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Clinical trials

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Additional written evidence

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Science and Technology Committee

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List of additional written evidence

		Page
1	Michael Power	Ev w1
2	Global Alliance of Publication Professionals	Ev w6
3	Cochrane NI Review Group	Ev w9
4	Margaret McCartney	Ev w13
5	Andrew Russell and John Hughes, Patient & Public Member, UKCRC Board	Ev w14
6	London School of Hygiene & Tropical Medicine	Ev w15
7	Stephen Senn	Ev w16
8	Christopher Lawrence Roy-Toole	Ev w18, Ev w24
9	The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust	Ev w27
10	Dr Elizabeth Wager	Ev w28
11	Sir Iain Chalmers	Ev w30
12	Sir Alasdair Breckenridge	Ev w33
13	Privacy and Clinical Trial Data	Ev w36
14	Trial Steering Committee	Ev w36
15	Cochrane Collaboration Individual Participant Data Meta-analysis Methods Group	Ev w39
16	Regius Professor of Medicine, Professor Sir John Bell FRS, FMedSci	Ev w43
17	Centre for Evidence-Based Medicine, University of Oxford	Ev w45
18	Medical Schools Council and Association of UK University Hospitals	Ev w49
19	PLOS	Ev w51
20	Parkinson's UK	Ev w55
21	Glyn Moody	Ev w56
22	Cardiff University School of Medicine and Cardiff and Vale University Health Board	Ev w57
23	The Migraine Trust	Ev w59
24	National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre	Ev w60
25	NHS European Office	Ev w61
26	BioIndustry Association (BIA)	Ev w63
27	General Medical Council	Ev w67
28	Committee on Publication Ethics (COPE)	Ev w68
29	British Heart Foundation	Ev w70
30	King's Health Partners	Ev w74
31	BioMed Central and Current Controlled Trials	Ev w77
32	Healthy Skepticism UK (HSUK) and Health Action International (HAI) Europe	Ev w80
33	UKCRC Registered Clinical Trials Units Network	Ev w84
34	UK Research Integrity Office	Ev w86
35	Ethical Medicines Industry Group (EMIG)	Ev w89
36	Dr Mark Edwards FRCA FSB	Ev w96

37	NICE	Ev w98
38	PatientsLikeMe UK	Ev w99
39	PharmAware	Ev w103
40	Association of Medical Research Charities (AMRC)	Ev w107
41	The Cochrane Collaboration & the Centre for Reviews and Dissemination	Ev w111
42	Clinical Contract Research Association (CCRA)	Ev w117
43	Royal Society	Ev w119
44	Royal College of Physicians	Ev w120
45	Royal Pharmaceutical Society and the National Pharmacy Clinical Trials Advisory Group (NPCTAG)	Ev w121
46	Empower: Access to Medicine	Ev w122

Written evidence

Written evidence submitted by Michael Power

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 two years of the planned termination date, or within two 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 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 reported[3] 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.

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

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

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*
Medical Research Council Good research practice: Principles and guidelines August 2012 www.mrc.ac.uk/consumption/idcplg?IdcService=GET_FILE&dID=36739&dDocName=MRC002415&allowInterrupt=1	**Weak** "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"	**Nil** "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)."
International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. Good Clinical Practice: ichgcp.net	**Nil**	**Nil** "2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation." 3.1.2 The IRB/IEC should obtain the following documents: 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 (eg advertisements), written information to be provided to subjects, 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.

Institution *Policy/guidance*	*Statement that data must be made available*	*Statement that informed consent should include making data available*
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	**Nil**	**Nil** "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: — 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."
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	**Nil**	**Nil** "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."
University of Newcastle Research and Enterprise Services Consent Form www.ncl.ac.uk/res/research/ethics_governance/ethics/toolkit/consent/consent_form.htm	**Nil**	**Nil** "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: … — 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**

Institution *Policy/guidance*	*Statement that data must be made available*	*Statement that informed consent should include making data available*
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/Pages/default.aspx The concordat to support research activity www.universitiesuk.ac.uk/Publications/Pages/concordattosupportresearchintegrity.aspx	**Weak** "Transparency and open communication in … in making research findings widely available, which includes sharing negative results as appropriate…"	**Nil**
Government Office for Science (www.bis.gov.uk/go-science) *Rigour, Respect, Responsibility: a Universal Ethical Code for Scientists* 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 products12, 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 … duly substantiated reasons for submission of the summary of the results of the clinical trials after more than one year	**NIL**

Written evidence submitted by the Global Alliance of Publication Professionals

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 two 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 five studies that compared industry-sponsored studies with independent studies, three 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 one 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

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Written evidence submitted by the Cochrane NI Review Group

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 update,[3] 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 eight 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 review.[4]

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 reports.[8] 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 three 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 Tamiflu[10]. 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 production.[10] 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 (eg pneumonia) and person-to-person transmission unproven.[10]

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 three 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" ie *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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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 1998–99. 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 €1,500 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: IJRSM 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 2008–09. 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 M A, Jefferson T. Rethinking credible evidence synthesis. BMJ 2012;344:d7898 doi: 10.1136/bmj.d7898*

10. Jefferson T, Jones M A, 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, 10 April 2012. URL: http://www.nytimes.com/2012/04/11/opinion/drug-data-shouldnt-be-secret.html Shortened URL: http://nyti.ms/Ivgh9c

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

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 Practioners. 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 two 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.

4. 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

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 (CRPD)

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 three 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

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.[4]

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.

[4] 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.

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; and*

(e) *the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject.*

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".[5,6]

(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), five 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

Written evidence submitted by Stephen Senn BA, MSc, PhD, CStat

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).[7]

[5] 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.

[6] 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

[7] Details of my qualifications and experience are available at http://www.senns.demon.co.uk/Consult.htm

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.

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

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Written evidence submitted by Christopher Lawrence Roy-Toole

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.

Evidence

Name of the Beast

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.

Failing to Consult

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"*.

Repeating "Mid Staffs"?

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 19 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.

Holes in the Safety Net

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*?

"Northwick Park" and the Cloud of Unknowing

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.

No Benefit Yet

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?

"Two Legs Bad, Eight Legs Good"

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".

Misadventures in NHS R&D

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.

Converge or be Damned

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.

Publication or Penalties

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?

