requirements for clinical studies to publish a summary of results within a year of when the data analysis is planned in their protocol, which is submitted as part of regulatory approval to set up a clinical study. It should be noted however that the planned analysis could be many years after recruitment to the study has ceased. Timings of analyses are not generally scheduled in terms of months and years but instead are event-driven. If a summary of results is not available within a year of the planned analysis then an explanation should be provided and publicly available. It may also be necessary to build in an annual reporting mechanism for studies that fail to report in a year, to ensure there is continued pressure to publish.

⁷ <http://www.alltrials.net/supporters/cancer-research-uk/>

⁸ <http://www.cancerresearchuk.org/cancer-help/trials/>

Patient level data

22. We believe that the issue of releasing patient level data is separate to that of releasing the summary of results from a clinical study.
23. There are important issues relating to patient consent and confidentiality to take into account when considering transparency of clinical studies data beyond the publication of summary results.
24. Requests to access patient level data from clinical studies need to be considered very carefully. We support the responsible sharing of patient level data, with investigators who have set out clear plans for how they will interrogate data through peer-reviewed studies.
25. On the issue of patient level data, the need for transparency must be balanced against the following concerns:
 - patient consent and confidentiality; patients may have only provided consent for their data to be used in a certain way; any measure to promote transparency would need to respect this historic consent;
 - the risks that information could be misrepresented which could undermine public understanding of a treatment or research finding;
 - maximising usefulness and minimising risks by balancing the level of detail in the data (e.g. aggregated findings versus patient level data) with how widely these data are shared (e.g. publicly available versus controlled access); and
 - the need to ensure the environment incentivises the funding and delivery of clinical studies, for example by granting a researchers a period of exclusivity for the use of their data.
26. It is important to ensure that full consideration has been given to ensuring solutions work across the range of clinical studies, not just trials of investigative medicinal products (currently covered by the EU Clinical Trials Directive).
27. This is a complex area so it is important that any action the Government takes is well thought through, aligns with actions taken at an international level, and doesn't inadvertently affect the ability to conduct research that will benefit patients.

Ethics

28. Ethics committees (which the HRA oversees in the UK) have a significant role in upholding the transparency of study data and other ethical concerns about missing data.
29. The Declaration of Helsinki makes it clear that the:

*“Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports.”*⁹

30. This is a guideline that should be upheld by ethics committees and deliberated upon when a study is being considered for approval. Many of the concerns raised on the issue of data transparency for clinical studies could conceivably fall within the remit of ethics committees as it their role to ensure the ethical conduct of research studies as well as ensuring the results of the study being used to advance medical knowledge.

⁹ World Medical Association, Declaration of Helsinki, Article 30

31. We welcome the Health Research Authority pilot to scope the feasibility of ethics committees ascertaining if researchers have failed to publish their previous research projects. It will be important that this extra check will not extend the time it takes to gain ethics approvals. The community should be consulted on what ethics committees would constitute appropriate and robust assurance from Sponsors and researchers. We therefore look forward to engaging further with the HRA as their pilot develops.
32. Cancer Research UK would not support a system where ethics committees automatically refused study approval to researchers based on failure to publish previous work. We believe such a system has the potential to be onerous and ineffective. We believe that the time taken for ethics committees to conduct comprehensive analysis of the principle investigator, investigational team, Sponsor or even on an IMP would cause severe delays in research without resulting in sufficient gains in transparency.

Clinical Trials Regulation

33. The draft Clinical Trials Regulation (as proposed in July 2012 and not taking into account any proposed amendments) supports greater transparency than exists under the current Clinical Trials Directive:
 - Article 78 of the current draft of the Clinical Trials Regulation states that a new database will capture all information relating to clinical trials in Europe and makes it compulsory for this to be made public while protecting patient and commercial confidentiality.
 - Article 33 also makes requirements for Sponsors to notify regulators of the start and end of the trial.
 - Article 34 (3) states that “within one year from the end of a clinical trial the sponsor shall submit to the EU database a summary of the results of the clinical trials” with the exception that results can be delayed when scientifically justified.
34. We view these as useful steps towards ensuring that all trials are registered and therefore can be followed up to ensure that the results have been published. While definitions could be clearer on the exact nature of the data that would be published and what exactly the legislation could define as commercially confidential, the Regulation does appear to give legislative backing to support a greater level of transparency than existed under the Directive.

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

35. The push for transparency must also involve the international research community if it is to be successful. Solutions to increase transparency must be discussed and implemented at an international level in order to improve standards for studies and benefit patients. Without these key discussions it is possible that isolated action at either the UK or EU level could further discourage clinical research from being located in Europe, without benefitting patients. Discussion with the US in particular should be encouraged due to its size and the influence the American market has on the global pharmaceutical industry.

February 2013

Appendix

Case study: Intercontinental trial

Intercontinental was a trial looking at intermittent versus continuous hormone therapy for prostate cancer that had continued to grow but had not spread - it was an international trial supported by Cancer Research UK.¹⁰

Doctors thought that hormone therapy given intermittently rather than continuously may work just as well and may also reduce side effects. The main aims of this trial were to compare intermittent and continuous hormone therapy to see the difference between how long the men lived and how it affected their quality of life.

Recruitment of patients:

Sample size - 1,386

Start 01/10/2002

End 30/11/2005

Publication date (N Engl j med 367;10 nejm.org September 6, 2012)

The Independent Data and Safety Monitoring Committee recommended halting the trial after a planned interim analysis showed that the trial had already offered the required results, i.e. that giving intermittent hormone therapy was not worse than giving continuous hormone therapy. This demonstrates why it is can be difficult to say when an analysis publication should happen.

The trial team found that the amount of time that men lived was not reduced when they had intermittent therapy. And that for many of the men side effects were reduced and could lead to an improved quality of life. The men were followed for an average of around seven years.

There are a number of reasons why trials may report later than expected as well. For example, when testing new therapies it may not be possible to predict participants' response in advance leading to delays in the trial.

Results should be reported as swiftly as possible to ensure that effective treatments get to patients quickly and any evidence of ineffectiveness is known to the medical community, patients and the public.

¹⁰ A trial looking at intermittent versus continuous hormone therapy for prostate cancer that has continued to grow but has not spread (Intercontinental), CancerHelp UK website, <http://www.cancerresearchuk.org/cancer-help/trials/a-trial-looking-at-intermittent-versus-continuous-hormone-therapy-for-prostate-cancer-that-has-continued-to-grow-but-has-not-spread>

Written evidence submitted by AMRC (CT46)

Key points:

- Clinical trials are integral to the development of new treatments and provide clinicians and patients the information that they require to make informed healthcare decisions.
 - We welcome the EU Commission's proposal to replace Directive 2011/20/EC, which has created barriers to the conduct of clinical trials in the UK and in Europe. We are pleased to see greater emphasis on the involvement of patients.
 - The HRA has a valuable role in streamlining regulation of clinical trials, helping important research to go ahead and make the UK an attractive place for investment. It also has an important role in maintaining public confidence in the regulation of clinical trials, including the promotion of transparency as part of ethical approval.
 - Medical research charities want to see the findings of research disseminated for the benefit of researchers, clinicians and patients. AMRC recommends that members that fund clinical trials stipulate in their grant terms and conditions that the results must be published.
 - Medical research charities are working with the wider medical research community to improve access to clinical trial data and findings.
1. We welcome the opportunity to respond to this consultation. Several of our members have also responded individually.
 2. The Association of Medical Research Charities is a membership organisation of the leading medical and health charities funding research in the UK. Working with our members, we aim to support the sector's effectiveness and advance medical research by developing best practice, improving public dialogue about research and science, and influencing government to ensure the best research can go ahead and be translated into new treatments.
 3. Medical research charities exist because the public choose to donate their money to support research to develop new treatments and cures. In 2010-11, AMRC members invested over £1 billion into health research in the UK. Through charities, the public fund clinical research, but they also wish to become involved in research - 72% of the public would like to be offered opportunities to be involved in trials of new medicines or treatments for conditions that affect their daily lives.¹ They want to be involved both because they hope that new treatments will benefit them, and because they want to improve treatment for others in the future. Ensuring data and findings are made available for others to learn from is key to delivering this.
 4. Many medical research charities have patient groups closely allied to them and as such are able to provide a unique perspective, representing the needs of both patients and researchers.

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?

5. The Directive 2011/20/EC governing clinical trials is widely considered to have placed barriers to the conduct of clinical trials in the UK and across Europe, including introducing delays in trial setup due to inconsistent implementation of the Directive by Member States, increased bureaucracy and inflexible regulation. AMRC supports a joint statement from non-commercial and commercial organisations welcoming the proposals for the introduction of a new

¹ Ipsos MORI poll commissioned by AMRC, Breast Cancer Campaign and the British Heart Foundation, 2011 - <http://www.ipsos-mori.com/researchpublications/researcharchive/2811/Public-support-for-research-in-the-NHS.aspx>

Regulation to replace the 2001 Directive.² The statement calls for further clarity on the scope of the new Regulation and states that any new regulatory framework should include steps to streamline authorisation processes; adoption of a risk-based approach to the regulation of clinical trials; and the provision of clearer guidance.

6. We believe EU institutions, national governments and national bodies need to work together to develop a supportive environment for conducting clinical trials. Revisions should focus on reducing bureaucracy, which acts as a disincentive to setting up clinical trials, while maintaining public safety and increasing confidence through transparency in the regulatory system and greater public involvement.
7. The proposed Regulation also provides a mechanism for involving patients and their representatives in the panel involved in the assessment of clinical trial applications. We welcome greater involvement of patients in all areas of clinical trials, from identifying need and research questions, trial design, authorisation and dissemination of outcomes.
8. There are also barriers within the UK that can be addressed outside of EU legislation. Researchers in the UK experience delays in obtaining NHS R&D permissions and find the process of gaining regulatory approval from multiple agencies (the MHRA, HTA and HRA for example) an overly-bureaucratic process.³ Multi-site trials confound these problems, requiring permissions to be sought at each site individually, leading to duplication of effort for the researcher. Time spent on these hurdles adds cost to the project and introduces delays. A “one-stop-shop” for researchers, whereby they would have one point of contact through which to negotiate all regulatory and governance approvals, would make it clearer and simpler for them to negotiate the processes to set up trials, so cutting the time and costs involved. As discussed further below, we welcome efforts by the National Institute for Health Research (NIHR) and the HRA to reduce complexity in the current system.

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

9. We welcome the work of the HRA since its creation as a Special Health Authority. We are also pleased to see proposals contained within the draft Care and Support Bill to establish the HRA as a non-departmental public body, which will provide important independence.⁴
10. To reduce the complexity of the regulatory and governance environment for health research in the UK, regulation must be proportionate, coordinated and standardised across the UK. We are pleased to see clarification of the HRA’s role in promoting this in the draft Bill. We also welcome the clarity provided in the Bill that the HRA will work closely with the health regulatory functions of the devolved administrations and is able to exercise some functions on their behalf where appropriate; the success of this relationship is vital to lead to well-integrated, proportionate regulation across the UK.

² http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@pol/documents/generalcontent/cr_077460.pdf

³ Academy of Medical Sciences, A new pathway for the regulation and governance of health research, 2011-
<http://www.acmedsci.ac.uk/p47prid88.html>

⁴ Department of Health, *Draft Care and Support Bill*, 2013 - <http://www.official-documents.gov.uk/document/cm83/8386/8386.pdf>

11. The process of obtaining R&D permissions from NHS Trusts has been identified as a significant barrier to research projects in the UK, introducing delays and increasing costs.⁵ This process remains the responsibility of NHS providers and we welcome action taken by NIHR to streamline this process but believe there is a role for the HRA as well.⁶ There is mention in Factsheet 8 accompanying the draft Care and Support Bill that the HRA would “continue work that has already started, through cooperation with other bodies, to create a unified approval process for research”.⁷ The HRA’s recently launched feasibility study to provide a single, quality-assured HRA assessment to replace duplicated aspects of local research governance will hopefully show how this will work in practice and is welcome.⁸ Should this prove successful the HRA should take on this quality-assurance role. We would welcome further clarification on how it will work with local NHS providers and other bodies involved in NHS research governance to take further opportunities for streamlining.
12. It is also important for the HRA to assess and demonstrate its effectiveness. This will both enable it to identify areas where action can be taken to improve its processes and the regulatory system and through publicly setting objectives and measuring progress, it can demonstrate to an international stage of potential investors progress in streamlining the regulatory and governance pathways for clinical trials and other types of health research across the UK.
13. The HRA also has an important role to play in maintaining public confidence in the regulation and conduct of clinical trials. Transparency is key to this. As part of the research approval process, applications to the Research Ethics Committees (RECs), which are part of the HRA, must include how the researcher intends to register the trial, publish and disseminate the findings of the research, make data and tissue available, and how they will tell participants about the outcomes of the research. We welcome plans set out by Dr Janet Wisely in her evidence to the Joint Committee on the draft Care and Support Bill, that from April, the HRA will check the final trial report received by RECs to confirm that commitments made in the application have been met and is looking at other ways to promote transparency.⁹ Should compliance be found to be low, mechanisms must be found to increase compliance without being disproportionately burdensome to researchers. Charities also recognise the importance of transparency and many also ask for this information as part of the grant application process. Audit of compliance will increasingly be supported by research evaluation systems to monitor and record the outcomes and impact of research (discussed further below).
14. Through RECs and its other functions, the HRA can play an important role in promoting transparency, it should and has committed to this but cannot be seen as the sole guardian of this responsibility. We would support a duty to promote transparency being placed upon the HRA in the Care and Support Bill but believe that the HRA can only perform this duty in concert with other bodies, most notably the Medicines and Healthcare Products Regulatory Agency (MHRA), which may be better placed to take a leading role. To be effective, other regulators, research funders, the NHS, sponsors, publishers and researchers must play also their part and recognise this as an important issue.

⁵ Academy of Medical Sciences, *A new pathway for the regulation and governance of health research*, 2011-
<http://www.acmedsci.ac.uk/p47prid88.html>

⁶ HM Treasury and BIS, *The Plan for Growth*, 2011 - http://cdn.hm-treasury.gov.uk/2011budget_growth.pdf

⁷ Department of Health, *The draft Care and Support Bill – Health Research Authority (HRA), Factsheet 8*
<http://www.dh.gov.uk/health/files/2012/07/Care-and-Support-Bill-Factsheet-8-Health-Research-Authority.pdf>

⁸ <http://www.hra.nhs.uk/hra-news-and-announcements/hra-given-go-ahead-for-feasibility-study-hra-assessment-for-approval-of-research-in-the-nhs/>

⁹ <http://www.parliament.uk/documents/joint-committees/Draft%20Care%20and%20Support%20Bill/HC822-viii%20Thursday%2031%20January%202013%20Uncorrected%20Transcript.pdf>

15. We are pleased that the HRA will be working with Sciencewise to hold a series of events with people around the UK to talk about how they want to be involved in research and how the HRA should work so that they can be confident in the system. This is vital if members of the public are to feel confident about taking part in clinical research.

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

16. Medical research charities fund clinical trials and are keen to ensure the whole system works to deliver the best healthcare for patients – this includes ensuring results and data are shared responsibly and effectively and clinicians have access to the best information to make decisions about how to treat their patients. This is true for all forms of research and consideration of transparency issues should not be limited to clinical trials of medicinal products – it is just as important for research involving devices and surgical techniques, for example.

17. It is also important to remember that research is an international pursuit and that action in the UK alone is not sufficient to increase transparency for the benefit of patients.

