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Science and Technology Committee

Clinical trials

Third Report of Session 2013–14

Report, together with formal minutes, oral and written evidence

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Science and Technology Committee

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Summary

Clinical trials are the experimental foundation on which modern medicine is built. Trials also make a significant contribution to the UK economy and can provide patients with an important means of accessing the most exciting and innovative new treatments, before they reach the market.

Unfortunately, in recent years the number of trials taking place in the UK has fallen steeply. This is partly due to the European Clinical Trials Directive (CTD), which since 2001 has posed a significant barrier to those wishing to conduct a trial in the European Union, and the ongoing revision of which we keenly welcome. However, the CTD aside, a unique regulatory and governance landscape means that the UK remains a particularly challenging place in which to conduct a clinical trial.

To date, the Government has failed to eliminate the biggest barrier to initiating a trial in the UK—the requirement for numerous, and potentially duplicate, governance approvals from participating NHS organisations. The newly formed Health Research Authority (HRA) was created to make it easier to conduct research in the NHS, but we have been unable to judge whether it has been successful in achieving this objective as the necessary performance indicators are not currently in place. We were also concerned to find that some important stakeholders are only dimly aware of the HRA and its intended role. In addition, despite positive public attitudes towards medical research, it is difficult for the public to find out about potential research opportunities and Government efforts to rectify this through the re-launch of the UK Clinical Trials Gateway have been only partially successful.

While we are confident that the Government is aware of these problems and the need to resolve them, its promises have yet to be matched by effective action. More can and should be done to make the UK a more attractive location for clinical trials.

Another key focus of our inquiry has been the issue of clinical trial transparency. We consider that information relating to trials should be shared in a way that is accessible, assessable, intelligible and usable, and we have differentiated in our recommendations between four distinct levels of trial transparency:

a) **Universal trial registration** is crucial to increasing transparency and, in future, all clinical trials conducted in the UK, and all trials related to treatments used by the NHS, should be registered. We extend this recommendation to past trials, and urge the Government to support the retrospective registration of all trials conducted on treatments currently in use by the NHS.

b) It is also important that **summary-level trial results** are made public, and we do not accept the argument that it is not possible to publish "negative" results in peer-reviewed scientific journals. We recommend that trial registration and publication of summary-level results be made contractual requirements for all publicly-funded trials, including those covered by the Charity Research Support Fund, and urge the Government to conduct a retrospective audit of all large public trial grants awarded

since 2000 to ensure that they have been registered and published.

c) It would be unduly burdensome to mandate that full trial reports—**clinical study reports** (CSRs)—be produced for non-commercial trials. However, in cases where they are already produced for regulatory reasons, CSRs can make a useful contribution to the scientific literature. Once a regulatory decision has been reached, there is no compelling reason why CSRs should not be placed in the public domain, with identifiable patient data redacted.

d) We are not in favour of placing anonymised **individual patient-level data** (IPD) in the public domain in an unrestricted manner, as the risk to patient confidentiality is too great. Instead, specific individuals should be provided with controlled access to IPD through carefully managed and secure "safe havens". Access should be facilitated by an independent "gatekeeper", responsible for ensuring that data is handled responsibly and in a way that makes a useful contribution to scientific knowledge.

We consider the current lack of trial transparency to be unacceptable and we have not been impressed by the Government's efforts to resolve this problem to date. We ask the Government to enhance its efforts to increase transparency and to consider the recommendations of this Report in preparing its response to the European Medicines Agency's ongoing consultation on access to clinical trial data.

1 Introduction

1. The UK has long been a world leader in the field of medical research. Since the birth of the pharmaceutical industry over a century ago, only the USA has discovered and developed more drugs, and British researchers have played a central role in many of the breakthroughs that have revolutionised both scientific understanding and standards of patient care in the past 100 years.[1] More recently, this strong heritage has underpinned the development of a life sciences industry described by the Government as "one of the most successful globally" today.[2] The UK's 4,500 pharmaceutical, medical technology and medical biotechnology firms together employ over 165,000 staff, generate annual turnover of over £50 billion and spend nearly £5 billion on research and development each year.[3] It is perhaps therefore unsurprising that the Government has stated its desire to make the UK "the location of choice" for the £700 billion global life sciences industry, ensuring that "life sciences will continue to be vibrant in the UK and a key contributor to sustained economic growth and health improvements".[4]

2. Clinical trials, which test the safety and efficacy[5] of medical treatments, provide the body of scientific evidence on which this industry is built. Human medicines cannot be sold without permission from a licensing authority and permission will not usually be granted unless a clinical trial has demonstrated the medicine's success in treating the condition for which it will be marketed.[6] Clinical trials, in addition to generating valuable scientific evidence, also provide patients with an important way of accessing products that have not yet reached the market, offering hope to those for whom existing treatments have failed.[7] The necessity for a clinical trial to be performed before a medicine can gain regulatory approval means that trials are also big business. The global market for outsourced trial services[8] alone is expected to be worth £19 billion a year by 2015 and the clinical trials market as a whole has been estimated at £29 billion.[9]

1 Ev 98; See also, for example, "History", *Pfizer,* pfizer.com; "Our history", *GSK,* gsk.com, both accessed September 2013

2 Department for Business, Innovation and Skills, Office for Life Sciences, *Strategy for UK Life Sciences*, December 2011, p 4

3 Department for Business, Innovation and Skills, Office for Life Sciences, *Strategy for UK Life Sciences*, December 2011, p 4

4 "What we do", *Office for Life Sciences*, Gov.uk, accessed September 2013; Deloitte, *2013 Global life sciences outlook*, p 1 (USD values converted approximately to GBP based on Oanda exchange rate on 29 August 2013)

5 Efficacy tests whether a treatment works under ideal conditions, while effectiveness tests whether a treatment works under real-world conditions. Generally, a treatment tested under trial conditions tests efficacy rather than real-world effectiveness, since trial conditions are usually to some extent artificial.

6 MHRA, *Medicines and medical devices regulation: what you need to know*, 2008, p 5; Council Directive 2001/83/EC

7 Q 92 [Professor Sikora]

8 Outsourced clinical trial services, performed by third parties known as contract research organisations (CROs), include activities such as trial planning and design, patient recruitment, bioanalysis and data analysis

9 "'The Clinical Trials Market Will Exceed $30BN by 2015' says visiongain Report", *PR Newswire*, 5 July 2011, prnewswire.co.uk, accessed September 2013; "Clinical trial basics: global clinical trial market", *James Lind Institute,* jliedu.com, accessed September 2013 (USD values converted approximately to GBP based on Oanda exchange rate on 29 August 2013)

3. Historically, the UK captured a large slice of the market for clinical trials, enjoying in 2000 the third largest share of global trials, behind only the US and Germany.[10] Between 2000 and 2006, however, the UK's ranking dropped to ninth and Britain's global share of patients in pharmaceutical trials fell sharply as trials moved to other jurisdictions.[11] Between 2007 and 2011, the total number of UK trials also decreased, putting jobs at risk and making it increasingly difficult for British patients to benefit from participation in cutting-edge medical research.[12] In the last two years, several efforts have been made to halt this decline. The Government's creation of the Health Research Authority in December 2011 was intended to streamline the process through which researchers could obtain permission to conduct a UK trial, making it easier to get trials up and running.[13] In addition, the Government has stated its hope that the planned revision of the 2001 EU Clinical Trials Directive—the key piece of legislation regulating trials across the EU—would make it easier to conduct a trial in the UK.[14]

4. There are also long-standing concerns that, wherever in the world they take place, the methods and results of many trials currently remain hidden from public view. This lack of transparency, say campaigners, undermines public trust, breaks the ethical pact between scientists and those participating in trials and leads to clinical decisions being made on the basis of incomplete evidence, potentially leading to poorer outcomes for patients.[15] The topic of clinical trial transparency received renewed attention in late 2012 with the publication of *Bad Pharma,* a book by Dr Ben Goldacre that accused the pharmaceutical industry of deliberately suppressing unfavourable trial results from public view.[16]

5. In December 2012, we issued a call for written evidence addressing 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 trial 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?