'Toothless Publication Tigers'

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.*

New Job for the MHRA

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 Versus Private Interests

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.

Data Access under the Regulation

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?

European Freedom of 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.

Fast Track Information Access for 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 Christopher Lawrence Roy-Toole

EXECUTIVE SUMMARY

The Joint Committee on the draft Care and Support Bill has already produced a report on the role of the Health Research Authority in ensuring transparency in research. But the ill-considered nature of its findings makes it more of a hindrance than a help to the Select Committee looking at Clinical Trials.

The Joint Committee's recommendation to place a statutory duty on the HRA to police research transparency overlooks the impact of the UK Freedom of Information Act and its exemptions from publication. The Information Commissioner makes decisions regarding FOI. So why is the Information Commissioner not being put at the centre of this? An expanded role for ICO would sit well with the recent recommendations of the House of Commons Justice Committee.

The Select Committee should hear evidence from members of research ethics committees before saddling them with any fruitless obligation to ensure research publication.

Any attempt by any agency to compel research publication is hampered by the lack of statutory powers. So this means that a consideration of US legislative solutions is central to this debate.

Lord Warner and the Joint Committee failed to spot the real solution to the problem. Unless ethics committees are put at the centre of the regulatory process, then the UK will be inefficient in competing with European rivals and it will be ineffective in protecting its patients. A proper and full inquiry into the Northwick Park Disaster might have revealed why ethics committees are still unfit for purpose. So the Select Committee should ask some probing questions about TGN1412.

The solution now is to examine real single regulator models that allow ethics committees and competent authority to work together within the narrow timeframe set by the proposed EU Regulation. Looking at streamlining NHS R&D processes is a quixotic distraction that we can ill afford.

EVIDENCE

1. This is additional written evidence to the Commons Select Committee, to be read alongside my original submission. These are the reasons behind it. On 19 March 2013, the Joint Committee examining the draft Care and Support Bill published its report [HL Paper 143 HC 822]. In it, the Joint Committee made recommendations affecting the roles of the Health Research Authority and the research ethics committees in the context of transparency in research. So I sent emails to the Clerks to both Committees expressing my concern at these recommendations. Amongst other matters, I thought that there was an obvious overlap between the work of the two Committees and a clear risk that each might arrive at an inconsistent or erroneous result. On the strength of these concerns, Victoria Charlton, the Committee Specialist, has allowed me to make an additional submission to the Select Committee about those matters that fall within its terms of reference. I also include

reference to recent publications and events that are relevant to this Inquiry. I would like this submission to be published if possible.

2. I challenge some of the comments and conclusions that were made in the course of the Joint Committee's oral evidence sessions and its report on the draft Care and Support Bill. Specifically:

(a) That under the draft Bill, the HRA should be given a "statutory objective" to ensure full publication of research results, consistent with the legal duty of patient confidentiality [Report paragraph 335]. The HRA is the wrong body to do it because it does not have the right legal powers.

(b) That under the draft Bill, the research ethics committee must be given guidance that places them under an obligation to ensure that ethical approval conditions for the publication of research are complied with [Report paragraph 336]. The REC has neither the opportunity nor the resources to do it.

(c) That research ethics committees are guilty of "mission creep" when they engage in their own review of the scientific merits of a research proposal and that steps must be taken to stop them, by legislative provision under the Bill if necessary [Lord Warner Q.299]. This is a complete fallacy. The REC should be given support in this aspect of their work by ensuring closer collaboration with the MHRA. If we do not do it, then the UK's competitors may well take the lead.

3. The Joint Committee has stated that the HRA should have a statutory objective to ensure publication of research results. By statutory "objective", I assume that means a statutory duty. If there is to be a statutory duty then there must be penalties that can be put upon the HRA if it fails to comply with that duty to ensure research publication. But the HRA and the REC cannot compel anyone to publish anything without a legislative power to penalise the research sponsor who fails to publish research results without good reason. And this they do not currently have. The need for legislative support was hinted at in the responses to Question 31 of the oral evidence on the draft Care and Support Bill. But no one mentioned the US experience with the Food and Drugs Administration Amendments Act 2007. So this question should now be at the centre of the Select Committee's inquiry into transparency in research.

4. By implication, if the HRA must be penalised for failing to ensure transparency in research, then those penalties must also be visited upon the unpaid volunteers in the research ethics committees. This is a prospect that can only set back future recruitment to the committees. So it would have been more useful for the Joint Committee to have taken evidence from members of research ethics committees as to whether they considered themselves to be capable of discharging this suddenly emerging burden. It is significant that in her haste to build a small administrative empire for the HRA, its Chief Executive did not bother to consult with the rank and file REC membership as to whether they thought that they could ensure transparency for a research sector in which other institutional players had already failed. And the members of research ethics committees were absent from the Department's circulation list of stakeholders who were consulted on the content of the draft Care and Support Bill. So if the Select Committee are insistent on following the Joint Committee's recommendation to make a small monthly committee of part-time volunteers responsible for policing the publication ethics of the global pharmaceutical industry, then I suggest that they first hear oral evidence from some members of those research ethics committees about what can and cannot be done. The point is that the research ethics committee has already finished its job and has exhausted its effective powers by the time that one might expect publication to occur.

5. The Joint Committee's recommendation to make the HRA responsible for publication of research results demonstrates a lack of knowledge of the legal impediments that stand in the way of it. The guarded enthusiasm of the HRA Chief Executive for a statement to that effect to be included in the Bill demonstrates a lack of facility with the legislative environment in which she and her subordinates are now expected to operate [Oral Evidence Q.291]. The Select Committee must undo the damage that the Joint Committee and the HRA Chief Executive have done by re-examining the legal fundamentals of the problem of compelling transparency in research.

6. As I have stated in my first submission to the Select Committee, the HRA is not a suitable choice to police the publication of research results because it has no powers of inspection, seizure or audit of any document or person outside an ethics committee. This is why I have recommended that the MHRA should be the prime choice to police the publication of research. But the real problem is that a duty to publish research results cannot be separated from the countervailing legal duty to protect the intellectual property rights of the sponsor or the researcher. This balancing of competing interests is already reflected in and managed by the UK Freedom of Information Act 2000. The Information Commissioner has the legal responsibility to decide whether information should be disclosed to the public or withheld pursuant to a FOI request. Any decision to publish research results would first have to consider whether there is material in it that the law requires to be withheld. So there is no sense in giving the HRA prime responsibility to ensure transparency when it has no legal powers to decide what can and cannot be published pursuant to a FOI request. FOI was never mentioned in the course of the Joint Committee's deliberations on the role of the HRA in research transparency. Recent cases commenced before the European Court of Justice by *Abbvie* and *Intermune* might go on to clarify the limits of transparency when measured against the protection of private legal interests [Cases T-44/13, T-73/13, T-29/13].