18. **Registering clinical trials**

Clinical trials of investigational medicinal products conducted within the EU are subject to the EU Clinical Trials Directive 2001, which is put into UK law by the Medicines for Human Use (Clinical Trials) Regulations 2004. Researchers in the EU have a legal responsibility to register their studies on the EudraCT clinical trials database.¹⁰ Registration is a pre-requisite for applying for authorisation from the MHRA and REC approval.

19. **Publishing results of clinical trials**

Under the Medicines for Human Use (Clinical Trials) Regulations 2004, trial sponsors (which in academia can be universities or NHS trusts) have a legal responsibility to provide an end-of-trial report to the MHRA and REC 12 months from the end of the trial. As outlined above, RECs can play an important role ensuring that results are reported for use by the medical research community. Research funders, including charities, also have an important role to play in this.

20. Charities have a responsibility to put useful research findings into the public domain and we advise all AMRC members to include a requirement to publish (within a reasonable time frame) in the terms and conditions of their awards.¹¹ When charities work in collaboration with industry we recommend a clear agreement and terms and conditions outlining each partner's expectations, particularly around intellectual property, publications and exploitation.¹²

21. We surveyed members of AMRC that are funding clinical research (41 charities in total), either individually or in collaboration with industry, other charities or public funders. 80% of respondents (17/21) include a requirement in their terms and conditions that the results of the research that they fund should be published. Many also request that published research be made “open access” (free to view) on sites such as Europe PubMed Central. This promotes the

¹⁰ Available at <https://eudract.ema.europa.eu/>

¹¹ AMRC, *Charities and medical research, 1998* - http://www.amrc.org.uk/research-resources_guidance

¹² AMRC, *An essential partnership: Principles & guidelines for working with industry, 2007*. Available at http://www.amrc.org.uk/research-resources_guidance

dissemination of results, ensuring researchers, clinicians and the public are not prevented from accessing them.

22. It is in the best interests of researchers to publish so that they receive the recognition for the work that they have done and also to improve the science base that all scientists benefit from – including preventing duplication and verifying findings. All forms of research, including basic research, are of greatest benefit when made widely available. Likewise, negative findings are valuable and should also be made available.

23. We welcome proposals by the European Commission to expand the EudraCT database to collect results and make them publicly available.¹³ But research findings must be accessible and understandable to the public. Resources such as CancerHelp UK¹⁴ provide plain English explanations of trials and their findings so that the public can make use of them. This is important to maintain public trust in the system and support for clinical research. The UK Clinical Trials Gateway is another valuable resource for the public seeking information about clinical trials and we welcome recent recommendations to improve the service.¹⁵

24. **Making data available**

The detailed data from clinical trials is also valuable for conducting further analysis. Some funders ask that researchers provide data management and sharing plans as part of their research proposals (e.g. the Wellcome Trust policy on data management and sharing¹⁶) and these are also considered by RECs in the ethical approval process.

Additional issues to consider when making data available include ensuring that:

- Patient confidentiality is protected and that data is published with their consent.
- The data sets and methodology are accessible in a useable format for researchers.
- The originating researchers have time to analyse the data before making it publicly available.
- That data sets linked to negative results are also published.
- That secondary analyses of data refer to the publication where the data were first analysed, and are linked to the original data.

25. The European Medicines Agency (EMA) has committed to making available clinical trials data for drugs that have been approved for license in the EU, and is currently working with a variety of stakeholders including research charities to develop plans on how best to achieve this.¹⁷

26. We are working with our members to review practices relating to trial registration, reporting of results and sharing of data. This includes considering what further steps charities funding clinical research can take to audit publication of results and ensure their terms and conditions are complied with. Many of our charities are developing research evaluation systems which will allow them to follow-up the impact of research they have funded. Researchfish¹⁸ is a prominent

¹³ http://ec.europa.eu/health/files/eudralex/vol-10/2012_302-03/2012_302-03_en.pdf

¹⁴ <http://www.cancerresearchuk.org/cancer-help/trials/>

¹⁵ NIHR, *UK Clinical Trials Gateway: Public and Patient Survey 2012*, 2012 - http://www.nihr.ac.uk/files/Publications/UKCTG%20Report_Jan%202013.pdf

¹⁶ Wellcome Trust, 2010. *Policy on data management and sharing*. Available at <http://www.wellcome.ac.uk/about-us/policy/policy-and-position-statements/wtx035043.htm>

¹⁷ http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000556.jsp&mid

¹⁸ <https://www.researchfish.com/>

example of such a system and AMRC is facilitating the adoption of this system throughout the medical research community in collaboration with the Medical Research Council.¹⁹

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¹⁹ http://www.amrc.org.uk/research-resources_tracking-the-impact-of-charity-research-funding

Written evidence submitted by the Faculty of Pharmaceutical Medicine (CT47)

- 1 The Faculty of Pharmaceutical Medicine is a professional membership organisation and standard-setting body, with 1,450 members, who are practising pharmaceutical physicians or those with a professional interest in the speciality. It was founded in 1989, and is a Faculty of the Royal Colleges of Physicians of the UK.
- 2 Pharmaceutical medicine is a medical specialty concerned with the discovery, development, evaluation, licensing and monitoring of medicines and the medical aspects of their marketing. The Faculty's members work in diverse environments; from front line clinical trials, to pharmaceutical marketing and medicines regulation.
- 3 Our mission is to advance the science and practice of pharmaceutical medicine by working to develop and maintain competence, ethics and integrity and the highest professional standards in the specialty for the benefit of the public. The Faculty seeks, through its activities, to bring about an improvement in the health of the public.
- 4 The Faculty welcomes the opportunity to submit evidence to this important inquiry and we would be happy to supplement this written evidence with oral evidence to explore these issues in more detail.

Question 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?

- 5 The Faculty has recently responded to the MHRA "Consultation on the European Commission's proposal for a clinical trials regulation." The following comprises an abridged version of that response which we feel relevant to the specific questions posed here.
- 6 We believe that the general scope and aims of streamlining and harmonization are to be welcomed. However, while it is stated that Directive 2001/20 is to be repealed, the Faculty is concerned that in practice national laws, customs and practices will be slow to change. There is a danger that for a significant time period additional requirements and complexity are being created rather than replacement ones.
- 7 The proposal is very unclear as to precisely which functions remain with the 45 national competent authorities (NCAs), the ethics committees which are currently affiliated with research sites (and not, by design, the NCAs), both when an NCA may opt in, or after it uses a qualified opt out.
- 8 The Faculty can see some merit in having a central body review the overall ethical aspects of a study. Such a body can include relevant scientific experts and professional ethicists and give a degree of consistency. However, the Faculty has major concerns over a single body making ethical determination for the whole of the EU. This is not the process in the United States of America where the FDA approves clinical studies but independent institutional review boards making ethical determinations. The delegation of ethics approval to NCAs, or even a single referring NCA, if that is what is meant by Article 6, para 1, is itself unethical. A referring NCA assessor in, say, London is highly unlikely to understand the cultural and medical position of a patient in, say, Valetta. If NCAs intend to retain local arrangements for Ethics Committees, then a layer of review has been added, not removed, by the Regulation; furthermore, there is the risk of mutually exclusive conditions for a clinical trial being imposed by the two reviews. We believe that there will be a risk to quality if the NCA ethics reviews supplant the local ones. If both are required, and the results conflict, then some compromise will be needed or the trial will not take place at all.
- 9 The Faculty believes that in practice there will remain a process of national and local review in many territories. The regional MREC is working well in the UK and a case could be made to adopt the same model Europe-wide with the same focus on ethics. This would deal with the regional differences and

allow responsiveness to local populations. The clinical trials authorisation (CTA) submission of a multi-national trial within the EU appears optimized by the implementation of Voluntary Harmonization Procedure (VHP), though not all EU countries participate in VHP because of various national regulatory (and probably cultural) differences.

- 10 From the point of academic research, this regulation provides no reduction in paperwork. It threatens an additional layer of ethical review. From the point of view of industry-sponsored clinical trials, the imposition of the timelines, taken together with the various extensions available to the regulators, would seem to be a slower, rather than faster, process compared to what has hitherto been the case in the United Kingdom, Sweden, and The Netherlands (and possibly also elsewhere).
- 11 We believe that the EMA may lack the manpower and expertise for these clinical trial applications, which will be in large volume.
- 12 Hence the Faculty considers that these proposed revisions will need refining if they are to enhance the speed and effectiveness of clinical trials in the UK and EU. Indeed there should be more focus on the needs of all researchers, both academic and in industry, if we are to make the EU more attractive for conducting clinical trials.

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

- 13 The National Research Ethics Service has transferred to the HRA. One such service has been the in-line submission of studies. This Integrated Research Application System (IRAS) was launched in January 2008, and has since become a successful system with an excellent record of system availability. To date, IRAS has been available 24 hours a day, 7 days a week with less than 0.1% 'downtime' for system upgrades and maintenance. The HRA will enable research ethics committee (REC) and MHRA electronic submissions through IRAS. This service has greatly simplified submission and will greatly enhance efficiency and should serve to improve the attractiveness of the UK as a country to conduct clinical trials in.

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

- 14 To provide clear direction to all pharmaceutical physicians the Faculty published its "Guiding Principles for Pharmaceutical Physicians" in 2006 and revised in 2010. This forms the basis for the ethical and professional standards of its members.
- 15 This document contains a section entitled 'Sharing Findings' which states:
- 16 *"All studies should be performed to increase knowledge in some useful way, and there should be openness and honesty in the sharing of this knowledge with the wider world. Trial findings need to be communicated, whatever the outcome, for the benefit of the community at large. The sponsor should have a clear policy regarding trial publication which should be agreed with the clinical researcher prior to trial initiation, and neither the sponsor nor the researcher should seek to prevent publication or the admission of trial results within the public domain. Communications on clinical studies must be a correct objective representation of all the findings, allowing others, in their turn, to give well-balanced risk-to-benefit advice to patients and their families. It is especially important that negative results or adverse safety data are communicated to regulators and clinicians in a timely manner where this information may affect prescribing practices and the protection of patients."*
- 17 This is a clear direction to pharmaceutical physicians to ensure open access to study trials.
- 18 However, even though there is a requirement that all clinical trial data are submitted to regulatory

agencies, there is clear evidence that not all clinical trial results have been made publicly available in medical or scientific journals. Research by Ross et al.¹ has demonstrated that most studies registered on the US-based ClinicalTrials.gov clinical trial registry and website had not lead to publication of study results; though nearly all had included all the data elements mandated by ClinicalTrials.gov, such as intervention and sponsorship. Looking at a sample of trials registered, less than half (311 of 677, 46%) of trials were published. Trials primarily sponsored by industry (40%, 144 of 357) were less likely to be published when compared with non-industry/non-government sponsored trials (56%, 110 of 198; $p < 0.001$), but there was no significant difference when compared with government sponsored trials (47%, 57 of 122; $p = 0.22$). Evidently there is a long way to go before the publication of all clinical trial data is achieved. However, it is obvious that the issue is not confined to the pharmaceutical industry and similar patterns of non-publication are found amongst non-industry and government sponsored trials.

- 19 Well known examples of clinical research where a lack of public dissemination of clinical trial data has been linked to an avoidable and detrimental health impact for patients treated with those drugs include viox and paroxetine. Over the last couple of years the ability and requirements to make results public has increased markedly especially with ClinicalTrials.gov. The ClinicalTrials.gov registration requirements were expanded after the Food and Drug Administration Amendments Act of 2007; more types of trials fell within scope for registration and there was a requirement for the submission of results for certain trials. This led to the development of the ClinicalTrials.gov results database, which contains information on study participants and a summary of study outcomes, including adverse events. The results database was made available to the public in September 2008. There are penalties for failing to register or submit the results of trials. However, it is often the case that not until meta-analyses of all clinical trials with a drug are conducted that some important safety signals emerge. These meta-analyses are often conducted by academics outside of industry and regulatory agencies; and they require full and complete access to the data on a drug to be reliable.

Question 4: How could the occurrence and results of clinical trials be made more open to scrutiny?

- 20 The amended Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) requires prospective trial registration with a statement that "Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject". In addition, many medical journals make it a pre-condition of acceptance for publication that a trial was registered. Relatively recent moves within the United States also make the provision of results from "applicable clinical trials" to ClinicalTrials.gov a requirement once the study has completed. The US FDA normally holds open public meetings with experts to discuss clinical trial data submitted as part of a new drug application though in other regions these types of meeting are normally closed sessions. Therefore there is public access to the occurrence of clinical trials and their key features are already well served via the requirements to enter clinical trial data into the US ClinicalTrials.gov clinical trial registry/website and, more recently, via the EMA supported EU Clinical Trials Register.
- 21 However the key question is how to enable the full set of raw clinical trial data to be made available to third parties to assess, review and analyse and not be restricted to just the trial sponsors and regulatory agencies. The Faculty has, for a long time, been supportive of greater transparency in clinical research and has promoted allowing third party access to clinical trial data. However this needs to be conducted in a fair and responsible manner. We believe that there is enormous potential for benefits to the broader research effort and public health if data could be more openly scrutinised by third parties. Under the current system, researchers are able to make their own assertions about the 'significance' of their research and data. However, it may be that other researchers can spot potential in the data that was not originally recognised, or can combine historical data with new information to highlight unforeseen benefits. Collaboration and transparency between researchers will also lead to less duplication of efforts and wasting of resources.

- 22 Overall, the Faculty favours a policy of both prospective and retrospective disclosure of data, but with a system that ensures adequate safeguards for both the anonymity of trial subjects and maintains safety for potential patients. Whilst open access should be enshrined in any new process of searching the data sets, there would need to be an orderly and scientifically sound process to facilitate access. We recommend the establishment of a ‘gate keeper’; an independent body reviewing requests for data. Third parties would be required to submit a statistical analysis plan or at the very least clear questions that they wish to address. The identities of those third parties requesting data should not be anonymous to the ‘gate-keeping’ body, but not necessarily made public. The cost of such a system could be shared by government, the sponsoring company and perhaps also the requesting party.
- 23 The Faculty would recommend that the following requirements should also be upheld for all clinical research:
- 24 *Sponsors and clinical investigators should make available the methods and results of their trial within one year of study completion.*
- 25 The task of policing this policy could fall on the Health Research Authority as an extension of the IRAS. The HRA is best placed to take account of local needs, but would need to integrate seamlessly with EMA, FDA and other national regulatory agencies, given the global nature of pharmaceutical product development.

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

- 26 Of note, the US FDA organises open advisory committee hearings for many new drugs, particularly where there is potential for significant public health impact, where FDA staff, external advisors and company representatives debate issues around the clinical trial results and implications for public health. The general public is also able to contribute to these meetings. The FDA assessment reports on the drugs reviewed become publically available on its website. The US ClinicalTrials.gov website and data registry now requires posting of the results of “applicable” clinical trials, this includes key clinical trials supporting marketing approval for new drugs and subsequent clinical trials with them. We believe that this system works well and would be appropriate and applicable in the UK/EU.
- 27 The EMA does now support the EU Clinical Trials Register and provides a publically accessible (commercially confidential material having been redacted) version of its assessment report for new drugs on its website. The EMA could look to mirror FDA in holding open public meetings when issues pertaining to new drug applications are debated with the medical and scientific experts. Given the ease of accessing information via the internet, international nature of major pharmaceutical companies and the fact that results from all relevant trials are available in the EMA assessment report for a drug.