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10 Kinapse, *Commercial clinical research in the UK: A Report for the Ministerial Industry Strategy Group (MISG) Clinical Research Working Group*, November 2008, p 19

11 Kinapse, *Commercial clinical research in the UK: A Report for the Ministerial Industry Strategy Group (MISG) Clinical Research Working Group*, November 2008, p 19; Ev 79

12 Ev 53, para 4

13 Ev 54, paras 10-12

14 Ev 53, para 6

15 See Q88 [Dr Ben Goldacre]; Ev 67, para 1-3, appendix; Ev w110, para 23; Ev 116, appendix, paras 48-51

16 Ben Goldacre, *Bad Pharma*, 2012, Chapter 1

e) Can lessons about transparency and disclosure of clinical data be learned from other countries?[17]

6. During the inquiry, we received written submissions from 62 organisations and individuals and took oral evidence from 21 witnesses, including:

- Researchers, clinicians and others involved in the running of clinical trials in the UK;
- Representatives of commercial and non-commercial funders of UK trials, including the pharmaceutical companies GlaxoSmithKline (GSK) and Roche;
- UK regulators and governing bodies, including the Medicines and Healthcare Products Regulatory Agency (MHRA), the Health Research Authority (HRA) and the Department of Health's National Institute of Health Research (NIHR); and
- The Government, represented by Lord Howe, Parliamentary Under-Secretary of State for Quality, Department of Health, (hereafter "the Minister") and David Willetts MP, Minister of State for Universities and Science, Department for Business, Innovation and Skills (hereafter, "the Minister for Universities and Science").[18]

We would like to thank those who provided written and oral evidence.

7. During our inquiry, several developments affected the regulatory landscape for clinical trials and the ongoing debate about trial transparency. This Report therefore considers these developments alongside the questions specified in the terms of reference. Chapter 2 defines the term "clinical trial" and outlines the current regulatory and governance requirements for those based in the UK. Chapter 3 considers the reasons for the recent decline in the UK's share of clinical trials, and offers suggestions for how this might be put right. Chapter 4 examines the subject of clinical trial transparency, considering the different levels of data that can be generated by and disclosed for a clinical trial, and evaluating recent developments designed to make trials more transparent. Chapter 4 also considers how emerging evidence from clinical trials can be better incorporated into clinical practice in order to improve medical outcomes. Chapter 5 sets out some final conclusions and recommendations.

17 "Committee to inquire into clinical trials and disclosure of data", *Science and Technology Committee*, 13 December 2012, parliament.uk/science

18 A full list of witnesses is provided at the back of this Report

2 Regulation and governance of UK trials

What are clinical trials?

8. There is no single definition for the term "clinical trial" and it can be used to describe several different types of research. Most commonly, the term refers to trials testing the effectiveness of experimental drugs. For example, Cancer Research UK told us that it used the term "only when referring to a clinical trial of an investigational medicinal product" (CTIMP),[19] using the alternative phrase "clinical study" when referring to other types of research conducted on humans.[20] The Medical Research Council (MRC) took a different approach, explaining that it considered clinical trials to include trials of investigational medicinal products (IMPs) but also trials "of medicines not defined as IMPs, or of devices or other interventions, such as surgical techniques or behavioural therapies".[21] In this Report, we employ a broad definition similar to that offered by the MRC, considering clinical trials to be experiments conducted on humans that are designed to assess the safety and efficacy[22] of a particular health intervention, be it a drug, medical device, surgical procedure, diagnostic test, public health programme or any other type of intervention.

9. Clinical trials are typically categorised into four phases, with each phase progressing only if the previous phase has been deemed a success:

- Phase I trials aim to determine how the human body responds to an intervention and how it will tolerate increasing doses. They can be high risk and therefore usually only involve very small numbers of healthy volunteers, or patients who are ill and have few other treatment options available to them.

- Phase II trials involve larger groups of patients—sometimes up to several hundred—and test for the first time whether a treatment works for a particular condition. They do this by helping to establish the most appropriate dosage, and by testing the treatment's efficacy.

- Phase III trials are large trials that aim to definitively assess a treatment's efficacy for a given condition. Large numbers of participants—often several thousand—may be necessary to provide reliable evidence and to enable scientists to identify less common side-effects of the treatment under investigation. Phase III clinical trials often cost many millions of pounds to design and conduct, and can continue for several years.[23]

- Phase IV trials occur after a treatment has been licensed for marketing. They are conducted for the purpose of safety surveillance (pharmacovigilance) to detect rare or long-term adverse effects in the wider patient population, and to compare further a

19 Clinical trials of investigational medicinal products, or CTIMPs, are discussed further in para 13

20 Ev 90, para 5

21 Ev 106, para 2; Q 39 [Dr Catherine Elliott]

22 See footnote to para 2 for a definition of "efficacy"

23 Manhattan Institute for Policy Research, *Stifling new cures: the true cost of lengthy clinical drug trials*, March 2012

treatment's performance against competitor products or current medical practice.[24] Phase IV trials are not specifically dealt with in this Report as they are subject to a somewhat different regulatory environment than other trial phases.[25]

Later phase trials, particularly phase III, often take the form of randomised-controlled trials (RCTs).[26] In a typical RCT, trial participants are randomly split into two groups, one of which receives the experimental treatment, the other of which receives either the standard treatment for that condition, or, if no treatment is available, a dummy treatment known as a placebo.[27] Where possible, RCTs are often also "double blind", meaning that neither the participant nor the clinician knows which of the two groups the participant belongs to, thereby minimising opportunities for bias to influence the results. Clinical trials can be conducted by commercial organisations hoping to develop a new product or by charities and publicly-funded researchers for various non-commercial purposes, such as testing a new use for an existing drug, comparing the performance of two alternative treatments already approved by regulators, or establishing the value of a new public health intervention such as a screening programme. Box 1 provides an example of a non-commercial phase III RCT.

Box 1: The COIN trial[28]

The COIN trial was a phase III trial that took place between March 2005 and May 2008. It was a non-commercial trial designed to test options for the treatment of advanced bowel cancer, and was funded by Cancer Research UK, the MRC, the Experimental Cancer Medicine Centre and the NIHR Cancer Research Network.