7. The need to police transparency in research raises the distinct prospect of an expanded role for the Information Commissioner or his Office. In the most recent time, the House of Commons Justice Committee has published its report on the functions and powers and resources of the Information Commissioner [HC 962]. The Select Committee need to take account of recommendations that the Information Commissioner be funded by Parliament and made directly accountable to Parliament, and that the Information Commissioner be given powers to compel a data audit of NHS organisations. All this supports the case for placing the Information Commissioner and the MHRA, not the HRA, at the centre of plans to compel research transparency. Expanding the role of the HRA without the support of relevant statutory powers is merely to create another puffed-up Quango that is likely to fail to deliver and within a short time.

8. My key recommendation is for something akin to a true single regulator for clinical trials that can combine the role of ethics committee and national competent authority to deliver a decision within the fastest time. The comments made by Lord Warner in the Joint Committee Inquiry seem to overlook this possibility entirely and in fact to work against it. Remember that Lord Warner chaired the review that produced the *Report of the Ad Hoc Advisory Group on the operation of NHS Research Ethics Committees* in 2005. This report was predicated on the wrong-headed assumption that the ethics committee should not reach decisions based on scientific review. The Warner review assumed that there could be a functional separation between the people examining the scientific merits of the research and the people who examine the ethical implications of it. Lord Warner and the other apologists for functional separation have never, as far as I am aware, cited any authority for their assumption and have never satisfactorily justified it.

9. The "Northwick Park Disaster" occurred soon after the publication of the Warner report. The worst clinical accident in over two decades would have been a timely opportunity to test the assumptions about the role of the ethics committee in dealing with scientific review. Given the management breast-beating that followed the NHS Mid-Staffs Inquiry, it is noteworthy that no public autopsy was held to examine the role of the Brent MEC in the approval that it gave to the TGN1412 protocol. *I want the Select Committee to ask the Department of Health and HRA/NRES why no such public inquiry was held, or why no public report was issued, that put the role of the research ethics committees and the quality of their management into the media spotlight.* If the Select Committee concludes that there has been a lack of transparency over Northwick Park, then we are faced with the grim irony that the institution or institutions that might be found to be at fault could in substance be the same as those now charged with the task of overseeing transparency in others.

10. The true significance of TGN1412 is therefore at risk of being buried and overlooked. It is that research ethics committees cannot do a proper job unless they are put at the centre of the information flow about the safety of test drugs and the "state of play" about existing research already conducted into those drugs. Only in this way can unsafe and unnecessary research be weeded out. This means close cooperation with the national competent authority that is the first and best source of this information. If the Select Committee reads the Duff Report, they will see that improving the information flow between ethics committees and regulators was one of the prime issues identified for further action. Yet this is the one thing that the HRA currently overlooks. There is no real initiative to enable REC and MHRA to share information in real time. The HRA Chief Executive confirmed to the Joint Committee that less than 5% of ethics committees have *any sort* of scientific review before them when they deliberate on a research application. This should have been the core priority and core function of the people who are meant to run the research ethics committees. But they have neglected this in favour of other "collaborative stakeholder initiatives" that make for better sound-bites. There is indeed "mission creep", but the ethics committees are not the ones engaged in it.

11. The delivery of close collaboration between ethics committee and competent authority is the most important strategic element of the research governance framework. But the Department, the HRA, and the Joint Committee have all overlooked this fact. Others have not. The Belgian competent authority has stated publicly that "*ethical and scientific reviews of clinical trials must be run simultaneously*" and it called for the inclusion of ethics committees in the Part I assessments of clinical trials under the proposed EU Clinical Trials Regulation. FAMHP sees the proposed regulation as an opportunity for competent authorities and ethics committees to reorganise themselves to be responsible for clinical trials "*hand in hand*" [see comments of Dr. Greet Musch at the EuropaBio Conference *The Future of Clinical Trials* on 28 January 2013].

12. The amendments to the EU Clinical Trials Regulation put forward in the ENVI report of 31 January 2013 demand that the ethics committee be included in the Part 1 assessment procedure. The turnaround time for completion of the Part 1 assessment is very short: in any case no more than 30 days. It is hard to see how any EU member state could comply with the ENVI proposals unless ethics committee and competent authority are cooperating right from the start. The single regulator concept is the obvious way to do this. But because of their skewed priorities, those in charge risk putting the United Kingdom at the bottom of the league table when it comes to the rapid start up of multi-national clinical trials.

13. If there is any ray of sunshine in this, it is that the draft Care and Support Bill allows for any group of persons to apply to the HRA to be approved as a research ethics committee [Draft Bill clause 71]. *In theory, the MHRA could seize the initiative and seek to establish its own internal research ethics committees in order to better comply with the new requirements emerging from Europe*. If the HRA refused to recognise these ethics committees, perhaps because of a perceived threat to its own monopoly in this area, then it might be

possible to subject the HRA to legal challenge by way of judicial review. The Select Committee should put these propositions to the MHRA in terms.

April 2013

Joint written evidence submitted by The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust

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?*

The EU Clinical Trials Directive has increased the regulatory burden on clinical trials, making them slower to set up and more expensive to run. The drafted revisions do attempt to ease the regulatory burden in some respects, but don't go far enough and aren't clear enough. In particular, the revisions make only a crude attempt at distinguishing between the different levels of risk that trials present, and so fail to properly reshape the directive's flawed, one-size-fits-all approach to trial regulation.

Our specific comments are as follows:

Scope The scope of the directive is not effectively clarified. The definitions provided (clinical study versus clinical trial versus non-interventional study) are confusing, which risks them being applied inconsistently across the EU and could even widen the scope of regulation.