Reference

ⁱ Ross JS, Mulvey GK, Hines EM, Nissen SE, Krumholz HM (2009) Trial Publication after Registration in ClinicalTrials.Gov: A Cross-Sectional Analysis. PLoS Med 6(9): e1000144. doi:10.1371/journal.pmed.1000144

Written evidence submitted by the Association of the British Pharmaceutical Industry (ABPI) (CT48)

Introduction

A.1. The Association of the British Pharmaceutical Industry (ABPI) welcomes the opportunity to submit evidence to the Committee's inquiry into clinical trials. Clinical trials are vital in order to demonstrate efficacy and safety of new medicines and are a regulatory requirement for every new medicine. In addition, clinical trials provide important information on the best ways of treating diseases with new medicines. Treatments discovered and developed in the UK help to save lives, reduce suffering and improve quality of life for millions of people all over the world. The UK has traditionally been at the forefront of international medicines research – only the USA has discovered and developed more medicines.

A.2. ABPI is committed to greater transparency in clinical trial information and in particular, the reporting of the occurrence and results of clinical trials. We believe access to trial information is vital and in the best interests of patients and the practice medicine – and that summary clinical trial results should be made available for both new and existing medicines.

A.3. Many steps are already being taken towards this goal:

- a) Since 2012, current and future trials must be registered within 21 days of enrolling the first patient and results, positive or negative, must be published within one year of marketing authorisation (or study completion for marketed products).¹
- b) ABPI is looking at a new, compliance monitoring system to ensure that the registration of clinical trials and publication of summary results takes place. A transparency toolkit will also be made available to assist companies with robust internal processes for compliance.
- c) For trials conducted in the EU from May 2004, summary reports will be made available via a central database (EudraCT), once the system has been upgraded by the end of 2013.²
- d) The ABPI has also produced guidelines to help improve access to clinical trial information including the ABPI Best Practice Model for the Disclosure of Results and Transparent Information on Clinical Trials and the Clinical Trial Transparency guidelines, produced with the Ethical Standards in Health and Life Sciences Group (ESHLG) in 2012.³ Both sets of guidelines are currently being reviewed.

A.4. We believe that one of the areas where more could be done is in the disclosure of information from past trials. The process of improving transparency is, however, an international one, governed by EU legislation. The industry in the UK is therefore working with partners in Europe and internationally to ensure that action is taken. We are working with our member companies and experts to participate in the European Medicine Agency's (EMA) working groups to find a real, effective and practical solution for the publication of summary results from clinical trials. As well as a global issue, this is also a complex issue. One challenge is to improve transparency while ensuring that disclosure policies protect patients: the consent a patient had provided at the time a study was conducted may not cover the general release of their data, even if the data had been effectively anonymised. In addition, it is important to protect both the integrity and effectiveness of the overall research and regulatory process and commercial information. The legitimate interests of companies in the protection of IP must also be protected in an appropriate way.

¹ ABPI Code of Practice for the Pharmaceutical Industry Second 2012 Edition, <http://www.abpi.org.uk/our-work/library/guidelines/Pages/code-2012.aspx>

² European Union Drug Regulating Authorities Clinical Trials database, <https://eudract.ema.europa.eu>

³ ABPI Best Practice Model for the Disclosure of Results and Transparent Information on Clinical Trials, (produced 2007, revised 2008), <http://www.abpi.org.uk/our-work/library/guidelines/Pages/best-practice-model.aspx> Clinical Trial Transparency guidelines, Ethical Standards in Health and Life Sciences Group, 2012, <http://www.eshlg.org/wp-content/uploads/ESHLG-Clinical-Trial-Transparency-Principles-and-Facts.pdf>

A.5. As well as improving transparency to clinical trial information, we believe that patients and the practice of medicine would benefit most when unnecessary regulatory hurdles to conducting clinical trials in the UK are removed. More progress is also required on attracting investment in research as the benefits of hosting clinical trials in the UK are well established, both for patients and society at large. Ambitious policy responses are therefore required for the UK to become and remain competitive as a centre for clinical research. We support the Government's efforts to streamline the regulation of clinical trials and to create a more positive environment for research in the NHS through the life sciences strategy.

A.6. From HIV to cardiovascular disease, neurological conditions to oncology, the pharmaceutical industry researches, develops and delivers medicines that radically improve patients' quality of life and bring a wide range of benefits to society. Clinical trials are a vital part of this and the UK pharmaceutical industry is committed to acting in the best interests of patients and to ensuring that patients continue to have access to the most effective treatments.

A.7. Please note that throughout this document, the term 'clinical trials' refers to all interventional, commercial sponsor led clinical trials, except where otherwise specified.

Question 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?

1.1. Yes, ABPI agrees that the European Commission's proposed revisions to the Clinical Trials Directive make positive steps to address the main barriers to conducting clinical trials in the EU, which would be beneficial for the UK. The current Directive has seen variation between member states on processes for submission, assessment and authorisation of clinical trials, timelines and safety data reporting, for example.

1.2. Revising the Directive as a Regulation will create a simpler, more efficient and uniform legal and regulatory framework for the authorisation and conduct of clinical trials in Europe. ABPI supports the proposed single submission of a Clinical Trial Authorisation (CTA) through an electronic portal with a coordinated assessment process resulting in a single decision per Member State (encompassing Regulatory Authority and Ethics Committee opinions) and competitive timelines for decisions. ABPI calls on the UK Government to ensure the UK can meet these timelines to ensure competitiveness.

1.3 At a national level, a significant administrative hurdle is the need to obtain separate NHS research and development (R&D) approval when the clinical trial is conducted in an NHS hospital or enrolling NHS patients. This is not addressed by the proposed Clinical Trials Regulation, but the Health Research Authority (HRA) has proposed to test a system for a single unified assessment for all research within the NHS (see response to Q. 2 for an assessment at a national level).

1.4 Overall, it is important that the Commission's proposals remain as intended for this legislation through the EU co-decision process and that all parties aim for agreement at first reading to avoid potential delays as a result of the upcoming European Parliament elections.

Question 2

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

2.1. ABPI strongly supported the creation of the HRA in 2011 to streamline regulation and to protect and promote the interests of patients and the public in health research. Streamlining regulation and making the UK a more attractive location to conduct clinical trials is at the core of the HRA's remit. Just over a year after its establishment, we believe it is too early to judge the effectiveness of the HRA in a comprehensive manner. Certainly, more can and should be done to make the UK a more attractive location to conduct clinical trials.

2.2. The HRA provides the Integrated Research Application System (IRAS), a UK-wide e-submission system through which applications for regulatory and governance approvals for health research are made. It is also the Appointing Authority for Research Ethics Committees (RECs) in England and provides the National Research Ethics Service (NRES), which regulates and guides ethics committees.

2.3. In addition, the Department of Health has agreed to the HRA's proposal to test the potential benefits of a simplified and streamlined HRA assessment for all research in the NHS. The devolved nature of the NHS means that trials often require many separate grants of permission, particularly where research is to be carried out across multiple sites, run by different NHS organisations. Securing several different permissions is an administrative burden for trial sponsors and does not provide additional protection for patients. A single HRA assessment would combine and replace aspects of the current review by NHS Research and Development and RECs. A single HRA assessment could potentially improve both study set-up times and the quality and consistency of ethical review, as well as improving transparency around the process.

2.4. ABPI believes the HRA should focus on building and maintaining competitive timelines for starting research studies in the UK, with particular emphasis on delivering the commitment to recruit the first patient within 70 days of receiving a valid research application, while consistently ensuring the delivery of patient recruitment to time and target.

2.5. The HRA also has a clear remit focused on protecting patients and would be well placed to ensure that precise information is given to Ethics Committees and trial participants on where to find trial registration details and ultimately, summary results.

Question 3

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

3.1. The pharmaceutical industry supports enhanced transparency of clinical research and safety information. Already, current and future trials must be registered within 21 days of enrolling patients and summary results, positive or negative, must be published within one year of marketing authorisation or within twelve months of study completion for marketed products.⁴

3.2. It is widely reported, however, that some clinical trial information is not in the public domain. It is true that compliance with the requirement to register clinical trials and posting of their summary results could be further improved, and we propose mechanisms to achieve this in our response to Question 4.

3.3. The charge that pharmaceutical companies withhold clinical trial information is commonly associated with a report published in 2012.⁵ This report relates to a study of all trials completed in 2009 which met the criteria for mandatory registration and summary results posting on www.clinicaltrials.gov under FDA regulations from 2007. The authors reported that 22% of all trials meeting the criteria were registered and had summary results posted; the figure was 43% for industry-sponsored trials and 9% for academic trials.

⁴ ABPI Code of Practice, 2nd Edition (2012), <http://www.pmcpa.org.uk/thecode/Pages/default.aspx>
International Federation of Pharmaceutical Manufacturers and Association's (IFPMA) Joint Position on Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2010), http://clinicaltrials.ifpma.org/clinicaltrials/fileadmin/files/pdfs/20100610_Joint_Position_Publication_10Jun2010.pdf

⁵ Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study, Prayle et al. 2012, <http://www.bmj.com/content/344/bmj.d7373>

3.4. At the Thirteenth Annual Pharmaceutical Regulatory and Compliance Congress and Best Practice Forum held in the United States in November 2012, a presentation by Dr Ann Meeker-O'Connell from the US Food and Drug Administration (FDA)

challenged the results of the above mentioned study, finding several flaws in the analysis. The US FDA's preliminary review of Prayle's results found that instead of 77.9% of trial summary results being overdue, 34.6% trial results were overdue by January 2011. Updating this analysis to May 31 2012, 21.1% of trial results were overdue, a compliance rate of 78.9%.⁶

3.5. ABPI is undertaking its own research to ascertain the extent to which pharmaceutical companies publish the results of clinical trials sponsored by them, irrespective of prevailing requirements. All company sponsored clinical trials conducted in patients for all new active substances (NAS) (excluding vaccines and combination products) approved by the European Medicines Agency (EMA) during 2009 – 2011 inclusive are being evaluated. This involves:

- Checking of the European Public Assessment Report (EPAR) for all studies conducted in patients in the individual Marketing Authorisation Application (MAA)
- Searching for all registered trials in the major international registries and company clinical trial registers
- Searching PubMed for all publications (limited to clinical trials), viewing the abstract field and matching to trial registry identifiers where they appeared in the abstract
- Cross-matching trial identification numbers from all sources, and minimizing duplication as far as possible
- Checking the dates that the studies were entered in a publicly available clinical trial registry (noting those that were not entered)
- Ascertaining which studies have reported results (either in the academic literature or in a section of the registry) by one year after the later of the date of first approval of the product or the date the study was completed
- Referring queries back to the companies concerned

3.6. The research is still ongoing, but ABPI found that for the 12 new products approved in 2010, the levels of trial registration and publication clearly exceed those quoted in Prayle et al, and are more in line with the FDA's preliminary findings – see table below.⁷ Our analysis shows that the publicly available evidence base for new medicines has improved in recent years. The research also suggests that clinical trials conducted prior to the existence of mandatory requirements or industry guidelines were less likely to be posted on registries and less likely to be published individually; this was particularly the case for smaller, early phase trials. In addition, problems commonly arise where products changed ownership after licensing deals or company mergers and acquisitions.

⁶ PhRMA Press release, <http://phrma.org/media/releases/phrma-statement-clinical-trials-bad-pharma> and personal communication

⁷ op cit. Prayle et al.

ABPI analysis of clinical trial registration and publication of summary results for all company sponsored clinical trials in patients for the 12 new active substances approved by EMA in 2010

Year	Trials registered and summary results posted /published within 12 months (%)	Trials registered and summary results posted /published (as of 31 January 2013) (%)
2010	115 of 145 (79%)	176 of 191 (92%)

NOTE: Of 213 trials identified as complete as of end of January 2012, 68 were non-evaluable due to the absence of one or other of the key assessment dates (eg, the precise date of study completion is missing or summary results have been posted, but the date of posting is not available). For some of these products, this includes trials conducted before any mandatory requirements for reporting summary results were in place. We are conducting a similar analysis for all NAS approved by EMA in 2009 and 2011.

3.7. It is important to stress that regulatory authorities have access to all the relevant information as part of the approval process for new medicines, and regular updates thereafter. A Freedom of Information (FOI) request can be made for any document within the MAA for any approved product. Certain documents should however be redacted to prevent personal data (as protected under European and national data protection laws) and commercially confidential information being disclosed, in consultation with the MAA holder.

3.8. Work is already underway to improve access to clinical trial data for existing medicines. Summary reports for clinical trials since 1 May 2004 will be entered on the EudraCT database when it has been upgraded to accept them later this year. EudraCT is the European Clinical Trials Database of all clinical trials within the scope of the EU Clinical Trials Directive.

Question 4

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

4.1. There are a number of steps which can be taken to ensure that clinical trial information can become more open in the future. Some immediate steps which ABPI recommends are:

- a) The global nature of clinical development means that an **international approach** is required. International agreement is needed on which trials to include in transparency measures (for example, all trials in humans, including healthy subjects, or all trials in patients) and on definitions of terms such as ‘study completion.’ Good Clinical Practice (GCP) is an international quality standard that is provided by the International Conference on Harmonisation (ICH), an international body that defines standards which governments can transpose into local legislation for clinical trials. ICH could be a mechanism to achieve harmonisation of an international approach. In the interim, ABPI recommends that **MHRA Good Clinical Practice inspections should be able to assess compliance** with trial registration and publication of summary results requirements.
- b) For all trials, the patient informed consent agreement between a trial participant and the sponsor should include a **statement from the sponsor that the summary results will be made publically available**. Precise information must be given to trial participants on where to find trial registration details and ultimately, summary results. Investigators and Ethics Committees should all receive summary results not later than posting dates of the results on the registry. These are activities which HRA should ensure are implemented immediately for all clinical research in the UK.
- c) **One global portal to which all clinical trials registries can be linked** would be ideal. For now, www.clinicaltrials.gov and www.clinicaltrialsregister.eu should be used. Companies may wish to also maintain their own clinical trial register, which should cross-reference the

entries in the international registries with the unique trial identifiers. Companies could state where disclosures can be found on their websites, as part of their compliance statements. Medical journal editors should demand that the unique trial identifier is mentioned in the **abstract** of journal publications.

- d) Already, Marketing Authorisation Applications **must be accompanied by all relevant clinical trial information**. ABPI recommends that for an MAA to be valid, the EMA in Europe and MHRA in the UK should require that all trials submitted as part of the application have been entered into an international registry, and the unique trial identifier from the registry must be listed against each trial.
- e) It is important to understand **what kind of information is required to be disclosed**, and what kind of information is being called for. Currently, semi-structured summary information for Phase II-IV clinical trials for licensed medicines can be disclosed through www.clinicaltrials.gov within 12 months of completion. With an upgrade of EudraCT planned to be completed in 2014, trials summary report information for Phase II-IV adult clinical trials conducted in the EEA for licensed drugs are to be disclosed within 12 months of completion and paediatric clinical trials of any origin when included in a Paediatric Investigation Plan are to be disclosed within 6 months of completion.

ABPI is closely following the progress of the five working groups set up by EMA to advise on the specific mechanisms that will govern whether and how final clinical study reports (CSR) and all available clinical trial information could be accessed by researchers and other interested parties. EFPIA, ABPI's European equivalent, has set up five parallel groups, each led by an industry representative who sits on the respective EMA group. The output from this work is critical as it will ensure that there is a consistent and clear understanding of what level of information should be released, in what format and when. ABPI will respond to the outputs of the EMA working groups in Q2 2013.