The COIN trial focused on two distinct questions of importance to patients with advanced bowel cancer. Firstly, whether adding the drug cetuximab—developed by the pharmaceutical company Merck and licensed for use in the EU in 2004[29]—to standard chemotherapy could benefit patients by increasing lifespan, and secondly, whether taking breaks from standard chemotherapy could improve patients' quality of life while having

[24] Parliamentary Office of Science and Technology, *POSTnote: Clinical Trials*, October 2011; "Types of trials: Phase 1, 2 , 3 and 4 trials", *Cancer Research UK*, cancerresearchuk.org, accessed September 2013

[25] "Overview of medicines legislation and guidance: pharmacovigilance", *MHRA,* mhra.gov.uk, accessed September 2013

[26] "About randomised trials", *Cancer Research UK,* cancerresearchuk.org, accessed September 2013

[27] A placebo is defined as any therapeutic procedure which has an effect on a patient, symptom, syndrome or disease, but which is objectively without specific activity for the condition being treated. For ethical reasons, placebos are only used in clinical trials if no standard treatment is available.

[28] "A trial looking at treatment for advanced bowel cancer (COIN trial)", *Cancer Research UK*, cancerresearchuk.org, accessed September 2013; "COIN trial in advanced bowel cancer – results presented at ECCO/ESMO conference and NCRI meeting", *Medical Research Council*, ctu.mrc.ac.uk, accessed September 2013

[29] "Human Medicines: Erbuitux: authorisation details", *European Medicines Agency*, ema.europe.eu, accessed September 2013

minimal impact on lifespan.

The trial recruited 2,445 patients from the UK and Ireland and split them into three groups. Group A, the control group, was treated with continuous chemotherapy, group B was treated with chemotherapy plus cetuximab, and group C was treated with intermittent chemotherapy.

Results from the trial demonstrated that, on average, patients given cetuximab alongside chemotherapy did not live any longer than patients treated with chemotherapy only. It also found that people who had received continuous chemotherapy lived, on average, six weeks longer than those who received intermittent treatment, but that patients receiving continuous chemotherapy also suffered from more side effects and underwent an average of ten weeks of additional treatment.

Cetuximab is not currently recommended by NICE for the treatment of advanced bowel cancer, having not been found to be cost-effective.[30] However, trials into the effectiveness of the drug in treating a particular sub-group of patients have recently taken place.[31]

10. The imprecision and inconsistency of terminology surrounding clinical trials has proved to be problematic. For example, Dr Catherine Elliott, the MRC's Director of Clinical Research Interests, told us that a common reason for grant-holders failing to comply with their terms and conditions was "a difference in definition" between what the two parties considered to constitute a clinical trial.[32] Dr Janet Wisely, Chief Executive of the Health Research Authority (HRA), stated that the HRA needed to be "absolutely clear what we mean" when categorising types of clinical research, and told us that the HRA was currently in the process of defining what it considered to constitute a clinical trial.[33]

11. **Clarity in use of the term "clinical trial" is essential. The establishment of consistent terminology would be an important first step towards making the UK an easier place to conduct clinical research.** ***We recommend that the Government agrees a set of simple definitions for the terms "clinical trial", "clinical study" and "clinical research" and ensures their consistent use across the Health Research Authority, Medicines and Healthcare Products Regulatory Agency, Medical Research Council, National Institute of Health Research and the NHS.***

Regulatory and governing bodies for UK trials

12. The regulation and governance of UK trials is shared between three main bodies:

a) **The European Medicines Agency** (EMA): the EMA is the EU agency responsible for "the scientific evaluation of medicines developed by pharmaceutical companies" for use

30 "TA242: Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy", *National Institute for Health and Care Excellence*, nice.org.uk, accessed September 2013

31 "A trial looking at chemotherapy and cetuximab for advanced bowel cancer (COIN-B)", *Cancer Research UK*, cancerresearchuk.org, accessed September 2013

32 Q 49

33 Q 152

in the European Union.[34] Before being legally permitted to market a medicine in the EU, a company must receive marketing authorisation either from a specific country or, more commonly, through a centralised procedure led by the EMA, which results in the award of a single marketing authorisation valid across all EU states.[35] While not currently directly responsible for the authorisation of clinical trials, the EMA holds significant amounts of clinical trial data and uses this when making regulatory decisions.[36]

b) **The UK Medicines and Healthcare products Regulatory Agency** (MHRA): the MHRA, an executive agency of the Department of Health, is responsible for the regulation of medicines, medical devices and healthcare equipment in the UK. It is also legally responsible for approving UK-based trials through its clinical trial authorisation process.[37]

c) **The Health Research Authority** (HRA): the HRA was established in December 2011 as a Special Health Authority, with a remit to "promote and protect the interests of patients and the public in health research".[38] Although not currently legally responsible for the conduct of clinical trials, it has a number of governance functions, including operating the National Research Ethics Service and the integrated research application system, a UK-wide e-submission system through which applications for various regulatory and governance approvals can be made.[39]

The European Clinical Trials Directive

13. The primary legislative instrument regulating clinical trials in the UK is the European Clinical Trials Directive (CTD), which sets out requirements for EU Member States participating in clinical trials of investigational medicinal products (CTIMPs). CTIMPs include most trials involving active pharmaceutical products such as drugs and vaccines, but exclude trials of non-medicinal interventions such as behavioural therapies and surgical techniques and "non-interventional" trials in which an approved medicine is prescribed in the usual (and non-randomised) manner with no additional diagnostic or monitoring procedures.[40] As such, the CTD applies to many, but not all, of the clinical trials currently taking place across the UK and Europe.

14. The CTD, passed by the EU in 2001, was implemented in the UK through the 2004 Medicines for Human Use (Clinical Trials) Regulations.[41] Under the terms of these

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34 "About us", *European Medicines Agency*, ema.europa.eu, accessed September 2013

35 Including the European Economic Area countries Iceland, Liechtenstein and Norway; "What we do: marketing authorisations", *European Medicines Agency,* ema.europa.eu, accessed September 2013

36 "Special topics: clinical trials in human medicines", *European Medicines Agency*, ema.europa.eu, accessed September 2013

37 "Licensing of medicines: clinical trials for medicines: is a clinical trial authorisation (CTA) required?", *MHRA*, mhra.gov.uk, accessed September 2013

38 Ev 103, para 1

39 Ev 99, para 2.2

40 "Is it a trial of a medicinal product?", *MHRA,* mhra.gov.uk, accessed September 2013; Council Directive 2001/20/EC, Article 1

41 The Medicines for Human Use (Clinical Trials) Regulations 2004

regulations, before a CTIMP can begin it must obtain Clinical Trials Authorisation from the MHRA, in addition to approval from an accredited Research Ethics Committee, currently managed through the HRA. All clinical trials conducted within the NHS, regardless of whether or not they fall within the scope of the CTD, also require sign-off from a Research Ethics Committee and, like all health research conducted in the NHS, are subject to approval from each NHS organisation taking part in the research—a process known as NHS R&D approval.[42] Some trials also require additional authorisation from bodies such as the Human Tissue Authority, the Human Fertilisation and Embryology Authority, the Administration of Radioactive Substances Advisory Committee and the National Offender Management Service.[43]

15. According to Sir Alasdair Breckenridge, former MHRA Chairman, the CTD was intended 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".[44] However, Sir Alasdair stated that "adoption of the CTD had a series of unintended consequences", which, according to the Academy of Medical Sciences, have led to the UK's strength in health research being "threatened".[45] As a result of similar concerns across Europe, the CTD is now undergoing revision and is expected to be replaced by a new Clinical Trials Regulation in 2016.[46] The CTD and the proposed new Regulation are discussed further in the next Chapter.