Risk The draft introduces the concept of "low interventional" trials (trials using drugs within their licensed indications or where their use is considered standard practice), which could be eligible for lighter-touch regulation. All other drug trials are considered to pose the same level of risk—so use of a well-established drug in a slightly different patient group from the one it is licensed for is treated the same as use of a novel therapeutic supported by little safety data. But for regulation to be proportionate, it needs to take into account other factors influencing risk including the safety profile of the drug and the patient population involved. In the UK, the MHRA and academic community have already established a three-tiered system adapting safety reporting and other elements of trial conduct to the level of risk, and we would like to see this approach refined and adopted by the EU.

Streamlining authorisations and approvals: The draft describes a streamlined process for authorising clinical trials and approving modifications through a single application via an EU portal and a single decision within each member state. But it is unclear how this will work in reality because of a lack of detail. Establishing such a system is likely to be costly and time-consuming for regulators and sponsors, and the lack of detail could result in divergent implementation. Ensuring a robust and reliable IT system which is compatible with national infrastructures will also be a major challenge.

Safety reporting: The draft does little to reduce the burdensome and duplicative safety reporting requirements for sponsors. Instead the reporting burden is increased with sponsors required to report all serious adverse events (rather than just those that are unexpected and related) to participating investigators at the end of the trial, and to report all serious adverse reactions to the marketing authorisation holder. This will be onerous and difficult to comply with, particularly where combinations of therapies are being evaluated or generic drugs are used. Nor do the revisions allow for a risk-adapted approach to safety reporting.

Sponsorship and indemnity: The revisions make a number of proposals which we feel should make it easier to collaborate internationally. We welcome the formal introduction of co-sponsorship, a model employed by non-commercial organisations in the UK but not widely recognised by other member states. The draft also clarifies the role of the EU contact person for sponsors established outside the EU and introduces a national indemnity mechanism across member states.

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 HRA only came into being on 1 December 2011 and it is too early to tell how well it is doing, although it does face some significant constraints. It has a separate set of responsibilities from the MHRA, whereas there had been hopes that those responsibilities would be brought together within a single organisation, with a clear remit for global R&D. The HRA also has responsibility only for England and Wales, and in Scotland approval mechanism for trials remain different. On occasion that has acted as a barrier to collaborations between researchers in different parts of the UK.

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

It is difficult to provide clear evidence that pharmaceutical companies are burying data. However, some of our senior clinicians have expressed concerns over instances where publication of data has been delayed, and there is a more general perception that if a pharma-sponsored trial has produced negative results, there is less impetus to see it published. These concerns relate in particular to formal, peer-reviewed publication in a

journal—trial data is normally presented in an abbreviated form at conferences where there will be public acknowledgment and discussion of the results.

Trials are sometimes stopped early because the benefits of a treatment appear to exceed pre-defined criteria. In these cases, sponsors should be encouraged to publish longer-term data in full and in a timely fashion. There are agreed procedures for deciding when to stop a trial early, but even so early analyses can be dominated by outcomes in a particularly sensitive sub-population, and striking early benefits may be attenuated once more mature results are available. If only the initial analysis of a trial is published, doctors and patients may gain a misleading picture of a drug's benefits and side-effects.

Assessment of safety data is critical in determining the overall risk/benefit ratio of any treatment and lack of access to full trial data could have a major adverse impact on public health. If trial results finding little benefit for a drug or concerning levels of side-effects are not published, there is potential for patients to receive ineffective or even dangerous treatments.

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

We would support some form of action to ensure trial results are published, in order to avoid deliberate or accidental publication bias. It will be important for regulators to monitor the expected completion dates of clinical trials, and any discrepancy between the number they have registered and the number which end up publishing their results. Ensuring registration on a trial registry such as clinical trials.gov makes available the status of the trial and would normally provide an approximate timeframe for the presentation of initial or final trial data. Use of databases like this can increase transparency in access to data. A legal requirement to publish clinical trial data within a certain timeframe might also reduce the potential for delayed publication of unfavourable results.

Currently, even a full trial publication may only present selected safety data. Any potentially serious adverse event that could be related to the study drug should normally be flagged, but there remains the potential for under-reporting. Trial sponsors are expected to provide study data in response to requests from researchers conducting meta-analysis of trials, but there can be delays in doing so, sometimes for technical reasons such as the failure of the original consent forms to cover secondary research. Legislative pressure to make all safety data available could help ensure that unfavourable safety data is not withheld. One possible way to prevent under-reporting of adverse events would be for journal publications to provide the entire safety listing as a supplementary online file, for open public scrutiny. However, moves to provide open access to raw trial data do need to be balanced against the requirement to avoid any breach of patient confidentiality.

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

Clinical trials are conducted and published in an international arena, and in general concerns about access to trial data relate not to UK law but to the approach internationally. Some countries may place a greater emphasis than others on transparency of data as opposed to patient confidentiality, but if anything the UK is more open to data access than most.

But the UK's regulatory authorities can play an important role. It should be possible to demand publication within a certain time limit for trials that have authorisation and there could be closer scrutiny of the completion rate of studies, which some analysis suggests is low. Regulatory authorities do continue to look at data on effectiveness and side-effects even after a drug has a licence, and must continue to be prepared withdraw a drug's licence if concerns arise about its risk/benefit ratio.

February 2013

Written evidence submitted by Dr Elizabeth Wager

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 2002–09 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 (ie 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 nine drugs approved by the FDA (the US regulator) in 2001–02. 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 (2002–11) 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); and

— 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 2007–08) 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

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

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Written evidence submitted by Sir Alasdair Breckenridge

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 shortbackground 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), and
- 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 reguated 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 ther 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 an 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 eg, "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 roles 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, ie 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 (eg 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

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

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 (ie 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 eg 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 (eg 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 (three to four 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 five 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; and

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 competiveness 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.

TP van Staa—Chair of Pharmacoepidemiology, London School of Hygiene & Tropical Medicine

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Gary Simons—Patient Representative on the Trial Steering Committee

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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.

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Written evidence submitted by Cochrane Collaboration Individual Participant Data Meta-analysis Methods Group

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 eg 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 polices 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

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 in 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.

February 2013

Written evidence submitted by the Centre for Evidence-Based Medicine, University of Oxford

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 2011/20/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 (one 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 seven-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 two 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 three-fold increase in mortality of 34 deaths among 1,069 rofecoxib patients compared to 12 deaths among 1,078 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 1,067 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 $2.5 billion 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. GSKs 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 publically.[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 form 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

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Written evidence submitted by Medical Schools Council and Association of UK University Hospitals

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.[8] 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 (eg 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 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

[8] Annex 1—Not printed

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 (ie once analysed, verified and peer reviewed).