- f) **Compliance is, of course, critical**. ABPI is preparing a **clinical trial transparency toolkit** (comprising good practice guideline, process flowchart, template SOP, compliance checklist etc) to assist companies to comply with their obligations. These will be available on the ABPI website during Q3 2013. In addition, ABPI will appoint a third party service provider to monitor compliance with current and future industry codes of practice on clinical trial transparency. **ABPI will take on the responsibility for reporting non-compliance in relation to trial registration and posting of summary results to the Prescription Medicines Code of Practice Authority (PMCPA), or where applicable to the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA).**⁸

4.2. All of the above initiatives should be taken for new clinical trials. There is also the additional issue of improving disclosure of information from past trials for existing medicines, where there are significant complexities over release of information. The EMA and EFPIA are currently looking at all of these issues as part of their work. The complexities include:

- a) **Patient consent:** complete anonymisation of patient data may not always be possible. Even if patient data is anonymised and all patient identifiers are removed, some patients may not have given their consent to release of their data from past trials.
- b) **Orphan (or rare) diseases:** it is much more difficult to protect patients' identities for clinical trial information for medicines for orphan diseases.

⁸ Prescription Medicines Code of Practice Authority <http://www.pmcpa.org.uk/Pages/default.aspx>
International Federation of Pharmaceutical Manufacturers & Associations <http://www.ifpma.org/>

- c) **Different data formats:** clinical trial information has been presented in quite different formats over time and between different companies and any system for release of this information would need to take this into account.
- d) **Paper archives:** much information for past clinical trials is held in paper format. Making all information available would require this information to be reproduced in electronic format.
- e) **Volume of information:** releasing all information for all trials would be an enormous undertaking. It is not unusual for a full CSR to be several thousands of pages in length. www.clinicaltrials.gov already has over 140,000 registered trials.
- f) **Ownership of information:** many medicines are bought and sold as part of licence deals or company acquisitions across the world. In some cases, there is insufficient clarity over responsibilities in connection with management of clinical trial information within legal agreements.
- g) **Start date:** a grandfathering clause date would need to be set before which it would be impractical and of questionable benefit to release clinical trial information for medicines. A mechanism for deciding this date needs to be agreed.
- h) **Different regulatory regimes:** clinical trial legislation and requirements have changed over the years, resulting in different sets of information being collected and analysed in different ways, especially across different EU member states prior to the EU Clinical Trials Directive.

Question 5

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

5.1. The international governance framework for clinical trial transparency already exists and is workable if appropriate attention is paid to detailed implementation. In the US, the FDA has made greater strides in this regard. The regulation is clear and the database employed, www.clinicaltrials.gov, is widely acknowledged as being user-friendly and easy to navigate for companies and researchers alike.

5.2. The most significant barrier to clinical trial transparency has been, and still is, monitoring and enforcement. Given the current trend towards greater transparency in all walks of life, the time is ripe to put in place robust measures to make clinical trial information easily accessible for patients, researchers and healthcare providers, as outlined in the response to question 4.

About the Association of the British Pharmaceutical Industry (ABPI)

The ABPI represents innovative research-based biopharmaceutical companies, large, medium and small, leading an exciting new era of biosciences in the UK.

Our industry, a major contributor to the economy of the UK, brings life-saving and life-enhancing medicines to patients. Our members supply 90 per cent of all medicines used by the NHS, and are researching and developing over two-thirds of the current medicines pipeline, ensuring that the UK remains at the forefront of helping patients prevent and overcome diseases.

The ABPI is recognised by Government as the industry body negotiating on behalf of the branded pharmaceutical industry, for statutory consultation requirements including the pricing scheme for medicines in the UK.

February 2013

Joint written evidence submitted by The Cochrane Collaboration & the Centre for Reviews and Dissemination (CT49)

Executive summary

1. Systematic reviews¹ are increasingly used as best evidence to inform decisions in health care. Researchers preparing systematic reviews aim to include all relevant data irrespective of whether they have been published in the scientific literature or not, and irrespective of whether it is favourable or unfavourable to the intervention, to provide reliable estimates of the benefits and harms of any given intervention.

2. There is substantial evidence that incomplete disclosure of data from clinical trials is widespread and impacts adversely on patient care and public health. Decision-makers, including health professionals, patients, carers, and clinical guideline developers, may be led to believe that treatments are more effective and less harmful than they really are. The effects of non-disclosure include:
 - 2.1. Patients are harmed by misinformed treatment decisions.

 - 2.2. Public and private resources are wasted on ineffective or harmful treatments.

 - 2.3. Clinical trial participants trust that their involvement in research will lead to better care for others, and when the data they provide are withheld, this trust is abused.

3. This submission, focusing on the Committee's questions three to five, from The Cochrane Collaboration and the Centre for Reviews and Dissemination shows how withholding of clinical trial data can cause harm to public health. It also describes some lessons that can be learned from experience outside the UK and presents our proposals for action.

Introduction to The Cochrane Collaboration and the Centre for Reviews and Dissemination

4. The Cochrane Collaboration (www.cochrane.org), established in 1993, is an international network of more than 27,000 people from over 100 countries including health professionals, researchers, methodological experts, policy-makers, and consumers such as patients and their advocates and carers. The primary purpose of The Cochrane Collaboration is to prepare, update, and promote the accessibility of high-quality systematic reviews of the effects of interventions in clinical care, health policy, and other aspects of health and social care. Over 5,000 systematic reviews ("Cochrane Reviews") have so far been published in the *Cochrane Database of Systematic Reviews*, part of *The Cochrane Library* (www.thecochranelibrary.com). The Cochrane Collaboration is the world's largest organization preparing and maintaining systematic reviews in health care. The Cochrane Collaboration's work is internationally recognized as a benchmark for high-quality information about the benefits and harms of healthcare interventions and has strong representation from the UK. The Cochrane Collaboration receives funding from a variety of public sources, with the National Institute for Health Research (NIHR) being a major contributor,

¹ A systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarize the results of the included studies.

as well as from royalties from sales of *The Cochrane Library*, and has a commercial sponsorship policy for its research.²

5. The Centre for Reviews and Dissemination (CRD) is part of the NIHR and a department of the University of York. Established in 1994 to support NHS decision-making, CRD produces freely available databases (www.crd.york.ac.uk/crdweb) of systematic reviews, economic evaluations, and health technology assessments based on the worldwide research literature, and maintains an international prospective register of systematic review protocols. CRD also undertakes systematic reviews and economic evaluations of health and public health questions and carries out underpinning methodological development.
6. Neither The Cochrane Collaboration nor the Centre for Reviews and Dissemination (CRD) receive funding from the pharmaceutical industry.

Factual information

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

7. Trials that appear to demonstrate beneficial effects of an intervention being tested are more likely to be published,^{3,4} published more quickly,⁵ and disclosed in greater detail⁶ than those that fail to show such benefit or which identify harm.
8. Full reports of drug studies identified by searching regulatory agency databases have often not been published, or contain far more information than published papers.^{7,8,9} Legal settlements with drug companies have identified many unpublished trials or data.^{10,11,12} Researchers have also identified unpublished trials and data by searching for trial protocols, such as records registered in a clinical trials database.^{13,14}

² The Cochrane Collaboration. Commercial sponsorship policy. [cited 21 Feb 2013]; Available from: <http://www.cochrane.org/policy-manual/23-commercial-sponsorship-policy>

³ Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database of Systematic Reviews*. 2009(1):MR000006.

⁴ Scherer RW, Langenberg P, von Elm E. Full publication of results initially presented in abstracts. *Cochrane Database of Systematic Reviews*. 2007(2):MR000005

⁵ Hopewell S, Clarke M, Stewart L, Tierney J. Time to publication for results of clinical trials. *Cochrane Database of Systematic Reviews*. 2007(2):MR000011

⁶ Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PLoS One*. 2008;3(8):e3081.

⁷ Rising K, Bacchetti P, Bero L. Reporting bias in drug trials submitted to the Food and Drug Administration: review of publication and presentation. *PLoS Medicine*. 2008;5(11):e217; discussion e217.

⁸ Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *New England Journal of Medicine*. 2008;358(3):252-60.

⁹ Melander H, Ahlqvist-Rastad J, Meijer G, Beermann B. Evidence b(i)ased medicine--selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. *BMJ*. 2003;326(7400):1171-3.

¹⁰ Steinman MA, Bero LA, Chren MM, Landefeld CS. Narrative review: the promotion of gabapentin: an analysis of internal industry documents. *Annals of Internal Medicine*. 2006;145(4):284-93.

¹¹ Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. *New England Journal of Medicine*. 2009;361(20):1963-71.

¹² Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *New England Journal of Medicine*. 2007;356(24):2457-71.

¹³ Dickersin K, Chan S, Chalmers TC, Sacks HS, Smith H, Jr. Publication bias and clinical trials. *Controlled Clinical Trials*. 1987;8(4):343-53.

¹⁴ Dwan K, Altman DG, Cresswell L, Blundell M, Gamble CL, Williamson PR. Comparison of protocols and registry entries to published reports for randomised controlled trials. *Cochrane Database of Systematic Reviews*. 2011(1):MR000031.

9. An international team of Cochrane researchers evaluating the effects of neuraminidase inhibitors (such as Tamiflu and Relenza) discovered that many more trials of these drugs had been conducted than had been published when they reconstructed the hidden trial programmes by cross-referencing publication bibliography, correspondence, conference abstracts, pharmaceutical, and regulatory sources.¹⁵ Eight studies were available from published sources in the Cochrane Review published in 2006¹⁶, compared with over 120 unpublished studies identified subsequently.¹⁷ Insufficient data were available from these studies to evaluate the effects of the agents on preventing severe complications of influenza. Oseltamivir (Tamiflu) was used widely within the UK during the 2009 influenza epidemic. The Cochrane team, led by Dr Tom Jefferson, has prepared a separate response for the Committee describing this research in more detail.
10. Researchers from the Nordic Cochrane Centre planned to assess the benefits and harms of two slimming pills, orlistat and rimonabant, but the European Medicines Agency (EMA) denied access to data they held on the unpublished trials. After the researchers complained to the European Ombudsman, the EMA reversed its position and has now taken steps to ensure greater transparency in the disclosing trial data it receives during the licensing of drugs and devices.¹⁸ Their success in persuading the EMA to release the data is well-described in Ben Goldacre's book, *Bad Pharma*.¹⁹
11. An analysis of 164 efficacy trials submitted to the US Food and Drug Administration (FDA) in 33 approved new drug applications found that a quarter of trials submitted remain unpublished five years after FDA approval of the drug.²⁰ All these trials were industry-sponsored. Among those trials published, unexplained discrepancies between the trials and their corresponding publications – the addition or deletion of outcomes, changes in the statistical significance of reported outcomes, and changes in overall trial conclusions – tended to lead to more favourable presentations of the drugs in the medical literature available to healthcare professionals. A further report from the same research team, again studying FDA data, showed that including unpublished studies in two meta-analyses led to changes in the overall results.²¹
12. A landmark review published in the *New England Journal of Medicine* in 2008 used reviews from the US FDA to investigate studies covering 12 antidepressant drugs.²² All of the studies were industry-funded. They demonstrated that about a third of studies, involving 3449 participants, were unpublished. Studies that demonstrated an overall beneficial effect of the drug in question were far more likely to be published. Limiting the analysis to published data only resulted in an overall effect that was 32% more favourable than if the analysis had included both published and unpublished data. This highlights the considerable risk of decision-makers relying solely on published reports; in this example these provided substantially over-optimistic results.

¹⁵ Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database of Systematic Reviews*. 2012;1:CD008965.

¹⁶ Jefferson TO, Demicheli V, Di Pietrantonj C, Jones M, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. *Cochrane Database of Systematic Reviews*. 2006(3):CD001265.

¹⁷ See Jefferson et. al., 2012.

¹⁸ Gøtzsche PC, Jorgensen AW. Opening up data at the European Medicines Agency. *BMJ*. 2011;342:d2686.

¹⁹ Goldacre B. *Bad Pharma: How drug companies mislead doctors and harm patients*. London: Fourth Estate; 2012.

²⁰ See Rising et al. 2008.

²¹ Hart B, Lundh A, Bero L. Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses. *BMJ*. 2012;344:d7202.

²² See Turner et. al., 2008.

13. A systematic review of the effect of a class of antidepressants, selective serotonin reuptake inhibitors (SSRIs), in children showed that including unpublished trials changed a favourable risk-benefit profile to an unfavourable one for several of the drugs.²³ The drug companies concealed for many years unpublished trial data suggesting that these drugs increase the risk of suicide in children and adolescents.²⁴ This was the subject of BBC Panorama programmes.
14. Even when trial reports are published the quality and completeness of the information presented may be inadequate and misleading. In an article from the *Journal of the American Medical Association* in 2004, researchers studied the results of 102 trials covering 3736 trial outcomes.²⁵ They found that only half of the positive outcomes and 35% of the harms were reported adequately, with a bias towards reporting findings that demonstrate a beneficial effect over those that do not. As the article authors report, “published articles as well as reviews that incorporate them, may be unreliable and overestimate the benefits of an intervention”.
15. There have been a number of high-profile court cases in the USA in which pharmaceutical companies have been found guilty of withholding data from clinical trials, resulting in settlements against them:
 - 15.1. In 2010, Forest Pharmaceuticals pleaded guilty to charges relating to three drugs – levothyroxin (Levothyroid), citalopram (Celexa), and escitalopram (Lexapro) – and paid costs of over \$313 million USD in the legal case against them. The company publicized positive results of a study of citalopram (Celexa) in adolescents but failed to disclose the negative results of a contemporaneous European study in a similar population.²⁶
 - 15.2. In July 2012, GlaxoSmithKline was the subject of the largest healthcare fraud settlement in US history. The company pleaded guilty to one count of failing to report safety data about the diabetes drug rosiglitazone (Avandia) to the FDA. The US also alleged that GlaxoSmithKline did not disclose data from two studies on the use of paroxetine (Paxil) for adolescents, both of which failed to demonstrate efficacy in treating depression in this age group.²⁷
16. Publication and outcome reporting bias is not limited to industry-sponsored research. For example, Cochrane researchers investigating the effects of vitamin A supplementation in low- and middle- income countries concluded cautiously, on the basis of evidence available to them at the time, that vitamin A probably saved lives when given to children.²⁸ However, they were aware of a publicly funded trial involving one million children completed at least four years earlier that was not available in any published form. They included preliminary results from the study based on

²³ Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet*. 2004;363(9418):1341-5.

²⁴ Healy D. *Let them eat Prozac*. New York: New York University Press; 2004.

²⁵ Chan AW, Hrobjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA*. 2004;291(20):2457-65.

²⁶ United States Department of Justice. Drug Maker Forest Pleads Guilty; To Pay More Than \$313 Million to Resolve Criminal Charges and False Claims Act Allegations. Wednesday, September 15, 2010. 2010 [cited 15 Feb 2013]; Available from: <http://www.justice.gov/opa/pr/2010/September/10-civ-1028.html>

²⁷ United States Department of Justice. GlaxoSmithKline to Plead Guilty and Pay \$3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data. Monday, July 2, 2012. 2012 [cited 15 Feb 2013]; Available from: <http://www.justice.gov/opa/pr/2012/July/12-civ-842.html>

²⁸ Imdad A, Herzer K, Mayo-Wilson E, Yakoob MY, Bhutta ZA. Vitamin A supplementation for preventing morbidity and mortality in children from 6 months to 5 years of age. *Cochrane Database of Systematic Reviews*. 2010(12):CD008524.

information contained in a set of PowerPoint slides posted on the Internet.²⁹ This reduced the size of the effect of vitamin A supplementation on mortality. With only limited information about the trial available, they could not appraise the study fully and await full publication of the study.