42 Department of Health, *Governance arrangements for research ethics committees*, May 2011, Section 2.3; "Approval requirements: NHS R&D approval", *National Research Ethics Service*, nres.nhs.uk, accessed September 2013

43 "Approval requirements: NHS R&D approval", *National Research Ethics Service*, nres.nhs.uk, accessed September 2013

44 Ev w33, para 1

45 Ev w33, para 3; Ev 79 para 2

46 "Fostering EU's attractiveness in clinical research: commission proposes to revamp rules on trials with medicines", *European Commission press release*, 17 July 2012

3 Barriers to conducting trials in the UK

Introduction

16. Between 2000 and 2006, the UK's global share of patients in pharmaceutical trials fell from 6% to 1.4%.[47] Between 2007 and 2011, the number of trials conducted in the UK also dropped by 22%, with the total number of trial applications to the Medicines and Healthcare products Regulatory Agency (MHRA) falling from 1208 in 2007 to 947 in 2011.[48] In its evidence to our inquiry, the Government acknowledged this drop, stating that recent years had seen "a decline in clinical trial activity" across the EU.[49] However, it also considered there to be "cause for optimism".[50] Lord Howe, Parliamentary Under-Secretary of State for Quality, Department of Health, stated that last year "over 99% of NHS trusts actively recruited patients" onto clinical studies and that there had been a 7% increase in the numbers of participants recruited onto clinical trials since the previous year, reaching 630,000 in 2012.[51] In addition, according to the Minister, "the number of new trials [...] in the NIHR clinical research network has more than doubled over the past five years".[52] Dr Bina Rawal, Director of Research, Medical and Innovation at the Association of the British Pharmaceutical Industry (ABPI), agreed that there had been an "upturn" in trial activity since around 2010, but considered that the UK had "suffered in recent years as a choice destination" for clinical trials compared with other parts of the world.[53] This Chapter examines some of the reasons for this decline.

European barriers to conducting a clinical trial

The Clinical Trials Directive

17. At least part of the decline in UK trial activity is the result of the Clinical Trials Directive (CTD), which, since its adoption in 2001, has imposed a significant burden on anyone wanting to conduct a clinical trial within the European Union. Both Cancer Research UK and the Association of Medical Research Charities told us that it was "widely" acknowledged that the CTD had "contributed to the general trend of decreasing numbers of clinical trials in Europe" while failing to deliver significant benefits to patients.[54] The NHS Europe Office, established to represent NHS organisations at EU level, argued that the CTD had "improved the safety and ethical soundness of clinical trials", but acknowledged that it had also:

47 Ev 79, para 2; "All together now: improving cross sector collaboration in the UK biomedical industry", *NESTA*, 2011

48 Ev 53; "2007 applications received by phase" and "2011 applications received by phase", available at "Clinical trials for medicines: UK clinical trial authorisation assessment performance", *MHRA,* mhra.gov.uk, accessed September 2013

49 Ev 53, para 4

50 Q 185 [Lord Howe]

51 Q 185

52 Q 185

53 Q 63

54 Ev w 108, para 5; Ev90, para 6

> 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.[55]

The European Commission, which was responsible for drafting the CTD, stated in its announcement of the CTD's revision that this legislation had created "an unfavourable regulatory framework for clinical research" which had contributed to the recent decline in European clinical trial activity.[56]

18. Witnesses highlighted several issues with the CTD. Oxford University's Centre for Evidence-based Medicine described it as "too burdensome, too slow and beset with unnecessary administration without clear upsides", while a study conducted by CR-UK suggested that the CTD had "resulted in a doubling of the cost of running non-commercial cancer clinical trials in the UK" and had increased the time to set up a trial by 65%.[57] Of particular concern was the CTD's perceived lack of proportionality, whereby trials of vastly differing degrees of risk carried the same regulatory burden. Professor Sir Michael Rawlins, Academy of Medical Sciences (AMS),[58] described how, under the CTD, trials that involved giving a patient a dose of paracetamol would require the same level of authorisation as those involving "rather more toxic agents".[59] Sir Michael went on to give an example of how the CTD's "one size fits all" approach had prevented a group of palliative care doctors from conducting a low-risk trial investigating whether high-dose morphine affected cognitive thinking in end-stage cancer patients.[60] Sir Michael told us that, despite testing what was a "normal" treatment for such patients, this trial was judged to fall within the scope of the CTD, and researchers therefore had to obtain insurance, materially increasing the cost of the research. According to Sir Michael, the researchers "decided to give up and do something else", adding that "this is the sort of problem that we have [with the CTD]".[61]

19. Sir Alasdair Breckenridge, former Chairman of the MHRA, also highlighted the problem of "inconsistent interpretation of the Directive among [EU] member states".[62] He cited the example of a trial investigating feeding formula for newborn babies, which was judged by the UK's MHRA to fall within the scope of the CTD, but was considered by Dutch regulators to be out of scope and therefore not subject to the same regulatory requirements.[63] The Clinical Contract Research Association, a trade organisation, agreed that the UK had been particularly stringent in its implementation of the CTD, claiming

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55 Ev 61, para 3

56 "Fostering EU's attractiveness in clinical research: commission proposes to revamp rules on trials with medicines", *European Commission press release*, 17 July 2012

57 Ev w45, para 6; Ev 90 para 6

58 Sir Michael Rawlins is a Fellow of the Academy of Medical Sciences and was Chair of the Academy's 2010 Working Group on regulation and governance in health research. When he gave evidence, Sir Michael was also Chair of the National Institute of Health and Care Excellence (NICE).

59 Q 5

60 Q 9 [Dr Bragman]; Q 7 [Professor Rawlins]

61 Q 7

62 Ev w33, para 4

63 *Ibid.*

that the legislation had been "gold-plated" in the UK compared with other countries and that, as a result, Europe had "not been a level playing field for clinical research".[64]

The proposed Clinical Trials Regulation

20. In December 2008, the European Commission announced and consulted on plans to review the functioning of the CTD and, in July 2012, the Commission adopted its proposal for a new Clinical Trials Regulation, intended to replace the CTD from 2016.[65] The MHRA launched a consultation on the draft Regulation in late 2012, the results of which were fed back to the Commission, and the draft has since been considered and voted on by the European Parliament's Environment, Public Health and Food Safety (ENVI) Committee. The Regulation is scheduled for first reading at the European Parliament's plenary session in March 2014.[66]

21. Overall, the Regulation was viewed positively by witnesses, with Professor Sir John Bell, Regius Professor of Medicine at the University of Oxford and a non-executive Director of several life science companies, echoing the views of many when he told us that it represented "a significant advance" over the CTD.[67] Roche told us that "as one of Europe's largest sponsors of clinical trials" it saw "the changes being introduced through the new clinical trials Regulation as positive" and the BioIndustry Association, a trade body representing healthcare-focused bioscience companies, stated that it offered "an improved, simplified and more efficient regulatory framework for clinical trials".[68] Key differences between the new Regulation and the existing CTD include the following:

- Legal form: as a Regulation rather than a Directive, the new legislation will automatically become law across all Member States, reducing the potential for inconsistent interpretation. Thus, according to CR-UK, "as a Regulation this legislation will achieve one of its principal goals in harmonising the regulatory system for clinical trials across Europe".[69]

- Proportionality: the Regulation contains a greater level of differentiation between high and low-risk trials than the CTD and the Government stated that it was "particularly pleased" to see "the concept of low-intervention studies" introduced.[70] However, the Institute of Cancer Research and the Royal Marsden NHS Foundation Trust argued that "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".[71] The Trial Steering Committee for two ongoing low-risk

64 Ev w117, para 1

65 "Medicinal products for human use: Clinical Trials, Revision of the Clinical Trials Directive", *European Commission,* ec.europa.eu, accessed September 2013; "Fostering EU's attractiveness in clinical research: commission proposes to revamp rules on trials with medicines", *European Commission press release*, 17 July 2012

66 "Procedure file for 2012/0192(COD): clinical trials on medicinal products for human use", *European Parliament,* europarl.europa.eu, accessed September 2013

67 Ev w 43, para 2

68 Ev 86, para 2.1; Ev w63, para 3

69 Ev 91, para 7

70 Ev 53, para 7

71 Ev w27, para 1

trials agreed that "the substantive barriers to low-risk, cost-effective trials" had "not been addressed by the 2012 proposed revision of the Directive".[72]

- Single submission and accelerated approval for clinical trials: Roche welcomed the proposed consolidation and acceleration of the clinical trial application process, stating that "a single portal for submission, with harmonised decision-making, is a major simplification and the proposal to introduce a timeline for the ethical committee approvals is most welcome".[73] The AMS agreed that "single submission via an EU portal" and "ambitious timelines to speed up the approval process" were strengths of the proposed Regulation.[74]

- Transparency requirements: plans to increase disclosure requirements for trials falling within the scope of the Regulation were generally welcomed, with the Government stating that it "view[ed] positively the elements of the proposal designed to do this".[75] However, not everyone felt that the Regulation went far enough. Dr Ben Goldacre, a practising clinician, author and campaigner for greater trial transparency, stated that "the current form of the draft EU Clinical Trials Regulation is weak, and does not adequately address the problem of missing results for medicines currently in use".[76] The topic of trial transparency is considered further in Chapter 4.

22. Although broadly welcomed, some agreed with the AMS that, while the Regulation represented a marked improvement on the CTD, "outstanding concerns remain".[77] In particular, it was suggested that a lack of clarity in the text of the Regulation might lead to it being interpreted as "more restrictive" than intended, potentially undermining the advantage of its more prescriptive legal form.[78] The Wellcome Trust referred to some of the terminology used in the Regulation as "confusing" and urged the Government to "seek further clarity on the amount of flexibility inherent in the Regulation".[79]

23. The Government stated that it welcomed the European Commission's proposal for a new Clinical Trials Regulation, and considered this to have "the potential to create a more favourable environment for the conduct of clinical trials in the EU".[80] It also stressed the active role it considered itself to have played in the Regulation's development, stating that it had been "fully engaged in the negotiations" taking place at European level.[81] The Minister told us that:

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72 Ev w38, para 12

73 Ev 86, para 2.1

74 Ev 79, para 3

75 Ev 53, para 9

76 Ev 117, appendix, para 71

77 Ev 79, summary

78 Ev w84, para 1.2

79 Ev 119, paras 9 and 13

80 Ev 53, para 6

81 Ev 57, para 35

> the MHRA has been very much at the forefront in all of these discussions and has influenced the EU Commission very heavily on the direction of travel it has taken throughout these negotiations. I think [the MHRA] deserves a lot of credit.[82]

Sir John Bell agreed that the MHRA had made a "substantial effort to ensure that the views of the UK were heard during the process of re-drafting the directive".[83] Overall, according to the Minister, the Government was "pleased by the tenor and direction of travel of the [European] Commission in putting together its proposals" for the new Regulation.[84]

24. **We recognise the significant barrier to research posed by the European Clinical Trials Directive and welcome proposals for a new European Clinical Trials Regulation. However, we are concerned that a lack of clarity in the detail of the Regulation could lead to inconsistencies in its implementation across Member States, and we are not persuaded that proposals go far enough in ensuring that low-risk trials are regulated in a proportionate way.** ***We urge the Government and MHRA to continue engaging at a European level to resolve these issues and to work together to ensure that, when the resulting legislation is introduced, the administration of clinical trials in the UK will be pragmatic and proportionate.***

UK barriers to conducting a clinical trial

25. Several witnesses pointed out that, while there were improvements to be made to the regulatory framework at European level, there remained several barriers to conducting a clinical trial "specifically within the UK".[85] The result, according to Roche, was that UK trials were becoming "increasingly costly and bureaucratic" compared to those conducted elsewhere in the EU.[86] This section of the Report examines these UK-specific issues.

Regulatory and governance complexity

26. Dr Catherine Elliott, Director of Clinical Research Interests, Medical Research Council (MRC), stated that, while there was "no doubt" that the CTD had contributed to difficulties in conducting trials across Europe, in the UK this legislation was "overlaid on to an already complex regulatory framework".[87] This framework is illustrated through the Clinical Trials Routemap (Figure 1)—an interactive resource developed by the Government in 2004 to "help clinical trialists and R&D managers understand the regulations and requirements" for conducting a trial in the UK.[88]