5.1.4 **Which trials?:** CTIMPs, Devices trials and other interventional trials (eg 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 (eg 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 (eg 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*.[9] 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.

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*[10] 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.

February 2013

Written evidence from PLOS

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.

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[9] http://www.bmj.com/about-bmj/resources-authors/article-types/research

[10] http://www.universitiesuk.ac.uk/Publications/Documents/TheConcordatToSupportResearchIntegrity.pdf

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" (eg, 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 1 July 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 polices 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.

February 2013

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Written evidence submitted by Parkinson's UK

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 lumber 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 in be more strongly and precisely framed. We recommend that clear standards should be developed for what the summary needs to contain eg 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.

February 2013

Written evidence submitted by Glyn Moody

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.

February 2013

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

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 four week 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 six 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 (eg 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 disfavours 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 three 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 three 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; ie 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

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 eight 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

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 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 results[11]).

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.

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

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%[12]), 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.

February 2013

Written evidence submitted by NHS European Office

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% 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.

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

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)

(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 atracuronium, 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 £7 million 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	£14 million 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 C. difficile.
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% 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

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.*[13]

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,*[14] which covers, for example secondary uses of data; and *0–18 years*,[15] 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.

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.

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[13] http://www.gmc-uk.org/static/documents/content/Research_guidance_FINAL.pdf
[14] http://www.gmc-uk.org/static/documents/content/Confidentiality_0910.pdf
[15] http://www.gmc-uk.org/static/documents/content/0–18_0510.pdf

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 1 July 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.

February 2013

References/Notes

[1] Committee on Publication Ethics (2013). Available: http://www.publicationethics.org Accessed 17 February 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 17 February 2013

[4] van de Wetering F T, Scholten R J P M, 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 R F, 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 17 February 2013

[7] The CONSORT Statement Website. Available: http://www.consort-statement.org/ Accessed 17 February 2013

[8] EQUATOR Network (2013). Available: http://www.equator-network.org/ Accessed 17 February 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 D G, Arnalz J A, Bloom J, Chan A-W, Cronin E, Decullier E, Easterbrook P J, von Elm E, Gamble C, Ghersi D, Ioannidis J P A, Simes J, Williamson P R: 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

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.[16]

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.[17] 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 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.

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

[17] 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

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*.[18] 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 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.

[18] British Heart Foundation. Clear and present data; 2012. Available at: http://www.bhf.org.uk/patientdata

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.[19] The finding led to a dramatic reduction in the usage of these agents, particularly in Europe and Australasia.[20] 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 lorcainide 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 lorcainide 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.[21] This highlights the importance of publishing results from clinical trials, as this mortality link could have potentially been established earlier. The issue of pharmacovigilence—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 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 six 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.[22] 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

[19] Echt D S, Liebson P R, Mitchell L B, Peters R W, Obias-Manno D, Barker A H, Arensberg D, Baker A, Friedman L, Greene H L. 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

[20] Campbell T J, Williams K M. 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/

[21] Cowley A J, Skene A, Stainer K, Hampton J R. The effect of lorcainide 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

[22] http://ec.europa.eu/health/files/eudralex/vol-10/2012_302–03/2012_302–03_en.pdf

Protection Study took substantial time to write, at a time when those that conducted the trial were conducting other trials during this period.

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 King's Health Partners'

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 (eg 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.[23]

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. Academics 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

[23] http://www.bmj.com/content/346/bmj.f105#aff-1

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 (eg 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 (ie 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 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 5th February (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

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No interests to declare

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Written evidence submitted by by BioMed Central and Current Controlled Trials

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 *Trial*s [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)

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, ssummaries 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% 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 (eg, 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). NRP 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 (ie 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 (ie 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 (ie 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, anonyomised 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 anther 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.

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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

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Written evidence submitted by UKCRC Registered Clinical Trials Units Network

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 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

SCOPE OF SUBMISSION

1. 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; and
- 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.

Declaration of Interests

19. 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.

About the UK Research Integrity Office

23. 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

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Written evidence submitted by Ethical Medicines Industry Group (EMIG)

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 £4 billion.

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 Directive.[24] 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.

3.2 In the UK, the Faculty of Pharmaceutical Physicians has publicly advocated full publication of study results for some time.[25] 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*

[24] EUCOPE's submission to the European Commission's proposed revisions to the Clinical Trials Directive is included in the annex of EMIG's submission.

[25] http://www.fpm.org.uk/policypublications/guidingprinciples.

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).**[26]

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 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 eg 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).

3.9.1 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.

[26] *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.*

3.9.2 **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.**

3.9.3 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.

3.9.4 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 ie 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 eg 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 ie 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?

4.9.1 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.

4.9.2 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; and**
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 (eg randomised, controlled),
  - comparators (medicines/other treatments) if this is part of the clinical trial, and
  - 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-toxilogical 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

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 ie 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 ie "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 ie 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 ie 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

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 Committee[27] and in published correspondence between NICE's chairman Sir Mike Rawlins and Dr Fiona Godlee, editor in chief, BMJ.[28]

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 appraisal[29]. 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

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" recommendations[30] 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

[27] www.publications.parliament.uk/pa/cm201213/cmselect/cmhealth/782/78202.htm
[28] www.bmj.com/tamiflu/nice
[29] See section 4.2, *Guide to the methods of technology appraisal*, available at www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
[30] www.nice.org.uk/usingguidance/donotdorecommendations/index.jsp

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 article[31] 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"*[32] 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 strongly believe that companies should make all the data they have available so that 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 PatientsLikeMe UK

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.

[31] 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

[32] www.acmedsci.ac.uk/p47prid88.html

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 ie 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 seven 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 (eg pain, insomnia, fatigue), lab tests (eg 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, ie 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 $300 million and $1.2 billion, 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

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.

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Declaration of Interests

Dr Ben Goldacre spoke among others at the conference "We Have a Drug Problem" in London on 24–25 November 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 AMRC

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.[33] 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.

[33] 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

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 Regulation to replace the 2001 Directive.[34] 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.[35] 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.[36]

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.