17. The events outlined above demonstrate that clinical trial data have been withheld. The impact on public health is considerable, including inappropriately optimistic assumptions about the benefits of treatments leading to misinformed healthcare decisions, harm to patients, and waste of resources. This can occur at the level of the individual patient consultation or at a population level when, for example, guidance provided by trusted bodies may be unknowingly founded on an incomplete and biased evidence base.

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

18. Governments should ensure that:

18.1. Central repositories or databases of results from trials are made available, so that data can be stored with appropriate safeguards. Collective responsibility for trial data, which is shared by sponsors, investigators, research ethics committees, trial participants, and the wider public, requires governments to ensure that adequate mechanisms, resources, and infrastructure are provided to facilitate access to the protocols, results, and data.

18.2. Government agencies should consider introducing legislation that makes it a requirement to register all trials and to provide the results from all trials to the public. Such legislation should make trial sponsors and researchers responsible for ensuring that:

18.2.1. All clinical trials are registered, in advance of recruitment beginning, on a publicly available database.

18.2.2. Full trial protocols are made publicly available free of charge and in easily accessible electronic formats, preferably before recruitment begins but certainly within 12 months following completion of the trial.

18.2.3. Results for all protocol specified outcomes, with analyses based on all participants, are made publicly available free of charge and in easily accessible electronic formats within 12 months after completion of all trials.

18.2.4. Anonymized, individual participant data are made available without restriction and free of charge, with appropriate safeguards to ensure ethical and scientific integrity and standards, and to protect participant privacy.

- 19. Research ethics committees should be responsible for ensuring that** all clinical trials and their protocols that they approve are registered (as approved – not necessarily as undertaken) on a publicly available database.

²⁹ Clinical Trial Service Unit and Epidemiological Studies Unit (CSTU). DEVTA (1999 - 2004; first results 2007). 2013 [cited 18 Feb 2013]; Available from: <http://www.ctsu.ox.ac.uk/research/research-archive/devta-de-worming-and-enhanced-vitamin-a>

20. Sponsors of trials should be responsible for ensuring that:

20.1. Full trial protocols are publicly available free of charge and in an easily accessible electronic form from the beginning of the study.

20.2. Sponsored research is made publicly available irrespective of study results.

21. Researchers and journal editors should be responsible for ensuring that:

21.1. Any trial report submitted for consideration for publication in a journal is registered in a public trials registry, according to the “Obligation to Register Clinical Trials” statement from the International Committee of Medical Journal Editors (ICMJE).³⁰

21.2. The results for randomized controlled trials that are reported in a journal meet the relevant reporting guidance, Consolidated Standards of Reporting Trials (CONSORT), which includes items on outcomes, changes to outcomes, and numerical results.³¹ The ICMJE refers journal editors and researchers to the CONSORT statement in its guidance.³²

21.3. **Members of the public should be encouraged to** participate only in trials where full disclosure of the trial protocol and its results are stipulated as a condition of participation on the informed consent form.

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

22. The Food and Drug Administration Amendments Act (FDAAA) of 2007 mandated that trials conducted in the USA, or conducted with the aim of pursuing an FDA new drug application, or of a drug manufactured in the USA needed to fulfil the following requirements:

22.1. Registration of the trial not later than 21 days after enrolment of the first participant.

22.2. Results to be submitted to ClinicalTrials.gov within 12 months of the study completion date.

23. This Act also expanded the remit of the ClinicalTrials.gov database to incorporate clinical trial results. A review of the extent and quality of disclosure of trials has, however, demonstrated that registration remains incomplete, and that the quality of entries and completeness of reporting of results are inconsistent.³³

24. In Germany, the Institute for Quality and Efficiency in Health Care (IQWiG) abandoned its analysis of study data based on published reports relating to the antidepressant reboxetine,

³⁰ International Committee of Medical Journal Editors (ICMJE). Uniform requirements for manuscripts submitted to biomedical journals: publishing and editorial issues related to publication in biomedical journals: obligation to register clinical trials. 2013 [cited 18 Feb 2013]; Available from: http://www.icmje.org/publishing_10register.html

³¹ CONSORT. Consolidated Standards of Reporting Trials. 2013 [cited 18 Feb 2013]; Available from: <http://www.consort-statement.org/>

³² International Committee of Medical Journal Editors (ICMJE). Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. 2007 [cited 18 Feb 2013]; Available from: http://www.icmje.org/2007_urm.pdf

³³ Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database--update and key issues. *New England Journal of Medicine*. 2011;364(9):852-60.

because it suspected that the manufacturer, Pfizer, was concealing a substantial volume of data from the trials that had been conducted.³⁴

25. Reboxetine is currently licensed as an antidepressant by the Medicines and Healthcare products Regulatory Agency (MHRA) for use in England and Wales, and the drug has been widely prescribed worldwide. When researchers at IQWiG were finally granted access to data from unpublished studies they found that data for two-thirds of the patients were missing in the published reports. While published data suggested the drug was beneficial, the complete data set did not. In particular, reboxetine performed poorly compared to other known selective serotonin reuptake inhibitors (SSRIs). The analysis also confirmed that there were harms associated with the drug. The agency concluded that “no proof of benefit from treatment with reboxetine could be deduced” from the data available at that time, either for acute therapy, or to prevent relapse.³⁵ The drug continues to be displayed in the British National Formulary without any comment on the findings of the IQWiG researchers.³⁶ Data from the NHS in England in 2010 show that there have been over 50,000 prescriptions written for reboxetine at a cost of over £838,000 GBP.³⁷
26. The European Medicines Agency (EMA) held a workshop in November 2012 to discuss access to clinical-trial data and transparency. This led to the agency establishing working groups to develop policies in five key areas: protecting patient confidentiality; clinical-trial-data formats; rules of engagement; good analysis practice; and legal aspects. Recommendations from these groups are expected in April 2013. Guido Rasi, the Executive Director of the EMA, stated that “We are not here to decide if we publish clinical-trial data, but how.”³⁸
27. Each of the above examples indicates a growing international awareness of harm caused by incomplete disclosure of the results of clinical trials. Withholding results breaches the trust of trial participants who might reasonably assume that their participation in the research will be used to develop scientific understanding and improve the care of future patients. Also, the wider public expects policy-makers and clinicians to have access to the totality of the evidence in making decisions about health interventions. When trial data are withheld, these expectations are undermined.

Recommendations for action

28. Many trials are international in their scope, which means that governments need to work together to ensure co-ordination of measures to improve the accessibility of trial data.
29. Government agencies should introduce legislation to ensure that:

³⁴ Institute for Quality and Efficiency in Health Care (IQWiG). Pfizer conceals study data. 2009 [cited 15 Feb 2013]; Available from: <https://www.iqwig.de/index.868.en.html>

³⁵ See IQWiG 2009.

³⁶ Joint Formulary Committee. 4.3.4 Other antidepressant drugs. Reboxetine. *British National Formulary* (online). London: BMJ Group and Pharmaceutical Press; 2013.

³⁷ National Health Service (NHS). Prescription Cost Analysis - England, 2010. 2010 [cited 18 Feb 2013]; Available from: <http://www.ic.nhs.uk/pubs/prescostanalysis2010>

³⁸ European Medicines Agency (EMA). Workshop on access to clinical-trial data and transparency kicks off process towards proactive publication of data. Press release. 2012 [cited 18 Feb 2013]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/11/news_detail_001662.jsp&mid=WC0b01ac058004d5c1

- 29.1. All clinical trials are registered at their inception, before recruitment of the first participant; see The Cochrane Collaboration's statement.³⁹
- 29.2. Full trial protocols become publicly available free of charge and in easily accessible electronic formats before recruitment begins; and that updates are made available with changes clearly documented.
- 29.3. Results for all protocol-specified outcomes, with analyses based on all participants, become publicly available free of charge and in easily accessible electronic formats within 12 months after completion of all trials.
- 29.4. Anonymized, individual participant data are made available without undue restriction and free of charge; with appropriate safeguards to ensure ethical and scientific integrity and standards, and to protect participant privacy.
- 29.5. It is a requirement for results from all trials to be made publicly available.
30. Government agencies should recognize collective responsibility for trial data, which includes sponsors, investigators, research ethics committees, trial participants, and the wider public; and to ensure that adequate mechanisms, resources, and infrastructure are provided to facilitate access to the protocols, results, and data.

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³⁹ The Cochrane Collaboration. The Cochrane Collaboration Supports Prospective Registration of Clinical Trials. 2004 [cited 19 Feb 2013]; Available from: <http://www.cochrane.org/about-us/our-policies/support-registration-clinical-trials>

Appendix. Contributor details and declarations of interest

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All contributors are members of The Cochrane Collaboration.

Ruth Foxlee, Toby Lasserson, Harriet MacLehose, and David Tovey are employees of The Cochrane Collaboration.

Martin Burton is employed by the Oxford University Hospitals NHS Trust as Director of the UK Cochrane Centre, funded by the National Institute for Health Research.

Mike Clarke is employed as Director of the All Ireland Hub for Trials Methodology Research, which includes a variety of work on the design, conduct, interpretation, and use of clinical trials. Attitudes, regulations, and legislation relating to clinical trials may have an impact on this work.

Lesley Stewart is Director of the NIHR Centre for Reviews and Dissemination (CRD) at the University of York. She is responsible for delivering programmes of work that include systematic reviews of both aggregate and individual participant data on which legislation relating to clinical trials may impact. She is Co-Editor in Chief of a journal that publishes systematic review protocols.

According to the ICMJE conflicts of interest form,⁴⁰ all contributors declare, that apart from those declarations stated above: neither they nor their institutions received payment or services from a third party for any aspect of this response; (2) no financial relationships with entities that could be perceived to influence, or that give the appearance of potentially influencing, this response; and (3) no other relationships or activities that could be perceived to have influenced, or give the appearance of potentially influencing, this response.

⁴⁰ International Committee of Medical Journal Editors (ICMJE). ICMJE uniform disclosure form for potential conflicts of interest. 2013 [cited 20 Feb 2013]; Available from: http://www.icmje.org/coi_disclosure.pdf

Written evidence submitted by the Health Research Authority (HRA) (CT50)

In this submission, the Health Research Authority (HRA) is responding in general terms to the call for evidence but in particular to the matter: What is the role of the HRA in relation to clinical trials and how effective has it been to date?

Background and remit

1. The HRA is a Special Health Authority with a remit to promote and protect the interests of patients and the public in health research.
2. The HRA is one of a number of bodies with responsibilities for the regulation and governance of research in the UK. However, it is in the unique position, as described below, to consider the overall framework of both the regulation and governance of research, and linked key roles for those responsible for funding, sponsoring, hosting, publishing and responding to research.
3. The HRA is widely recognised as having transformed the systems for ethical review in the UK by providing an efficient, proportionate and effective system for NHS Research Ethics Committees (RECs) which approve research, including clinical trials, within the research governance framework. The HRA has also already taken responsibility for the Gene Therapy Advisory Committee (GTAC) and will take on further functions at the end of March when the National Information Governance Board closes and responsibility for approving the processing of confidential patient information transfers to the HRA.
4. The Government intends to legislate to establish the HRA as a non-departmental public body, and the draft Care and Support Bill has now been published for pre-legislative scrutiny.

The HRA – making it easier to do good quality ethical research in the UK

5. As well as making it easier to do good quality ethical research in the UK, the HRA has set out an ambitious programme of work to deliver practical solutions and inform further improvements to the framework for managing and supporting research in the NHS. To this end, the HRA has established a Collaboration and Development Steering Group to oversee a set of projects to improve the environment for research in the UK. Recognising that the HRA has a lead role, it will need to work effectively with partner organisations to deliver improvement and unify processes for application and approval, so that tasks are worthwhile, proportionate and undertaken once by the most appropriate organisation to remove unnecessary activity and duplication, and the associated delays and inefficiencies.
6. The HRA received around 6000 applications from across the UK last year, 1000 of which were Clinical Trial Investigational Medicinal Products and needed expert review from the Medicines and Healthcare products Regulatory Agency (MHRA), which is coordinated and managed through a Memorandum of Understanding. In addition, a further 1000 applications now proceed through the REC Proportionate Review Service, and are completed in an average of eight days.

7. The HRA is currently testing the potential benefits of a simplified and streamlined HRA assessment for all research in the NHS, including clinical trials, in one of a portfolio of projects under the HRA Collaboration and Development Steering Group. The assessment would combine and replace aspects of the current review by NHS Research and Development (R&D) and RECs. Scoping work for the project has suggested that a quality-assured HRA assessment could potentially improve both study set-up times and the quality and consistency of ethical review. NHS organisations would be able to rely on the HRA assurance and devote their review to confirming their capacity and capability to host and deliver the research, whilst RECs would be able to focus their expertise on projects raising ethical issues. If successful, this radical simplification across R&D and ethics review would potentially provide a simplified platform for other improvements planned by the HRA and other partners.

Working with others to support research

8. The HRA recognises that to deliver its ambition to make it easier to do good quality research in the UK it needs, not only to work in collaboration with other bodies, but also to influence and lead change with them. The collaborations forged through the National Research Ethics Service (NRES, now part of the HRA) and Integrated Research Application System (IRAS) partnership demonstrate the HRA's successful track record of improving the UK research environment.
9. The HRA also has well-established partnerships with the MHRA, the Human Tissue Authority, the UK Health Departments, and other organisations regulating and governing research.
10. The HRA coordinates a UK-wide steering group to ensure that identified solutions are adopted widely to maximise further improvement. The HRA chairs the UK Ethics Committee Authority (UKECA), which has responsibility for establishing, recognising and monitoring ethics committees under the Medicines for Human Use (Clinical Trials) Regulations 2004.

Influencing EU regulations for clinical trials

11. The HRA is an active member of the MHRA steering group, which is formulating the UK response to the revision of the EU regulations for clinical trials, and with them contributes to negotiations in Europe.

Transparency in research

12. The HRA is committed to transparency, in the conduct of its own business and in promoting transparency in research and improving public confidence in research. As part of the IRAS application process, researchers are asked to provide information about the registration of their study on a publicly accessible database, and their plans for dissemination of results; and these aspects are reviewed by RECs.
13. As well as publishing research summaries for all applications, the HRA is developing a policy framework for transparent research. It is engaging key stakeholders in developing the framework to

describe the HRA's role in promoting transparency of research, through registration, publication, dissemination, access to data, access to tissue and providing results to study participants.

14. The HRA fully supports the European Commission's ambition, as part of the revision of the EU Clinical Trials Directive, to increase and improve transparency in clinical trials.

Declaration of interest

The author has no declarations of interest.

February 2013

Written evidence submitted by INVOLVE (CT51)

Key points

- Public involvement in research is critical to its quality and relevance but also to ensuring that it is conducted to the highest standards and in the public interest
 - Lack of disclosure of clinical trial results has been a perennial issue of concern to patients and the public.
 - Reducing research regulation is equally important to patients but not if it is at the expense of issues of importance to them
 - We welcome the work being done by the Health Research Authority (HRA) to address issues around bureaucracy but also transparency of reporting etc. We welcome the HRA's forward-thinking attitude to patients and the public.
 - All research funders should commit to making sure that research participants receive the results of trials they have taken part in as well as how the research has improved knowledge into their condition.
 - We welcome the work that NIHR is doing in partnership with INVOLVE and others to make information on open trials and the results of trials more openly accessible through the provision of plain English summaries.
 - The UK Clinical Trials Gateway (UKCTG) is a potentially important vehicle for making clinical trial results and data more publicly available.
-

INVOLVE welcomes the opportunity to submit written evidence to the House of Commons Science and Technology Select Committee inquiry into clinical trials and disclosure of data.