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82 Q 202

83 Ev w43, para 2

84 Q 215; Q 217

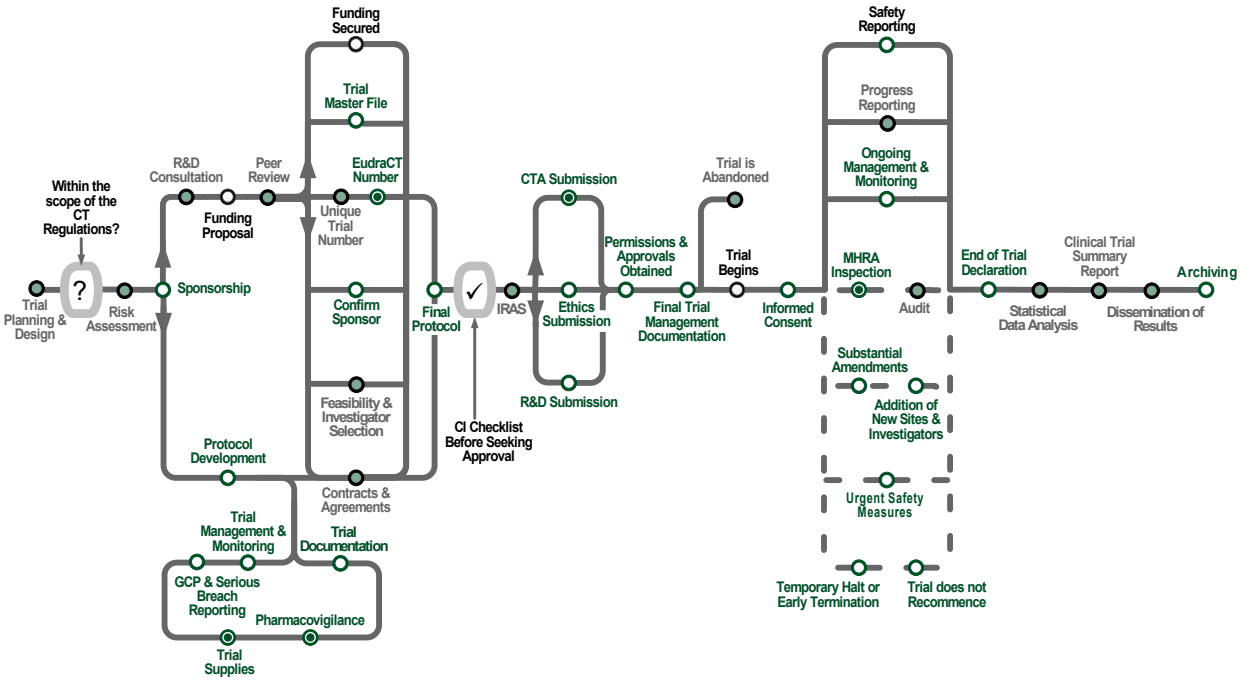
85 Ev w72, para 13

86 Ev 86, para 2.2

87 Q 41

88 Clinical trials toolkit, "About this site", *National Institute for Health Research,* ct-toolkit.ac.uk, accessed September 2013

Figure 1: The Clinical Trials Routemap[89]



Key to Symbols

	Standard process	Legal requirement	Good practice
Specific for trials within scope of the CTD	◉	◉	◉
Relevant to all trials	○	○	●
Demonstrates processes that can be done in parallel	→		
Demonstrates that not all processes will apply to all trials	- - -		

27. The complexity of this environment was widely acknowledged, including by the Government: Bill Davidson, Acting Deputy Director and Head of Research Standards and Support at the Department of Health, agreed that "the regulatory framework for research has become increasingly complex, which is one of the main reasons why we established the [HRA]".[90] When we asked Dr Janet Wisely, Chief Executive of the HRA, how easily researchers were able to find their way through this framework in order to initiate a clinical trial, she told us that "many do have a good understanding", but acknowledged that "others find it difficult to navigate what is a complex system".[91] She considered that, "however much we improve the efficiencies around approvals, it is still going to be quite a complex task" to initiate a clinical trial, and that researchers needed to make themselves familiar with the system.[92] Sir Kent Woods, Chief Executive of the MHRA at the time of our inquiry, told us that this was particularly difficult for those "relatively new to the clinical trials field and without the resources of a regulatory affairs department behind them"—a view borne out by a May 2013 report published by the Association of Medical Research

89 "Clinical trials toolkit: Routemap", *National Institute for Health Research,* ct-toolkit.ac.uk, accessed September 2013

90 Q 149

91 *Ibid.*

92 Q 150

Charities, which found that 40% of polled hospital doctors "cited difficulties navigating regulatory processes as a barrier to them taking part in medical research in the last two years".[93] The BioIndustry Association (BIA) pointed out that delays in the commencement of trials acted as a "significant drain on [...] companies' finite resources", and was particularly detrimental to small to medium enterprises which were often "pre-revenue and equity-backed" and were less likely to possess regulatory expertise.[94]

The performance of the Health Research Authority

28. A 2011 Academy of Medical Sciences report commissioned by the Department of Health, *A new pathway for the regulation and governance of health research*, recommended the establishment of a new independent agency, intended to bring together existing approval processes and simplify the UK regulatory and governance landscape for clinical trials.[95] In response, the Government established the Health Research Authority (HRA) in December 2011.[96] The HRA's remit is to "promote and protect the interests of patients and the public in health research" and, according to Dr Wisely, the HRA also has "a much wider role, which is largely about making it easier to do good quality research within the NHS".[97] Key HRA functions currently include:

- operating the National Research Ethics Service;
- acting as the appointing authority for Research Ethics Committees (RECs) in England;
- operating the integrated research application system, which is "a UK-wide e-submission system through which applications for [selected] regulatory and governance approvals for health research" can be made;[98]
- providing access to confidential patient information under Section 251 of the NHS Act 2006;[99]
- encouraging patient and public involvement in health research, and
- encouraging transparency, both in the HRA's own operations and by promoting good research conduct.[100]

29. Witnesses generally considered it too early to judge whether the HRA had been successful in meeting its objectives, although its positive attitude was widely praised: the

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93 Q 150; Association of Medical Research Charities, *Our vision for research in the NHS*, May 2013, p 36

94 Ev w65, para 28

95 Academy of Medical Sciences, *A new pathway for the regulation and governance of health research,* January 2011

96 The HRA was created through a Direction of the Secretary of State, in exercise of the powers conferred by sections 7, 8, 71(4), 272(7) and (8) of the National Health Service Act 2006(a); See "The Health Research Authority Directions 2011", *Department of Health*, gov.uk, accessed September 2013

97 Ev 103, para 1; Q 148

98 Ev 99, para 2.2

99 Section 251 was established to enable the common law duty of confidentiality to be overridden in certain circumstances to enable disclosure of confidential patient information—for example, for the purpose of important medical research where it is not possible to use anonymised information and where seeking patient consent is not practicable; See "What is section 251?", *Health Research Authority*, hra.nhs.uk, accessed September 2013

100 Health Research Authority, *HRA Business Plan 2013-14*, p 3; p 13

BIA commended the HRA's "open and transparent spirit of engagement" which it stated had been "warmly welcomed by the sector" and the Clinical Contract Research Association considered that the HRA had already "streamlined clinical trials ethics regulation", making the UK "a more attractive location to conduct clinical trials".[101] However, the UK Clinical Research Collaborations Registered Clinical Trials Units Network, a group responding on behalf of 15 UK clinical trial units, while welcoming "the spirit of the HRA" argued that it was yet to have "demonstrable impact [...] on the operations of clinical trials units".[102] King's Health Partners (KHP), one of England's first academic health sciences centres,[103] stated that "most clinical researchers and R&D staff in KHP have very little awareness of the HRA aside from the fact it exists"—a statement echoed by the Royal Pharmaceutical Society and the National Pharmacy Clinical Trials Advisory Group.[104]

30. According to its most recent Business Plan, the HRA is expected to spend £9.68 million in 2013–14, over half of which relates to the operation of its ninety-one Research Ethics Committees.[105] Roche questioned whether this budget was congruent with the HRA's objectives, claiming that there were concerns that it had "not been given the resources to achieve its role effectively and therefore may be at risk of either scaling back its remit or slowing down its work and the research and trials that rely upon it".[106] Although other witnesses did not comment on the HRA's budget, the Association of Medical Research Charities emphasised the need for it to "assess and demonstrate its effectiveness", and the AMS agreed that the development of "reliable metrics" would be "extremely important both in terms of providing feedback on the success of initiatives [and] communicating success internationally to companies and researchers seeking locations for clinical trials".[107] This need for formal performance measurement appears to have been recognised by the HRA, which stated in its 2013–14 Business Plan that it needed to "do further work over the coming months with stakeholders to identify what success will look like, feel like and measures that can be used to demonstrate it".[108] Nevertheless, it was the Minister's view that "by common consent the HRA has got off to a very good start indeed".[109]

31. **We commend the establishment of the Health Research Authority (HRA) and note that feedback on the HRA's performance to date has been largely positive. However, we are unable to judge whether the HRA has so far been effective in achieving its objectives, as the necessary performance indicators are not currently in place.** ***We recommend that the HRA establishes and publishes a suite of relevant key performance metrics and targets in its 2014/15 Business Plan, and monitors performance against these***

101 Ev w64, para 22; Ev w117, para 2; See also Ev w99, para 12; Ev w27, para 2; Ev w72, para 19; Ev 81, para 13

102 Ev w85, para 2.5

103 Academic health science centres are partnerships between leading universities and NHS organisations, intended to function as centres of excellence for UK health research. They were established by the Department of Health in 2009.