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.[37] 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.[38] 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".[39] The HRA's recently launched feasibility study to provide a single, quality-assured HRA assessment to replace duplicated aspects of local research governance

[34] http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@pol/documents/generalcontent/cr_077460.pdf

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will hopefully show how this will work in practice and is welcome.[40] 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.[41] 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.

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.

Registering clinical trials

18. 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.[42] Registration is a pre-requisite for applying for authorisation from the MHRA and REC approval.

Publishing results of clinical trials

19. 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.

[40] 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/

[41] http://www.parliament.uk/documents/joint-committees/Draft%20Care%20and%20Support%20Bill/HC822-viii%20Thursday%2031%20January%202013%20Uncorrected%20Transcript.pdf

[42] Available at https://eudract.ema.europa.eu/

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.[43] 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.[44]

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 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.[45] But research findings must be accessible and understandable to the public. Resources such as CancerHelp UK[46] 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.[47]

Making data available

24. 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 (eg the Wellcome Trust policy on data management and sharing[48]) 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.[49]

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

[43] AMRC, *Charities and medical research, 1998*—http://www.amrc.org.uk/research-resources_guidance

[44] AMRC, *An essential partnership: Principles & guidelines for working with industry, 2007.* Available at http://www.amrc.org.uk/research-resources_guidance

[45] http://ec.europa.eu/health/files/eudralex/vol-10/2012_302–03/2012_302–03_en.pdf

[46] http://www.cancerresearchuk.org/cancer-help/trials/

[47] NIHR, *UK Clincal Trials Gateway: Public and Patient Survey 2012,* 2012—http://www.nihr.ac.uk/files/Publications/UKCTG%20Report_Jan%202013.pdf

[48] 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

[49] http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000556.jsp&mid

[50] https://www.researchfish.com/

[51] http://www.amrc.org.uk/research-resources_tracking-the-impact-of-charity-research-funding

funded. Researchfish[52] is a prominent 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.[53]

February 2013

Joint written evidence submitted by The Cochrane Collaboration & the Centre for Reviews and Dissemination

Executive Summary

1. Systematic reviews[54] 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, as well as from royalties from sales of *The Cochrane Library*, and has a commercial sponsorship policy for its research.[55]

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.

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[52] https://www.researchfish.com/

[53] http://www.amrc.org.uk/research-resources_tracking-the-impact-of-charity-research-funding

[54] 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.

[55] The Cochrane Collaboration. Commercial sponsorship policy. [cited 21 Feb 2013]; Available from: http://www.cochrane.org/policy-manual/23-commercial-sponsorship-policy

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,[56,57] published more quickly,[58] and disclosed in greater detail[59] 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.[60,61,62] Legal settlements with drug companies have identified many unpublished trials or data.[63,64,65] Researchers have also identified unpublished trials and data by searching for trial protocols, such as records registered in a clinical trials database.[66,67]

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.[68] Eight studies were available from published sources in the Cochrane Review published in 2006,[69] compared with over 120 unpublished studies identified subsequently.[70] 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.[71] Their success in persuading the EMA to release the data is well-described in Ben Goldacre's book, *Bad Pharma*.[72]

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.[73] 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.[74]

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[68] Jefferson T, Jones M A, Doshi P, Del Mar C B, Heneghan C J, Hama R, *et al*. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database of Systematic Reviews*. 2012;1:CD008965.

[69] Jefferson T O, 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.

[70] See Jefferson *et al*, 2012.

[71] Gøtzsche P C, Jorgensen A W. Opening up data at the European Medicines Agency. *BMJ*. 2011;342:d2686.

[72] Goldacre B. *Bad Pharma: How drug companies mislead doctors and harm patients*. London: Fourth Estate; 2012.

[73] See Rising *et al*, 2008.

[74] Hart B, Lundh A, Bero L. Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses. *BMJ*. 2012;344:d7202.

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.[75] 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.

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.[76] The drug companies concealed for many years unpublished trial data suggesting that these drugs increase the risk of suicide in children and adolescents.[77] 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.[78] 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.[79]

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.[80]

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.[81] 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 information contained in a set of PowerPoint slides posted on the Internet.[82] 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.

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[75] See Turner *et al*, 2008.

[76] Whittington C J, 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.

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[79] 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, 15 September 2010. 2010 [cited 15 Feb 2013]; Available from: http://www.justice.gov/opa/pr/2010/September/10-civ-1028.html

[80] United States Department of Justice. GlaxoSmithKline to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data. Monday, 2 July 2012. 2012 [cited 15 Feb 2013]; Available from: http://www.justice.gov/opa/pr/2012/July/12-civ-842.html

[81] Imdad A, Herzer K, Mayo-Wilson E, Yakoob M Y, Bhutta Z A. 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.

[82] 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

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.

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).[83]

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.[84] The ICMJE refers journal editors and researchers to the CONSORT statement in its guidance.[85]

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.[86]

[83] 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

[84] CONSORT. Consolidated Standards of Reporting Trials. 2013 [cited 18 Feb 2013]; Available from: http://www.consort-statement.org/

[85] 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

[86] Zarin D A, Tse T, Williams R J, Califf R M, Ide N C. The ClinicalTrials.gov results database—update and key issues. *New England Journal of Medicine*. 2011;364(9):852–60.

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, because it suspected that the manufacturer, Pfizer, was concealing a substantial volume of data from the trials that had been conducted.[87]

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.[88] The drug continues to be displayed in the British National Formulary without any comment on the findings of the IQWiG researchers.[89] 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.[90]

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."[91]

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:

- 29.1 All clinical trials are registered at their inception, before recruitment of the first participant; see The Cochrane Collaboration's statement.[92]
- 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.

February 2013

[87] 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

[88] See IQWiG 2009.

[89] Joint Formulary Committee. 4.3.4 Other antidepressant drugs. Reboxetine. *British National Formulary* (online). London: BMJ Group and Pharmaceutical Press; 2013.

[90] National Health Service (NHS). Prescription Cost Analysis—England, 2010. 2010 [cited 18 Feb 2013]; Available from: http://www.ic.nhs.uk/pubs/prescostanalysis2010

[91] 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

[92] 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

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Declarations of Interest

All contributors are members of The Cochrane Collaboration.

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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,[93] 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.

Written evidence submitted by the Clinical Contract Research Association (CCRA)

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

[93] 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

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.[94]

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 write papers themselves), then the cost of writing the paper is usually far higher than any journal charges.