INVOLVE is the national advisory group for the promotion and advancement of public involvement in all forms of health and social care research. Established in 1996 we have been funded by the National Institute for Health Research (NIHR) since 2006 and remain one of the few publicly funded organisations for public involvement in research across the world.

The perspectives of patients and the public are crucial to any discussion on clinical trials. They are key as both participants in trials and ultimately as the people for whom the research is aimed to benefit.

Active public involvement in research and research governance is vital to ensure that the interests of patients and the public are considered alongside those of researchers and clinicians. For example they can bring a patient perspective on important issues such as consent, anonymity, risks, safety, transparency and the acceptability and relevance of research. Whilst the public as well as researchers recognise the importance of streamlining and reducing bureaucracy this needs to be done in a way that is acceptable to patients and for patient benefit.

INVOLVE's primary focus is on improving and strengthening public involvement in the design and delivery of research. Nonetheless, over the last decade, we have built up considerable knowledge and expertise in the issues and concerns of patients and the public about the conduct and impact of research more generally. This includes the registration of clinical trials and reporting of trial results.

It has been a perennial complaint of clinical trial participants that they are very rarely told the results of trials they have taken part in and how it has benefited medical research into their condition. Where they take it upon themselves to track down results and any accompanying data they often find it impossible to do so. As patients and the public become more knowledgeable about their condition through the web and other sources, we believe it is imperative that ways are sought to improve transparency in this area so that patients, with their doctor, can make appropriate treatment decisions informed by the latest evidence available.

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

At our recent INVOLVE Conference Sir Iain Chalmers presented evidence published in an article in the Lancet that research is underreported with for example over 50% of studies not publishing in full and over 50% of planned study outcomes not being reported. (Chalmers, I and Glasziou, P. (2009), Avoidable waste in the production and reporting of research evidence, 374: 86-89)

For the public to trust and have confidence in research and to improve patient care and treatment, there needs to be far greater openness and transparency in the publishing and accessibility of research findings. Researchers should be required to make all research findings publicly available as well as to feed back findings to participants. Patients who participate in clinical trials do so with the wish to improve treatments and outcomes for the future. If such research isn't published then both their time and contribution as well as any learning for future research and treatment is wasted.

It is disappointing that, to the best of our knowledge, the pharmaceutical industry has taken no proactive steps in recent months to meet with and discuss the concerns of patients and patient groups on this subject. In our view this has only compounded the perception among many patients and the public that the industry is not acting in their best interests. We would welcome and hope that the Select Committee will encourage a more open dialogue among all relevant parties.

What is the role of the Health Research Authority in relation to clinical trials and how effective has it been to date?

The Health Research Authority and NRES have to balance protecting and promoting the interests of patients and the public alongside addressing unnecessary bureaucracy in research governance.

Since the establishment of the HRA in 2011 they have been proactive in their aim to create a unified approval process and to promote proportionate standards for compliance and inspection within a consistent national system of research governance. They have also recently announced plans to develop an HRA policy framework for transparent research, looking at registration, publication, dissemination, access to data, access to tissue and providing information on study results to participants.

Since 2006, INVOLVE has worked closely with NRES to support and develop the role and contribution of the public to ethical review and research governance. With the establishment of the HRA they have continued to work with ourselves and others to ensure that patient and public

perspectives are integral to the way that they operate and are in the process of developing their strategy for public involvement. We also welcome the steps that HRA is taking to improve the evidence available on public attitudes to research regulation generally with its recently announced Sciencewise public engagement project.

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

The NIHR is working to improve guidelines and policies to ensure that all NIHR funded research is reported fully and publicly available when the research has been completed. Similar guidance and self regulation is needed for the pharmaceutical industry and other funders. However, in addition there is a role for the Health Research Authority and MHRA working with patients and the public to regulate and monitor the reporting and publishing of research.

In view of the new statutory duties on all NHS organisations to advance and promote research (Health and Social Care Act 2012, and the Government's welcome drive to increase research participation among patients, we would also support any steps to ensure that patients are told the results of trials they have taken part in and thanked for their role in making research happen. This sort of commitment can only help to encourage more patients to choose to take part in research.

Finally, the UK Clinical Trials Gateway (CTG) - one of the few patient-facing pledges in the Government's Life Sciences Strategy - has the potential to be the central point for accessing and recording the progress of all clinical research, providing publicly available information on current research as well as the outcomes of the research in an accessible language and format.

A recent NIHR commissioned survey showed strong support for the idea of the Gateway among patients and the public. Nonetheless respondents identified a range of improvements and modifications to UKCTG with transparency a common theme. For example, in recent months INVOLVE has been leading work as part of an overall drive to include both plain English summaries of all studies as well as plain English summaries of the findings of research. This would help to raise public awareness of both the nature of research being undertaken as well as the extent of reporting of research findings.

February 2013

Written evidence submitted by the Clinical Contract Research Association (CCRA) (CT52)

Introduction

The Clinical Contract Research Association (CCRA) welcomes the opportunity to submit evidence to the Science and Technology Committee's inquiry into clinical trials. The United Kingdom has a worldleading track record of biopharmaceutical research and development, discovering and developing as many leading medicines as the rest of the European Union combined. The UK continues to build on this with its renowned experience and expertise in clinical research. Specialist research infrastructure and support are available for all major therapy areas and trial types. Dedicated facilities and partnerships are established for early phase research. Research networks embedded in the NHS support the efficient set up and delivery of later phase and multi-centre clinical studies. A number of UK headquartered Contract Research Organisation (CRO) companies also have enviable reputations for successfully managing trials internationally.

CCRA

The Clinical Contract Research Association is a not-for-profit government accredited trade organisation (ATO) for companies directly involved in, or supporting clinical contract research. It works closely with government agencies and other professional and trade associations to ensure that the highest standards of scientific, ethical and clinical practice prevail in the United Kingdom.

- It supports its membership by:
- Representing the industry to Government and regulators
- Creating business opportunities
- Supporting export activities
- Being a conduit for Government funding and initiatives
- Giving information, advice and support

Setting standards and adding credibility – all CCRA members must comply with the Code of Practice and are proud to use the CCRA logo on their promotional materials

Question 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?*

In part yes. Although it was in theory a positive addition, it was a mistake to add the extra sections on serious breaches into the UK's Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 - SI 2006/1928. Now this appears to be going EU wide at least it is a level playing field for the UK again. A single regulatory approval portal should help bring more trials to the EU and hence the UK. New definition of low intervention trial should help approval process. Changes to safety reporting should also reduce burden on sponsors wanting to carry out trials in the EU.

In the UK the previous EU Clinical Trials Directive was a 'gold plated' implementation while other EU countries were slow to adopt it or toned down their enforcement. Consequently Europe has not been a level playing field for clinical research. In particular the UK has suffered badly in pre-clinical and early phase clinical studies. The number of Phase 1 clinics in the UK has decreased substantially over the last 10 years and those remaining are challenged and a number are likely to go out of business in the next few years.

Research and Development (R&D) committees continue to be a barrier to research in the UK. R&D committees need to be subject to statutory performance control. The EU directives need to start to look at how to support trials that allow many more patients access, look at reducing the complexity of informed consent documents and data protection documents that put patients off taking part for almost purely theoretical risks, reducing further cross border delays in trial logistics – critically with regions outside the EU and which allow greater integration of the routine, non-trial related health care that patients may need.

In addition sponsors from emerging markets find it difficult to travel to the EU. So often they will look at providers in the Schengen Area where they can travel freely without having to get an additional visa and this is therefore to the disadvantage of the UK.

Clinical trial insurance – a specific issue

The insurance industry in the UK (as well as rest of Europe) is extremely concerned about the ill-considered recommendations regarding the implementation of state (non-insured) schemes to compensate “injured” trial subjects. The UK of course has never even implemented mandatory legislation to govern insurance of trials – unlike 22 other EU member states. HM Government should be very concerned about being forced to implement the suggested National Indemnification Mechanism (NIM). An analysis of the specific issues relating to insurance has been prepared on behalf of the UK insurance industry by Steptoe and Johnson LLP. The Steptoe and Johnson LLP report is given in full in Appendix 1.¹

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

The formation of the Health Research Authority (HRA) has streamlined clinical trials ethics regulation and is making the UK a more attractive location to conduct clinical trials. The Integrated Research Application System (IRAS) provided by the HRA simplifies UK-wide e-submission of applications for regulatory and governance approvals for health research. However, as pointed out above, Research and Development (R&D) committees continue to be a barrier to research in the UK. R&D committees need to be subject to statutory performance control and perhaps integrated within the HRA.

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

It is misleading to say that "pharmaceutical companies withhold data". It's true that pharmaceutical companies haven't always published the results of all their trials, and that's a bad thing, but it's a general problem of clinical research, and not something specific to pharmaceutical companies. In fact research has generally shown that studies sponsored by pharmaceutical companies are more likely to be published than independent studies (Schott *et al* 2010). So it's important to realise that any attempt to fix the problem must be across the board, and not focus only on pharmaceutical companies.

Generally withholding of clinical trial data is extremely difficult to do for trials that have been performed in recent years. Auditing and regulatory oversight has ensured high level of record keeping, process documentation and audit trail. The approval process also compares reported outcomes with individual reported data and these data are in turn compared with the original source data records. Hiding data or misrepresenting these data inappropriately is not easily achieved. Many campaigners for completeness of clinical trials publication quote a statistic that only 50% of trials are published. It's not clear where they get that statistic from, but it seems unduly pessimistic. Guidelines published in the last decade have called for complete publication, and they may be helping to ensure gradually rising rates of publication of trials. A reasonably recent study found that 80% of clinical trials were either published or had results disclosed on a website (Bourgeois *et al* 2010). It is likely, however, that rates of publication were lower in the past. This means that there is a large backlog of trials that were done in the past but never published. It would be highly desirable if those trials could be published, on the principle "better late than never".

It is important to recognise that publication of clinical trials does require resources. It would therefore be helpful if any grants given for clinical trials by grant giving bodies such as the MRC were to ring-fence a proportion of the grant to cover the costs of publication. Note that costs include not only any journal charges, but also the resources needed to write the paper. If the time of the person writing the paper is properly costed (this would generally be done accurately if an external medical writer is hired, but may be hidden by not treating it as a separate item for accounting purposes if researchers

¹ Not printed

write papers themselves), then the cost of writing the paper is usually far higher than any journal charges.

Bourgeois FT, Murthy S, Mandl KD (2010) Outcome reporting among drug trials registered in ClinicalTrials.gov. *Ann Intern Med* 153:158-66

Schott G, Pacht H, Limbach U, et al (2010) The financing of drug trials by pharmaceutical companies and its consequences. Part 2: a qualitative, systematic review of the literature on possible influences on authorship, access to trial data, and trial registration and publication. *Dtsch Arztebl Int* 107:295-301

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

All trials must be approved by an ethics committee before they can begin. It would be expected to help with clinical trials disclosure if ethics committees were to routinely demand a commitment from researchers to publish their results, and, crucially, to have a mechanism to enforce that commitment. This could, for example, be by refusing approval for future studies to any researchers who have not met their publication commitments in the past.

There needs to be a “journal of failed clinical studies” that is set up and run to the same level of scrutiny of any other scientific publication. In the reporting of negative data it is far more important that robust peer review occurs than positive trials. An example would be histology screening for cancer. The potential sequela from a false negative is far more serious than a false positive. It is not only Pharma companies that do not publish negative results but also academics. In most cases it is not because they do not fundamentally do not want to publish but rather because no reputable journals would accept the papers. In academia publishing papers is one of the biggest pressures on scientists and journals like to publish “exciting” results. So the responsibility for publishing of “failed” clinical trials is multi-faceted. Pharma and academia should publish their results, within a defined timeline, as a condition of getting approval to perform them. Peer review journals should take responsibility to ensuring negative clinical trials are published with the same priority as data which appears to push back the boundaries of science. Alternatively, a fee could be levied on applications to carry out clinical studies in order to fund “The Journal of Negative Clinical Trials”

Another way of improving the transparency of clinical trials would be if regulators were to make the reports submitted to them as part of the drug licensing process publicly available. Regulatory reports are generally far more detailed than publications, so this would greatly improve transparency.

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

There is no evidence that the UK has a unique problem in this area or that it is managed better elsewhere. Gold plating the guidelines or adding further layers of bureaucracy and control will simply overburden an already creaking UK system. This will push research and sponsors elsewhere where less stringent guidelines exist and increase the risk of data misrepresentation.

February 2013

**Joint written evidence submitted by the Biological Secretary and Vice-President Jean Thomas
FRS and Physical Secretary and Vice-President John Pethica FRS (CT53)**

1. The Royal Society has noted the Committee's consultation on Clinical Trial data with interest. This is an area the Society has touched upon in its report *Science as an open enterprise* published in June 2012. The report addressed the broader issues around making scientific data intelligently open. This letter will be addressing the Committee's questions 3, 4 and 5.
2. The principal tenets of open data apply particularly to the topic of clinical trial data. This letter explains the reasons for this and why the UK should be opening up clinical trial data, the benefits and limitations of doing this, and the potential methods for doing it.
3. Open scientific data can benefit society in four main ways: it provides a layer of transparency that engenders public trust; it can quicken the pace of scientific discovery; it is a source of wealth creation; and it is a potential deterrent to scientific misconduct and fraud.
4. There are limitations to openness that need to be observed. In clinical trials where the data generated contains a large amount of personal information about individuals, limitations on the openness of that data are likely to be necessary for opening up the trial to outside parties. There are also occasions where the disclosure of data threatens security and safety and this is a legitimate reason for not opening up data, but must be explicitly stated. There are also legitimate reasons for embargoes of data for the purposes of commercial viability, but it is reasonable to expect the data to be made open within a specified time period.
5. Open clinical trial data would also lead to greater scrutiny of trial methodologies and chemical compounds. Clinical trials registries address the limits of what companies know about what is currently being (and has been) done, and would lead to more efficient use of resources. Clinical trial registries and compliance to them are vitally important.
6. There is also the concern, central to the movement to make clinical trial data open, that pharmaceutical companies conducting trials could selectively publish results, which may skew the understanding of how effective the clinical trials have been¹. There is evidence that this selective publication of clinical trial results can create favourable bias towards the uptake of a new drug². The partial reporting of clinical trials results distorts understanding and can be viewed as a form of scientific misconduct³. Partial reporting of data may be due to innocent error, but can also be fraudulent if data is cherry-picked to demonstrate a relationship that would not be apparent if the full dataset were used and published⁴. Non-reporting of trials slows down the progress of science and wastes public money.
7. In cases where it is essential for researchers to be able to access clinical trial data with personal information intact, there are ways in which this can be done safely and securely. "Safe Havens" are one method⁵, where there is a fixed physical point of access to data, and the dataset is prepared for the specific, limited needs of the researcher. However, issues around the permission for access to this information need to be clear to all parties.

¹ Hart B, Lundh A and Bero L (2012). Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses. *British Medical Journal*, 344, d7202

² Turner E H, Matthews AM, Linardatos E, Tell R A & Rosenthal R (2008). Selective Publication of Antidepressant Trials and its influence on apparent efficacy. *The New England Journal of Medicine*, 358, 252-260. Available at: <http://www.nejm.org/doi/full/10.1056/NEJMsao65779>

³ Chalmers I (1990). Under-reporting research is scientific misconduct. *Journal of the American Medical Association*, 263, 1405-1408.

⁴ Boulton, G., Rawlins, M., Vallance, P. and Walport, M. (2011). Science as a public enterprise: the case for open data. *The Lancet*, 377, May 14.