104 Ev w75, para 2; Ev w121, para 2

105 Health Research Authority, *HRA Business Plan 2013-14*, p 20; REC figure based on a search of all active RECs on nres.nhs.uk, performed in September 2013

106 Ev 87, para 3.1

107 Ev w109, para 12; Ev 81, para 18

108 Health Research Authority, *HRA Business Plan 2013-14*, p 18

109 Q 179

targets annually. We further recommend that a triennial review of the HRA takes place no later than December 2014, three years after its creation as a Strategic Health Authority.

32. **Over a year after its creation, some stakeholders (including an academic health science centre, intended to be a centre of excellence for UK health research) remained unaware of the function, or even the existence, of the HRA. Although these stakeholders also bear some responsibility for their own awareness of such developments, we consider that the HRA should now place greater emphasis on engaging with the clinical research community and raising the profile of its work.** ***The HRA should detail in its response to this Report how it intends to do this.***

NHS research and development approval

33. According to many, "by far the greatest impediment" to conducting a clinical trial in the UK is the requirement for researchers to obtain separate approvals from each NHS organisation involved—a requirement referred to as NHS R&D approval.[110] Professor Sir Michael Rawlins, Academy of Medical Sciences (AMS), explained that most trials take place across multiple NHS locations, each of which have their "own governance arrangements, with all of them looking [separately] at things like criminal records reviews and patient consent forms".[111] He gave the example of a principal investigator for a study involving 62 hospitals, who underwent 62 Criminal Records Bureau checks before being able to begin the trial.[112] A further example was provided by the British Heart Foundation (BHF), which told us about a study that "took more than a year to get started because of delays caused by governance and NHS funding issues".[113] According to the BHF, "the longest delays occurred in agreeing the contracts between the lead site at the University of Cambridge and seven other centres", which, as a result of each NHS site requesting separate agreements for each of the three trials making up the study, led to the university having to prepare 21 different contracts for a single study.[114] The BIA emphasised the "added cost, both in terms of staff and time and financial outlays" incurred as a result of such delays, which meant that many businesses found that conducting trials could be "demonstrably cheaper and more efficient in other jurisdictions".[115]

34. The problem of NHS R&D approval was strongly underscored by the AMS's 2011 report, which recommended the creation of a National Research Governance Service (NRGS) to streamline this process.[116] The AMS envisaged that the NRGS would form a "core component" of the HRA and would "oversee a streamlined, common process for NHS R&D permission for all single and multi-site studies in the NHS in England".[117] The

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110 Q 3 [Professor Rawlins]

111 Q 3

112 Q 3

113 Ev w72, para 16

114 Ev w72, para 16

115 Ev w64, para 27

116 Academy of Medical Sciences, *A new pathway for the regulation and governance of health research,* January 2011, Section 4.5, pp 38-41

117 Academy of Medical Sciences, *A new pathway for the regulation and governance of health research,* January 2011, p 41

Government has not, to date, taken up this recommendation, although the Minister told us that the HRA was "looking at ways to speed up the whole research journey".[118] He added that the HRA was currently "running a feasibility study, including a number of pilots, to test the effect of rationalising and combining NHS study-wide review with elements of the Research Ethics Committee review into a single HRA assessment".[119] This study, announced in October 2012 and commenced in June 2013, was widely welcomed and Cancer Research UK stated that, if successful, this would be the "biggest step" towards achieving a more streamlined governance process for clinical trials.[120] The Minister cautioned that "we cannot expect overnight results" and was unable to provide us with any milestones for next steps.[121] The report of this study was considered by the HRA's Board in June 2013, following which recommendations were made to the Department of Health.[122] The HRA stated in August that the results of the feasibility study had demonstrated that "both study-wide and local R&D assessments [could] be integrated into an HRA assessment" and that a business case for implementation was currently being prepared.[123]

35. **We welcome moves by the HRA to streamline NHS governance arrangements and stress the importance of this initiative, which, in our view, should be given the highest priority.** ***Following completion of the feasibility study, we recommend that a timeline detailing the next steps be published as part of the HRA's response to this Report. The Government should assist the HRA in its efforts to meet this priority, including making additional resources available if necessary.***

Monitoring NHS Trust performance

36. The Government has repeatedly pledged to monitor "how many Trusts are getting clinical trials started quickly" and stated, in 2011, that Trust performance against a 70 day target would be published from 2012.[124] Oxford University's Centre for Evidence-based Medicine, however, considered this target to be "unobtainable for drug trials" since, "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".[125] When asked in June 2013 how NHS Trusts were performing compared with this benchmark, the Minister replied that he did "not yet have robust data" and would not be in a position to answer our question until later in the year.[126] The Minister explained that the benchmark had been included in all new contracts with NHS Trusts since April 2012 and that a process to track performance was currently being tested. When we asked if this target was likely to be achievable, the Minister

118 Q 183

119 Q 183

120 Ev 91, para 13

121 Qq 183–184

122 Health Research Authority, "HRA assessment for the approval of research in the NHS: feasibility study", *Health Research Authority*, hra.nhs.uk, accessed September 2013

123 "HRA assessment", *Health Research Authority*, hra.nhs.uk, accessed September 2013

124 "Increasing research and innovation in health and social care", *Department of Health,* Gov.uk, accessed September 2013; HM Treasury and Department for Business, Innovation and Skills, *The plan for growth*, March 2011, para 2.192

125 Ev w46, para 11

126 Q 180

replied "yes" but considered that "it may take a little time before we see majority compliance".[127]

37. **We are disappointed that the Government has failed to meet its own 2012 deadline for measuring NHS Trust performance against a 70-day benchmark for clinical trial initiation and we query whether this target is realistic in the short-term.** ***We recommend that the Government updates us on current performance and on how many NHS Trust contracts now include this benchmark in its response to this Report.***