Bourgeois F T, Murthy S, Mandl K D (2010). Outcome reporting among drug trials registered in ClinicalTrials.gov. Ann Intern Med 153:158–66

Schott G, Pachl 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

[94] Not printed

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 sequalea 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 Royal Society

1. The Royal Society has noted the Committee's consultation on Clinical Trial data with interest. This is an area the Society has a 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 been.[95] There is evidence that this selective publication of clinical trial results can create favourable bias towards the uptake of a new drug.[96] The partial reporting of clinical trials results

[95] 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

[96] Turner E H, Matthews A M, 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/NEJMsa065779

distorts understanding and can be viewed as a form of scientific misconduct.[97] 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 published.[98] 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 method,[99] 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.

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 trials.[100] 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.[101,102] 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.

February 2013

Written evidence submitted by the Royal College of Physicians

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.[103]

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".[104] 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.

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[97] Chalmers I (1990). Under-reporting research is scientific misconduct. Journal of the American Medical Association, 263, 1405–1408.

[98] 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.

[99] Thomas R & Walport M (2008). Data Sharing Review. Available at: http://www.justice.gov.uk/reviews/docs/data-sharing-review-report.pdf

[100] http://www.guardian.co.uk/society/2012/oct/11/glaxosmithkline-clinical-trials-data?CMP=twt_fd

[101] http://www.alltrials.net/

[102] http://www.alltrials.net/supporters/gsk-statement/

[103] http://www.rcplondon.ac.uk/sites/default/files/documents/2012_joint_statement.pdf

[104] For more: http://www.eshlsg.org/our-work/#clinical-trials

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.

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.[105]

— 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

Joint written evidence submitted by the Royal Pharmaceutical Society and the National Pharmacy Clinical Trials Advisory Group (NPCTAG)

The Royal Pharmaceutical Society (RPS) is the professional body for pharmacists in Great Britain. We are the only body that represents all sectors of pharmacy in Great Britain.

The RPS leads and supports the development of the pharmacy profession including the advancement of science, practice, education and knowledge in pharmacy. In addition, we promote the profession's policies and views to a range of external stakeholders in a number of different forums.

The National Pharmacy Clinical Trials Advisory Group, originally a subgroup of the National Pharmaceutical Quality Assurance Committee, was established in its current form in 2010. Membership includes representatives from a range of hospital pharmacy disciplines and other relevant specialist groups, Medicines and Healthcare products Regulatory Agency and the National Institute of Health Research. The group's objectives are to provide advice to NHS pharmacy services, to the National Institute of Health Research Clinical Research Networks Coordinating Centre, to support education and training of pharmacy staff, and to provide a forum for communication with MHRA about clinical trials.

Herewith our response to the Inquiry:

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?*

We welcome the proposed revisions to the Clinical Trials Directive, and strongly support the aims to drive consistency across the European Union and to adopt a risk-adapted approach to the approval and conduct of clinical trials. The introduction of a coordinated authorisation process should help to reduce the regulatory burden on investigators and sponsors, and to optimise efficiency and maximise system capacity to undertake clinical trials. However, the proposal as it stands is very low on detail, and the practical implications therefore remain unclear and we recommend the development and publication of guidance to support applicants.

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

We believe that, in the UK, more could be done to improve effectiveness in clinical trials; there are still too many barriers and sponsors continue to look elsewhere to conduct clinical trials, particularly where regulatory and financial hurdles are considered less onerous. Timeliness, cost, effective patient recruitment and inability to embed clinical research as part of standard practice are still areas for concern. Furthermore, there is a perceived reluctance to become involved in clinical research and in particular clinical trials for a variety of reasons including time, cost, resources, increase in workload and lack of appropriately trained clinical research staff.

Although the HRA has existed since December 2011 there seems to have been little awareness amongst pharmacists until publication of the statement on GCP training last year. From our point of view, HRA would therefore seem to have had little impact.

[105] For more: http://www.eshlsg.org/our-work/#payments-to-health-care-professionals

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

The majority of sponsors register their trials on the US database;[106] a registry and results database of publicly and privately supported clinical studies of human participants, conducted around the world which provides patients, family members and the public with information about current ongoing clinical research studies. We believe that registration of trials on this database should be an expectation of *all* clinical trial sponsors. To identify the gap between those studies registered and those subsequently published would provide valuable information.

The Society is strongly committed to increased clinical trial transparency and has signed up to active membership of the AllTrials campaign. Encouragingly, GlaxoSmithKline has recently announced that they will make results on all their trials available. This obviously will not happen overnight, but we believe this is a step in the right direction and would be keen to see all pharmaceutical and biotechnology companies follow suit.

The European Union requires end of study reports to be filed on all trials involving IMPs within a specified time—so it is difficult and illegal to withhold clinical data. However, while most sponsors will agree to publish, timeliness of publication may be an issue. Some journals may not be keen to publish some of the less interesting, negative trials, which may still have great importance when undertaking systematic reviews of the available evidence. Ways need to be investigated to ensure the rapid publication of all data, which would apply to the entire research community, not just those engaged in clinical trials.

It is frequently challenging to obtain clinical information on medicines outwith the Summary of Product Characteristics and published clinical trials, such as information on drug stability in solution, or administration by a route not referenced in the SPC. Additionally, transition during merger of Pharmaceutical Companies can also lead to reduced access to, and in some cases, even apparent loss of data. Furthermore, Pharmaceutical Companies often make reference to "data on file" but these original data are difficult to access or may be quoted without full context. It is extremely frustrating, and unacceptable from a patient safety view point, when access to data is refused (sometimes for unverifiable reasons) even though the manufacturer admits to having the information.

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

In the UK, regulatory access to allow inspection against academic data and publications as well as against commercial data would make clinical trials more open to scrutiny, especially trials initiated in the non commercial/academic sectors. The HRA is best placed to be responsible for this.

In the European Union, a database of all trials and their results could be published as the data is already in the system. We would suggest that the European Medicines Agency be responsible for this activity.

Q5. *Can lessons about transparency and disclosure of clinical data be learned from other countries?*

We are not aware of evidence that other countries fare any better or worse and are unable to comment on this point.