⁵ Thomas R & Walport M (2008). Data Sharing Review. Available at: <http://www.justice.gov.uk/reviews/docs/data-sharing-review-report.pdf>

8. It should be noted that GlaxoSmithKline announced in October 2012 that they were embarking on a programme of making their clinical trial data open starting with existing treatments and most relevant advances, then opening up their archive of trials⁶. They have also signed up to Ben Goldacre's initiative AllTrials.net to register all clinical trials and disclose their clinical trial results and clinical study reports^{7, 8}. This is a key development and GSK is to be commended.
9. The Royal Society continues to be interested in Open Data issues and awaits the outcome of the Committee's inquiry.

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⁶ http://www.guardian.co.uk/society/2012/oct/11/glaxosmithkline-clinical-trials-data?CMP=twf_fd

⁷ <http://www.alltrials.net/>

⁸ <http://www.alltrials.net/supporters/gsk-statement/>

Written evidence submitted by the Medical Research Council (CT54)

Introduction

1. The Medical Research Council (MRC) is a UK-based non-governmental organisation funded by a grant-in-aid by the UK tax payer. The mission of the MRC is to improve human health and support economic growth through supporting the delivery of world class medical research. The MRC has a long-standing interest in the development and implementation of clinical trials; and is a major funder of academic clinical trials in the UK and internationally. The MRC is grateful for the opportunity to provide evidence to the Committee and is strongly committed to transparency in registration and publication of clinical trials.

The MRC and Clinical Trials Funding

2. The MRC funds a wide spectrum of medical research from basic and preclinical work through experimental medicine studies to early proof of efficacy trials. It also provides support for a range of population based epidemiological and public health studies. In considering the area of this inquiry it is important to have clearly agreed terminology. The term '*Clinical trial*' includes trials of *investigational medicinal products* (IMPs) as defined in the current UK and EU legislation. However, the Committee will be aware that there are also clinical trials that assess the safety or efficacy of medicines not defined as IMPs or of devices or other interventions, such as surgical techniques or behavioural therapies. There are also *clinical studies* – a term that MRC uses to describe other research involving people, often with the aim of understanding the pathways to disease or health but not assessing the safety or effectiveness of interventions. The need for clarity in these definitions is very important in determining the optimal means of ensuring transparency of clinical trial findings and assessing whether these are appropriately adopted.
3. The MRC has a long history of funding early and late phase clinical trials conducted in the UK and internationally. In 2006 there was an alignment of the remits of the MRC and the National Institute for Health Research (NIHR) in clinical trials funding in England. The MRC has responsibility for funding first-in-man and early phase trials and NIHR has responsibility for funding later phase trials through the Health Technology Assessment (HTA) panel with intermediate (efficacy and mechanism) trials being funded under the joint MRC-NIHR EME programme. The MRC also funds Global Health trials, in coordination with DFID, at both early and later stages.

Clinical Trial Findings and Data

4. In relation to questions about publication and transparency it is again important that consistent terminology is used to allow clarity as to what is required from all involved in any aspect of clinical trials. The MRC considers it is important to differentiate between:
 - a. Clinical trial findings or outcomes – the final outcomes of the trial after appropriate statistical analysis. These should be published in accordance with the CONSORT guidelines¹, where these apply, and this is a requirement for MRC funded clinical trials.

¹ <http://www.consort-statement.org>

- b. Research Datasets – these range from aggregated to anonymised to complete identifiable datasets for each participant. The MRC requires researchers to allow access to their research data in accordance with the Data Sharing Policy².

MRC Funded Clinical Trials: Registration and Publication

5. The MRC is committed to promoting the highest standards of good practice in the conduct of the research that it funds. Prior to the adoption of the EU Clinical Trials Directive the MRC led the way in providing guidance on Good Clinical Practice for Clinical Trials (published in 1998) which included requirements for Independent Data Monitoring Committees and Trial Steering Committees for clinical trials. These two committees provide a very important role in independent review of clinical trial data, analysis and outcomes. The MRC was a founder member and has Board representation on ISRCTN – one of the first global clinical trial registers which accepts registration of all clinical trials assessing efficacy of any intervention (not restricted to IMPs) in people. The MRC also funds the CONSORT group which provides authoritative guidelines on transparent clinical trials reporting.
6. The MRC requires access to funded research data and sharing through policy requirements and supports this through the MRC Data Sharing Initiative³. The MRC has been a lead partner in development of Open Access to research publications. The MRC initially developed the MRC-DH Clinical Trials toolkit⁴ (now hosted by NIHR) and continues to provide authoritative advice and guidance on best practice in all areas of clinical research through the MRC Regulatory Support Centre⁵.
7. These initiatives support our commitment to best practices in transparent reporting and access to research data, however, there may be further needs to address gaps in this area and the MRC is committed to providing resource to address these, acting with relevant partners and stakeholders.
8. The MRC policy on publication of clinical trial (and other clinical study) results states that:

Results of MRC-funded clinical studies (whether positive or negative) must be published within a reasonable period (generally within a year of completion) following the conclusion of the study. Results should be reported in accordance with the recommendations in the CONSORT statement [Schulz et al. BMJ 2010;340:c332]. Data should be made available in line with the MRC Policy on Data Sharing.

9. In the MRC data sharing policy it is stated that:

The MRC expects valuable data arising from MRC-funded research to be made available to the scientific community with as few restrictions as possible so as to maximize the value of the data for research and for eventual patient and public benefit. Such data must be shared in a timely and responsible manner.

10. Advances in information systems, grant coding and tracking are making confirmation of registration of clinical trials more accurate and less resource-intensive. In order to establish a current baseline for registration and reporting of MRC funded work we are undertaking an initial review of registration and publication of outcomes for MRC funded clinical trials. The baseline position from this review will also provide the opportunity to identify whether and

² <http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/datasharing/index.htm>

³ <http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/datasharing/index.htm>

⁴ <http://www.ct-toolkit.ac.uk/>

⁵ <http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/RegulatorySupportCentre/index.htm>

how MRC policies and compliance review might need to be more explicit or stringent in relation to registration and publication. It is likely that there is scope for improvement in ensuring a joined-up approach from initial clinical trial registration to recording final outcomes and publications. The MRC is committed to supporting improvements that may be required, in partnership with other funders and sponsors across the spectrum of clinical trial funding.

Responses to the questions of the Science and Technology Committee

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?

11. The proposed revisions will address only interventional clinical trials of IMPs and so are not relevant to non-IMP clinical trials. The main regulatory barriers to clinical research in the UK have been reviewed by the MRC in partnership with other funders and academic societies. The MRC, on behalf of RCUK, submitted two responses to the Academy of Medical Sciences Working Group⁶ which published the report '*A New Pathway for Regulation and Governance of Health Research*'⁷. The MRC supported the recommendations in this Report which identified that there are barriers to conducting clinical trials in the UK that arise from the current Clinical Trials Directive. However, further significant barriers do not stem from the Clinical Trials Directive, but from other aspects of the complex regulatory framework for clinical trials and other clinical research in the UK. This is particularly marked for clinical trials that occur across several sites and for those that require access to patient data for follow-up of outcomes. The underpinning issues include a lack of clarity on roles which are often duplicative; requirements for multiple NHS R+D approvals; and the particularly complex framework relating to access to and use of NHS patient data for clinical research.
12. The proposed revisions to the EU Regulations have been welcomed by the MRC and partner organisations^{8 9}. As drafted, they will address many of the barriers that have arisen from the current Clinical Trials Regulations. In particular, the revisions allow for a more risk-proportionate framework and improved harmonisation of review of multinational trials.
13. However, there are remaining issues in relation to the scope of the revised legislation, for example, in its definition of interventional clinical trials; in the delineation of risk categories and the requirements for reporting adverse events. Many of the proposed amendments to the draft legislation from the Rapporteur are welcome in addressing these issues although there is a risk that some of the amendments will further increase the regulatory burden without improving protections for patient safety, rights and well-being. In particular we are concerned at an emphasis on publication of Clinical Study Reports (CSRs) as an assurance of transparency. Such reports are provided for marketing submissions but not for the vast majority of clinical trials in the academic sector where their provision can take at least three months. Therefore, requiring this for each academic clinical trial would be a significant burden on academic funders¹⁰. The CSR is unlikely to provide any more relevant information than ensuring publication of outcomes and access to appropriate final data, including the

⁶ Academy of Medical Sciences review of regulation and governance of medical research: Call for evidence: June 2010 - <http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC007048> and August 2010:

http://www.rcuk.ac.uk/documents/submissions/RegulationMedicalResearch_Aug2010.pdf

⁷ <http://www.acmedsci.ac.uk/index.php?pid=99&puid=209>

⁸ Joint statement on the Clinical Trials Regulation: <http://www.acmedsci.ac.uk/p47prid118.html>

⁹ MHRA consultation on the draft EU Regulation for Clinical Trials for Medicinal Products: December 2012: <http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC009007>

¹⁰ The MRC Clinical Trials Unit completes an average of eight trials a year. Provision of a CSR for each would require up to £100,000 per annum.

statistical analysis plan. The MRC will be submitting comments on the proposed amendments to the draft Regulations and can provide these to the Committee once available.

14. The proposed revisions will not address other regulatory barriers to research in the UK as outlined above, for example, access to records or Registers for follow-up of participants of a clinical trial. This currently requires approval from an NHS research ethics committee, from NHS R+D at each NHS Trust or body involved as well as the local Caldicott guardian and/ or s251 approval. These approvals are not coordinated so duplicative or contradictory views can be provided and the timescale for completion of approvals is often long. We are extremely concerned that proposed amendments from the LIBE Rapporteur on the draft European Regulations on Data Protection may make such research much more difficult, if not impossible.

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

15. The role of the HRA includes the role previously delivered by the National Research Ethics Service (NRES) in coordination of governance and guidance for the NHS research ethics committees (RECs) which provide review of clinical trials. In addition, the HRA will oversee the s251 approvals process through which researchers request access to NHS health records when explicit consent is not in place. The HRA is a relatively new body and so there has been a very short period over which to judge its effectiveness.
16. Prior to establishment of the HRA, NRES fulfilled a commendable role in developing consistency across RECs; providing governance and streamlining approvals such that a single REC approval applied to all clinical trial sites in the UK. In addition, development of the Integrated Research Approvals System (IRAS) is widely recognised as a very positive step to a single portal for applications for approvals of research studies.
17. To date the HRA has shown a commitment to continue the positive approach of NRES and also to commence a review of the processes and requirements for research approvals in the UK. The proposed pilot on facilitating NHS research approvals is very welcome. The effectiveness of the HRA in improving the clinical trials environment will be predicated upon its ability to conduct such a review; to ensure that its findings can be implemented and effective collaboration with other regulators, in particular MHRA. An optimal approach that will streamline research approvals in the UK while protecting participant safety and rights may require amendments to legislation or Codes of Practice as well as significant changes in how other Regulators and NHS Trusts deal with local and central research approvals.

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

18. There have been widely publicised examples of large fines imposed on pharmaceutical companies for not making relevant data available to Regulatory authorities. Where this has occurred there are potential risks to public health and to the progress of medical research in identifying new effective and safe therapies. Regulators need the most complete information available to take a balanced view as to the risk/benefit ratio of the use of a drug. In addition, other researchers benefit from knowing results from previous trials in order to avoid duplicative approaches. There may also be unidentified benefits of treatments in clinical trials that could be found from access to appropriate datasets. These last two benefits need to be balanced with the commercial interests of companies in proprietary data whereas the requirement of disclosure to regulators is absolute.

19. There have also been recent announcements of steps that companies are taking to increase transparency and access to trial data. One example is the recent announcement by GSK of its intention to allow access to clinical trial data¹¹.
20. The MRC collaborates in research funding with industry partners and considers this a valuable and important approach to medical research. Such collaborations are funded under an MRC Industry Collaboration Agreement (MICA) which includes agreement on publication of results and data in accordance with standard MRC policies with the potential to recognise a period of exclusivity for commercially privileged information¹²
21. It should be noted that there are also failures of non-commercial trials to publish outcomes or make data available in an appropriate and timely way. The factors and consequences of non-publication may differ from those relating to commercial trials. However, there is good evidence that trials which give negative results have been under-reported, leading to bias in the available body of evidence towards positive outcomes of new interventions. One consequence of this is seen when meta-analyses clarify from large, authoritative trials that the benefits of an intervention are lower than originally supposed, or absent altogether – revealing a waste of time and resources invested in conducting unnecessary further trials.

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

22. In order to ensure transparency for the public, regulators and other researchers, the MRC strongly agrees with the need for all clinical trials to be registered on publically accessible registers. This applies to all clinical trials of investigational medicinal products as an absolute minimum. However, there should also be registration of non-IMP interventional trials, as provided by, for example, ISRCTN. Other approaches to enhance registers and make them more accessible are also valuable - for example the NIHR sponsored Clinical Trials Gateway. The MRC, with other Research Councils also makes publically available the full portfolio of funded research alongside information on outputs¹³.
23. It should also be mandated that the outcomes of all clinical trials are published in peer-reviewed journals or otherwise made publically accessible - this is a requirement of MRC clinical trial funding. Further, there needs to be clear linkage of publications of the results to the registration in order to facilitate discovery of the relevant data and also to provide a straightforward check on compliance. There also needs to be a means for clinical trial findings that are not accepted for peer-reviewed publication or that are not completed be made publically available.
24. The MRC is committed to ensuring that clinical trials are registered and that outcomes are accessible and will provide additional support for this. It is important that approaches to registration and publication of findings are easily accessible to all ensuring that a full overview of open clinical trials is available to patients as are the outcomes of all clinical trials relevant to their condition. There are improvements that could be made to the current approaches to these and the MRC will support the development of improvements needed in this regard in relation to its remit in clinical trials support.
25. Once optimal systems are in place to allow discovery of which clinical trials have been undertaken and what their outcomes are, there also need to be mechanisms to ensure compliance with requirements for all clinical trials be recorded in this way. The MRC has

¹¹ <http://www.bmj.com/content/345/bmj.e6909>

¹² http://www.mrc.ac.uk/Fundingopportunities/Grants/MICA/Specification/MRC005438#P26_1314

¹³ RCUK Gateway to Research: <http://gtr.rcuk.ac.uk/>

identified that in order to implement effective monitoring of compliance there needs to be appropriate and consistent definitions of projects to be tracked; effective systems to track projects from funding to trial registration to outcomes and sufficient resources to complete the analysis. Many of the challenges can be addressed through improvements to evaluation and IT systems.

26. The MRC strongly supports the requirement for researchers to facilitate access to appropriate clinical trial data to inform and support further research and to review clinical trial findings. The mechanisms by which such access should occur are currently under discussion and expert reports from the Caldicott review, the Royal Society and European Medicines Agency (EMA) are due to be published in the first half of 2013 and will inform conclusions on the preferred model. It is clear that such access needs to provide a straightforward and timely route to disclosure of usable datasets that do not breach participant confidentiality; vitiate their consent or undermine data integrity. One approach, that MRC has endorsed, is to use 'safe havens' to store, collate and provide access to single or combined datasets. There are also examples of Centres of Excellence that facilitate access to requested data without transferring to a safe haven – as is the case for the MRC Clinical Trials Units. Whichever mechanisms are adopted, it is important to ensure that the data made available are high quality, reliable and provided in a usable format within a reasonable timeframe. The MRC has supported development of 'safe havens' and appropriate standards of research data for sharing through the MRC Data Sharing Initiative.