March 2013

Written evidence submitted by Empower

1. Introduction

1.1 Empower is a new platform to open the debate around the lack of drug development for patients with rare or life-threatening conditions.

1.2 Online social networks are helping to revolutionise the way people across the world can share information about their condition with similarly affected individuals, often without the involvement of medical professionals.

1.3 Given how long it can take to find the right combination of drugs to treat life-threatening conditions, Empower is keen to harness this collaboration to ensure that patients and doctors across the world share their experiences in an effort to improve knowledge and accelerate the timescales within which new drugs are developed and approved.

1.4 With this approach in mind Empower has reached out to patients with serious and life threatening conditions and other stakeholders for input and views on a submission to the inquiry. The campaign was lucky enough to have been a central feature of a Westminster Hall debate in the House of Commons (23/01/13) on access to medicine for people with terminal illnesses.

1.5 Empower welcomes the opportunity to make a submission to the Committee's Inquiry and is particularly encouraged by the Committee's recognition of the urgency of the issue.

[106] www.clinicaltrials.gov

1.6 Below is the Empower response to the Inquiry; instead of addressing the terms of reference point by point we have outlined our views on the broad issues and have included a copy of the recently launched (15/04/13) Halpin Protocol (Appendix 1).

1.7 On 15 April Empower started a formal consultation on "The Halpin Protocol", a blueprint framework for patients suffering from serious and life-threatening diseases.

1.8 The protocol sets out principles that would allow patients to make their own informed choices about the risks of participation in Clinical Trials or taking drugs and therapies originally intended for other conditions.

1.9 It is the latest stage of the campaign Empower: Access to Medicine which was founded to put the patient voice at the centre of discussions about the law and ethics around drug development for life threatening conditions where there is insufficient treatment.

2. Further Comments

2.1 Empower welcomes the NHS's aspiration to put patients at the heart of everything it does.

2.2 Recent proposals to amend several rights and pledges in the NHS Constitution, to reflect more clearly that the NHS supports individuals to manage their own health and involve them, is hugely important.

2.3 At the core of the Empower campaign is the drive to give patients more say in their treatment, the use of their data and the medicines they are prescribed. Therefore a proposed new pledge to involve patients in care planning discussions and to offer a written record of their care plan is a step that Empower wholeheartedly supports.

2.4 Particularly relevant in this area is the Constitution right "to be given information about your proposed treatment in advance, including any significant risks and any alternative treatments which may be available, and the risks involved in doing nothing."

2.5 Empower believes drug regulations should be adapted to allow people with serious and life-threatening diseases to try out new combinations of drugs and to have access to drugs and treatments that are still in the test stage of development—this would include an enhanced ability to participate in clinical trials.

2.6 Further to this are the following three rights that are integral to making Empower's mission a reality:

2.7 "You have the right to drugs and treatments that have been recommended by NICE for use in the NHS, if your doctor says they are clinically appropriate for you."

2.8 "You have the right to expect local decisions on funding of other drugs and treatments to be made rationally following a proper consideration of the evidence. If the local NHS decides not to fund a drug or treatment you and your doctor feel would be right for you, they will explain that decision to you."

2.9 "You have the right to be given information about your proposed treatment in advance, including any significant risks and any alternative treatments which may be available, and the risks involved in doing nothing."

2.10 Empower believes that the above are fundamentally important rights for a patient.

2.11 However, in practice they are not always applied to their full extent—particularly in relation to patients with serious and life threatening diseases.

2.12 These patients are sometimes denied drugs/treatments that may help them manage their condition. The "risk ratio" (risk of harm vs. potential benefits) is different for these patients due to the severity of their condition.

2.13 With this in mind it is extremely important that they are fully involved in the decision making process of which treatment course to take "*following a proper consideration of the evidence*."

2.14 In the spirit of pursuing treatments "*rationally*", where a doctor believes a treatment is "*clinically appropriate*" and it is "*recommended by NICE*" it can only be right that a patient can make the final call on whether the risk of taking an untested combination of drugs outweighs the risk of "*doing nothing*."

2.15 As the Committee has already heard from Dr Fiona Godlee, many patients want to enter clinical trials. Dr Godlee cited a hypothetical patient which we fully recognise "*I am entering this trial because I want my results to be used for the widespread advancement of science. I am not in this trial to help industry. I am in it to help science*."

2.16 If patients were freer to decide on their course of treatment, and participation in clinical trials, it would have a number of consequences.

2.17 It would mean more drugs were used to treat a variety of diseases and there would therefore be an improved base of evidence to help fight disease.

2.18 If pharmaceutical companies believed that the drugs they develop could be applied to a wider number of conditions this would encourage significantly more investment in new drugs and benefit society as a whole.

May 2013

APPENDIX 1

THE HALPIN PROTOCOL

BACKGROUND

Many people wish to assist in creating the conditions for the speed of drug and therapy innovation in rare diseases to accelerate. There is a sense that the joint effect of the regulation of Clinical Trials and the principles of legal liability that currently govern such Trials works against those interests and that a mechanism should be devised that provides a framework for patients suffering from certain life-threatening diseases to make their own informed choices about the risks of participation in Clinical Trials of unregistered drugs and therapies.

This will require the collaborative participation of patients, regulators, physicians and the developers of drugs and therapies.

Regulators will be required to approve a Schedule of Unmet Clinical Need where acceleration of drug and therapy innovation is particularly important, justifying the controlled relaxation of restrictions on participation in clinical trials of unregistered drugs and therapies for patients suffering from those life-threatening diseases.

Physicians will be required to certify that the Patient has an acute unmet clinical need and to supervise the administration of the drug or therapy during the Clinical Trials.

Patients will be required to give informed consent to their participation in the Clinical Trials and also to give informed consent to the required modification of their right to strict liability protection.

Developers will be required to undertake that the Clinical Trials will be conducted in a properly controlled environment, under medical supervision and that the results of the Clinical Trials will be fully published whatever the results.

THE HALPIN PROTOCOL

1. Does the Patient suffer from a life-threatening illness to which there is currently no sufficient medical treatment?
2. Does the Patient give informed consent to the modification of his/her legal remedies against the Developer of the Drug and against those conducting the Clinical Trials?
3. Has the Developer undertaken that:
   (a) the Clinical Trials will be conducted in a properly controlled environment and under medical supervision; and
   (b) the results of the Clinical Trials will be published whatever the results.

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