27. The question of whether these datasets should be made openly and publically available without any access "gatekeeper" or redaction is more complex. The key factors to be considered include the information and consent provided to and given by clinical trial participants; the risks of inadvertent identification of participants (particularly pertinent to smaller sample groups; rare diseases or stratified approaches). There is also the risk that data may be used for methodologically flawed research which may be linked to the original research group or funder to give an impression of quality or authority; or which might be used to promote agendas which the trial participants would not have consented to. In addition, there is a serious risk of deliberate misuse, such as deductive identification of trial participants to link to their health details or outcomes. The MRC's view is that the use of neutral 'safe havens' or Centres of Excellence to curate and provide data through an independent access procedure provides the best way of balancing the need to respect the concerns of participants; to ensure governance and ownership of research is clear; and to realise the benefits from broadening access to clinical trial data. The MRC has welcomed the increased emphasis on the potential benefits of research participation for patients in the NHS Constitution and recognises the desire of many people to be more aware of research outcomes and current clinical trials relevant to their condition. The MRC would welcome enhanced measures to make information about relevant clinical trials more easily available to patients, clinical teams and carers at the point of care.

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

28. The position in the EU is being reviewed by EMA building on its workshop in November 2012. The MRC does not have further specific examples to provide at this point.

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Written evidence submitted by Dr Ben Goldacre (CT55)

1. I am a medical doctor, currently working as a Research Fellow in Epidemiology at London School of Hygiene and Tropical Medicine. For the past ten years I have written about problems in science for the Guardian, and in two books: *Bad Science*, and *Bad Pharma*. I am also a co-founder of alltrials.net, a widely supported non-profit campaign group seeking to improve access to clinical trial results.
2. **Background:**
3. Healthcare professionals and patients need the results of clinical trials to make informed choices about which treatment is best. Currently, drug companies and researchers are allowed to withhold the results of clinical trials, on treatments currently in use, from doctors and patients if they wish to. This means that we are misled about the benefits and risks of treatments. We can be misled into prescribing an expensive new drug, for example, when in reality an older cheaper one is more effective. As a consequence, patients are exposed to avoidable harm, and money is wasted unnecessarily.
4. Withheld results are a problem for both industry and academic trials. The best currently available evidence, from the most current systematic review, estimates that only half of all trials are published, and trials with positive results are twice as likely to be published. A systematic review is the most robust form of evidence, since it is an unbiased overview of the evidence. This systematic review is published by the NHS NIHR HTA programme.
5. <http://www.hta.ac.uk/fullmono/mon1408.pdf>
6. The ongoing problem of withheld trial results has not been adequately addressed by any of the initiatives in place today. The FDA Amendment Act 2007, for example, requires that results for a subset of trials (one research site in the US, studying a currently licensed drug, etc) are posted at clinicaltrials.gov within one year of completion. This legislation is widely cited as evidence that the problem of missing trials has been fixed. However there was no routine public audit of implementation, and when one was finally conducted, and published in the *BMJ* in 2012, it found that this law has been ignored by four trials out of five.
7. *Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. BMJ. 2012;344:d7373.*
8. <http://www.bmj.com/content/344/bmj.d7373>
9. In any case, this and other interventions would have done little to improve medicine today, even if they were effective. This problem cannot be addressed prospectively, by ensuring access to trials finishing after 2008, or after 2013: around 85% of medicines prescribed in the UK are “generic”, and came to the market a decade ago or more. It is the evidence from this era of clinical trials that we need most – 2003, 1999, 1993 - to ensure prescribing today is safe and effective. In almost all cases (although perhaps not for aspirin trials six decades ago) this information still exists. Doctors and patients should be given access to it to make informed decisions.

10. **“What is the role of the Health Research Authority (HRA) in relation to clinical trials and how effective has it been to date?”**
- 11.
12. I am working with colleagues on low cost randomised controlled trials, seamlessly embedded in routine clinical care, using the General Practice Research Database, and have submitted a response with them on the separate issue of administrative barriers to doing clinical trials more efficiently in the UK.
13. So far ethics committees have not sought to address the issue of withheld trial results. This is problematic, as it is one of the key ethical problems in medical research. Patients participate in trials in the belief that they are helping to improve knowledge and treatments for future patients. Where trial results are withheld, those patients have been misled. I understand that Janet Wisely, the new head of the HRA, is keen to engage on this issue. In my view there are certain elements that should be laid down in the legislation for this body.
14. Research ethics committees should ensure that researchers do not have a previous track record of leaving trial results unpublished, before granting them permission to conduct further studies on trial participants. This can be done at almost no administrative cost, by simply requesting a signed statement from the lead medic or primary investigator that they are not withholding the results of any trials more than one year after completion. Similarly the HRA should insist on a commitment to publication, then publicly monitor and audit compliance. Again this would not require any significant administrative or investigative activity: an ethics committee can simply make a diary note, write to the primary investigator, and ask for a link to results publication, whether in an academic paper or on a results registry, one year after completion of the trial.
15. **“What evidence is there that pharmaceutical companies withhold clinical trial data and what impact does this have on public health?”**
16. I have addressed this in an attached memorandum, as suggested, because it is adapted from an earlier document which I initially drafted as a briefing note for Earl Howe, and then as a briefing note for alltrials.net.
17. **How could the occurrence and results of clinical trials be made more open to scrutiny? Who should be responsible?**
18. In my view there has been a widespread systemic failure by regulators, industry, universities, policy makers, and medical and academic professional bodies to take ownership of this problem. As a consequence we have seen an incomplete patchwork of interventions that have failed to address the core issue – we need doctors and patients to have access to all results of all trials on all currently used treatments. Instead we have engaged with peripheral details.
19. “Clinical trial registries” are a clear illustration of this problem. Registers are public lists that contain a small subset of all the trials that have been conducted on a medicine. They are incomplete by design. The European Clinical Trials Register is a list of trials conducted within Europe over the past few years. It is not a list of all the trials that have been conducted on all the medicines currently available in Europe. It should be, or it should at least strive to be. Clinicaltrials.gov, similarly, is mostly trials conducted in the US, mostly from the past ten years, and with compulsory registration only since 2007 (though even here compliance is uncertain). These limitations reflect the early administrative origins of these registries. They are not what trial registries should be, or need to be, to inform evidence based clinical practice, and to achieve the clear goal of access to all results.

20. The European Clinical Trials Register should simply be a list of all the trials ever conducted, on all the medicines currently prescribed in Europe. It should include results. Where and when these trials were conducted is irrelevant. It is clear to me, from my experience of talking to the public, journalists, doctors, policy makers and academics about these problems, that many people believe a trials register to be just this: a complete list of all the trials that have been conducted. This is indeed what they should be.
21. There are many stories of how companies have refused to hand over information. These in turn have generated discussions about what levers are available, and how we can force companies (in particular) to hand over trial results. I am struck that we have never tried simply asking, in a systematic fashion. The European Medicines Agency could say: "You have a marketing authorisation to sell your medicine in Europe. We maintain a list of all trials ever conducted on all uses of all medicines currently prescribed, so that doctors and patients can make informed decisions. Here are the forms: please tell us about all the trials you hold, or are aware of."
22. However there are many other stages where influence could be brought to bear. IQWiG, the German equivalent of NICE, has developed a reputation for demanding high standards of evidence before approving a drug for use, and also for requiring all trial results to be shared with them, and then making those public. It is through this mechanism that we have become aware of major problems with currently used medicines such as reboxetine.
23. <http://www.bmj.com/content/341/bmj.c4737>
24. We could use this more robust approach in the UK. We could also insist that a treatment is only available for prescription after all the trial results have been made publicly available.
25. Universities could also insist that all results are published, and that all collaborative contracts between academics and industry include the right to publish, and the right of access to data.
26. There is also the matter of culture. I am concerned that the impact of withheld results on patient care is currently a cultural blindspot in medicine and academia, even despite systematic review evidence showing that half of all trials do not go on to be published. It is a peculiar paradox that we spend so much money on each individual trial, investing huge effort to ensure that they are free from bias, carefully appraising their strengths and weaknesses, then allow so many of them to be simply deleted from the record. This non-publication reintroduces all the biases we spend so much time and money avoiding back into the evidence base.
27. We need wider recognition that this is a serious problem, and that it gravely undermines our attempts to practice evidence based medicine and make informed decisions. If a researcher selectively deletes the unflattering data points from one single trial, in order to massage the results and get the result they want, they are rightly regarded as being guilty of research misconduct. This is a serious business, since they are misleading doctors and harming patients. However, if a group of researchers delete whole trials from the overall research picture, then there are no reputational or professional consequences, even though we know that this will distort the apparent benefit of the treatment, just as surely as one researcher fraudulently manipulating the results of a single trial.
28. This could be addressed in part through medical and academic membership bodies. They could demonstrate leadership on this issue, state clearly that withholding the results of clinical trials is research misconduct, and impose sanctions or even ejection where appropriate.

29. I am concerned that currently most major UK medical and academic bodies have done the opposite. Many are currently signatories to a pair of documents produced by the “Ethical Standards in Health and Life Sciences Group” that give false reassurance around the issue of withheld trial results. The ESHLSG is co-chaired by the ABPI (the UK pharmaceutical industry body) and the Royal College of Physicians. Engaging with industry on ethical challenges is plainly a good thing. However the ESHLSG documents appear to make misleading statements about the problem of withheld results. For example they make extensive reassuring comments about current regulations, while failing to disclose the best currently available evidence, from fully published academic papers, in leading peer reviewed journals, which demonstrates that these regulations have been routinely ignored. I believe this issue may be covered in more detail in a submission by the “Bad Guidelines” group, but I am happy to give more details.

30. “Can lessons about transparency and disclosure of clinical data be learned from other countries?”

31. No. The European Clinical Trials Register is incomplete even by its own standards, with many trials still withheld from the public form of the register, and the EMA has failed outright to deliver on key objectives, such as their promise to carry results on their register by 2012. The US registry at clinicaltrials.gov is incomplete by design, as discussed above – it is not retrospective, and does not cover all trials on a treatment - and even for its limited remit the FDA Amendment Act 2007 has not been adequately implemented, with trial results still routinely withheld, as shown by Prayle et al 2012 referenced above. Even if similar legislation was perfectly implemented, and muscularly enforced, any beneficial impact of getting trial results from now onwards would only be felt in several decades’ time.

32. We need to ensure that doctors and patients have access to all results of all trials that have ever been conducted on all treatments currently in use, in order to make informed decisions about which treatment is best. We need serious working groups to discuss how to achieve this objective, urgently.

33. We need a credible public process to explore the details of the costs involved to industry and academia of retrospective disclosure, in either summary results form or Clinical Study Reports, where those exist. The EMA now discloses Clinical Study Reports on the small proportion of trials that they hold, and the European Ombudsman said that the administrative burden of doing so – and of removing some identifiable patient information where appropriate - is not significant. GSK have also committed to releasing Clinical Study Reports, in signing up to alltrials.net

34. I would also suggest a pilot of full disclosure, either for some commonly used drugs, or for some commonly used classes of drugs. This would allow us to identify any costs, the changes to the evidence base for current decisions, and therefore the public health benefits.

35. I believe Sir Iain Chalmers, co-founder of the Cochrane Collaboration, has made a submission on how he has been told this problem is being fixed for three decades now. There are many who use the reassuring language of “engagement” on missing trials, but act inconsistently. We should not lose momentum on this important public health issue.

36. Declaration of interests:

37. I am currently a Research Fellow in Epidemiology at London School of Hygiene and Tropical Medicine. I earn income as a doctor, academic, writer and broadcaster. In my work I discuss problems in science, including publication bias, which is a major theme in my book *Bad Pharma*. I am a co-founder of alltrials.net with the BMJ, Oxford University Centre for Evidence Based Medicine, the James Lind Library and Sense About Science. Alltrials.net is a

non-profit campaign group to improve access to clinical trial results with extremely broad support.

February 2013

Written evidence submitted by the Wellcome Trust (CT56)

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 available.

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.

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 Directive¹ 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.
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

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

trials of investigational medicinal products.² 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 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.

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

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 2006.³ 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.

March 2013

³ www.ukcrc.org/index.aspx?o=2874

Written evidence submitted by the Royal College of Physicians (CT57)

The RCP welcomes the opportunity to respond to the House of Commons Science and Technology Committee's inquiry into clinical trials and disclosure of data.

The RCP is progressing its work in relation to this issue, and other ethical issues relating to the relationship between health professionals and the life sciences industry, as part of the Ethical Standards in Health and Life Sciences Group (<http://www.eshlsg.org/>). This is a cross-sector group, consisting of 20 organisations, that aims to evolve the relationship between healthcare professionals and commercial life science organisations to ensure that it meets the expectations of stakeholders and creates a platform for increased collaboration and partnership for the benefit of patients. The group is underpinned by the belief that the best way to improve this relationship is through collaboration and draws its membership from the health and medical community and the pharmaceutical, medical device and diagnostic industries in the UK.

We welcome the committee's inquiry into this important issue and the opportunity to provide input. The RCP is committed to raising standards and clinical research is vital to improving patient care. We welcome the government's commitments to place research at the heart of the NHS. Clinical research studies are a vital part of establishing whether a medicine or healthcare product is safe and effective. It is important that UK retains its world leading status in health research and remains an attractive place to carry out clinical trials. We welcome efforts to improve the EU legislation on clinical trials to ensure that genuine harmonisation is delivered across the EU, as outlined a recent joint statement, to which we were a co-signatory, with other supporters and funders of health research.¹

We are supportive of the objective to see full disclosure of clinical trials results. In 2012, the ESHLSG published a statement on clinical trials transparency, 'Clinical Trial Transparency Principles and Facts'.² This document is currently under review; however it stresses our belief that investigators involved in clinical trials have an obligation to report the trial in a timely and non-biased manner. There is a moral responsibility to study participants and society to share results freely – and thus assist in the development of further research involving better trial design, fewer patients and to avoid unnecessary duplication.

There are a number of legal and voluntary accountabilities that currently exist to deliver clinical trials transparency. Unfortunately, not all of these measures are as effective as they should be and the evidence demonstrates that the results of many clinical trials are not published in a timely manner. Greater adherence to these procedures, accompanied by monitoring to assess compliance and appropriate sanctions to drive positive behaviours, could play an important role in progressing towards greater clinical trials transparency. The committee will need to consider how this can be achieved and whether further measures are also needed.

Serious consideration needs to be given to *how* we can achieve and enforce effective clinical trials transparency. Indeed, this is a topic of current discussion for the ESHLSG. Implementing a system of full disclosure will have implications, for example in terms of cost, time commitment and feasibility. This should not, of course, deter efforts to deliver transparency, but will require development of realistic goals in terms of what should be published, when and how. In addition, the legal and voluntary accountabilities currently in place do not address the important issue of retrospective data publication, which is key to enabling decision-makers to draw conclusions based on all the evidence and consequently to make decisions that are in the best interests of patients. Serious consideration is therefore also required as to how retrospective publication should be delivered.

The potentially forceful influence of health professionals should also not be underestimated. Those who take part in trials are in a position to hold the companies to account and to ensure they are delivering on transparency. We see such principles as key to the collaborative approach of the ESHLSG.

¹ http://www.rcplondon.ac.uk/sites/default/files/documents/2012_joint_statement.pdf

² For more: <http://www.eshlsg.org/our-work/#clinical-trials>

The ESHLSG's work to evolve the relationship between healthcare professionals and industry will only succeed if it is built on transparency. The ESHLSG is currently also working to address such transparency in additional of areas, including:

- The disclosure of financial relationships that exist between the life sciences industry and health professionals. We are currently carrying out a consultation on this topic.³
- Pharmaceutical support for medical education. We recently undertook an online survey seeking views on this topic from healthcare professionals, to inform our work.

February 2013

³ For more: <http://www.eshlsg.org/our-work/#payments-to-health-care-professionals>