Patient recruitment

Public attitudes to and awareness of clinical trials

38. Simon Denegri, NIHR National Director for Public Participation and Engagement in Research and Chair of INVOLVE, the national advisory group for public involvement in research, highlighted that clinical trials "would not happen if patients and people did not come forward voluntarily and freely contribute their time".[128] Fortunately, public attitudes to clinical trials in the UK are generally positive—according to a 2011 survey commissioned by the Association of Medical Research Charities (AMRC), 72% of people would like to be offered the opportunity to be involved in a clinical trial.[129] Mr Denegri suggested that many patients felt "as though they might get better care" as a result of participating in a clinical trial, in addition to believing that they might benefit from a new treatment or therapy.[130] Others confirmed that, for some conditions, clinical trials represented an important treatment option. Professor Karol Sikora, Medical Director of Cancer Partners UK and Dean of the University of Buckingham Medical School, said that for cancer patients there was often "a sense of desperation" among those who have failed to get better with conventional treatments, meaning that they "actively seek out centres where there are clinical trials".[131] Professor Peter Johnson, Chief Clinician at Cancer Research UK (CR-UK), added that different groups of people had "different levels of enthusiasm to take part in research", and considered that "in general, people diagnosed with cancer have a very high level of motivation".[132] As a result, patient participation in cancer research is high, with around one in five people diagnosed with the condition taking part in one of CR-UK's trials.[133] However, positive attitudes appeared to be weaker when trials were known to be funded by industry. A 2013 public dialogue exercise commissioned by the HRA found that "the general public were deeply suspicious of the pharmaceutical sector and many held a view that making a profit was incompatible with developing products of

127 Q 182

128 Q 92

129 For conditions that affect their daily lives; See Ev w107, para 3

130 Q 92

131 Q 92

132 Q 46

133 Q 46 [Professor Johnson]

benefit to patients".[134] In addition, pharmaceutical trials were thought to develop in isolation to the NHS and the links between different organisations were not recognised.[135]

39. When asked what might prevent someone from becoming involved in a clinical trial, Mr Denegri highlighted the issue of public awareness and told us that knowledge about clinical trials was "pretty low in the general population".[136] He continued, "it probably increases as one becomes a patient, particularly if one has a condition such as cancer or if one is going to be treated for a long period of time" but described the process through which people could find out about clinical trials as "quite hit and miss".[137] Sharmila Nebhrajani, Chief Executive of the AMRC, agreed that there was "definitely a knowledge and access barrier" for people wanting to participate in a clinical trial, telling us that "patients want to do it, but they have no idea how".[138] According to Professor Johnson, "a much higher level of awareness among the general population would be enormously helpful".[139]

40. Despite generally positive public attitudes to clinical research, Roche told us that recruiting the requisite number of patients to UK trials was "often a more time-consuming process than in other EU countries".[140] William Burns, a Member of Roche's Board of Directors, considered that there was no "hesitancy from patients themselves" and that difficulties in patient recruitment were down to "an issue of process".[141] Roche considered that this was because "the NHS does not see clinical trials as part of its day to day operation" and others also highlighted what the British Heart Foundation called the absence of a "research-oriented mentality" in the NHS.[142] A recent NIHR "mystery shopper" survey, involving 82 hospital sites across 40 NHS Trusts, found that 91% of hospitals did not have any public information about studies they were supporting in "basic point of contact areas" and only 34% had information about clinical research on their websites that was useful to patients.[143]

41. Health professionals also appeared to be relatively uninformed about research opportunities, making it difficult for them to talk to patients about potential participation. Mr Denegri told us that a patient's relationship with their doctor was "pivotal" in influencing their decision about whether to take part in a trial but, according to the AMRC, a third of surveyed GPs and nurses said that they were not very confident talking about research with their patients, and 21% of health professionals were either unaware of, or failed to use, any of the tailored information resources available to support such conversations.[144] A reluctance to discuss research also appeared to exist on the part of

134 "Most people don't understand health research", *Health Research Authority press release*, 20 May 2013

135 "Most people don't understand health research", *Health Research Authority press release*, 20 May 2013

136 Q 92

137 Q 92; Q 95

138 Q 41

139 Q 46

140 Ev 86, para 2.3

141 Q 67

142 Ev 86, para 2.3; Ev w72, para 15; Q 68 [Dr Rawal]

143 Association of Medical Research Charities, *Our vision for research in the NHS*, May 2013, p 7

144 Q 94; Association of Medical Research Charities, *Our vision for research in the NHS*, May 2013, p 9; p 20

patients: a recent poll found that "only 21% of patients and the public said that they would feel confident asking their doctor about research opportunities".[145] Mr Denegri considered that health professionals, who in the past had "not been very helpful" to patients wanting to find out about research opportunities, were gradually being excluded from the decision-making process, as patients increasingly attempted to "self-refer to take part in research".[146]

42. The Government has responded to this reluctance to talk about research by launching the OK to Ask campaign, which promotes "the fact that it's OK to ask about clinical research".[147] The Minister explained that this campaign was intended to:

> raise awareness among patients and patient groups about the role of research in the NHS; the role of patients in research; that it is okay to ask your doctor about clinical research and, at the same time, to encourage clinicians and those working in the clinical environment—for example, people working in care homes—to think positively about research in the context of those they look after.[148]

The launch of the OK to Ask campaign followed the March 2013 update of the NHS Constitution, which strengthened the NHS's commitment to health research by pledging to "inform" patients of "research studies in which [they] may be able to participate".[149] Professor Johnson welcomed this change as "extremely positive" and Nicola Perrin, Head of Policy at the Wellcome Trust, agreed that the new pledge would "hopefully" be "very helpful", while adding that it needed to be "accompanied by much better information" for patients.[150] The AMRC agreed that patients needed to understand "what this commitment means to them" and pointed out that staff also needed guidance on "how they should meet this pledge and why", concluding that the change to the NHS Constitution was "welcome, but not sufficient".[151] The Minister told us that as a result of this "pledge to promote the existence of clinical trials" there was now "an onus on the system itself to do this".[152]

43. **We welcome changes designed to make the NHS Constitution more research-focused and the launch of the Government's OK to Ask campaign. However, we are cautious of any suggestion that the system, as a result of this new onus, will automatically act to promote the existence of and encourage involvement in clinical trials.** ***We recommend that the Government provides details of how changes to the NHS Constitution and the OK to Ask campaign have been communicated and promoted, both within the NHS and to the general public. In twelve months' time it should publish evidence on how the measures have affected both public and professional attitudes to, and participation in, clinical trials.***

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145 "OK to ask campaign", *National Institute for Health Research,* nihr.ac.uk/oktoask, accessed September 2013

146 Q 109

147 "OK to ask campaign", *National Institute for Health Research,* nihr.ac.uk/oktoask, accessed September 2013

148 Q 189

149 National Health Service, *The NHS Constitution for England*, March 2013, p 8

150 Q 41 [Professor Johnson]; Q 44 [Ms Perrin]

151 Association of Medical Research Charities, *Our vision for research in the NHS*, May 2013, p 8

152 Q 186

44. **We note the apparent lack of public confidence in the pharmaceutical industry and are concerned that this may increasingly pose a barrier to conducting trials in the NHS. Industry should act to regain trust lost through past examples of poor behaviour by engaging more effectively and transparently with the public in the future. *In addition, Trusts need to do far more to educate patients about the benefits, both to them and to the wider community, of participating in research and allowing properly controlled sharing of patient data.***

The Clinical Trials Gateway

45. In its 2011 *Strategy for UK Life Sciences*, the Department for Business, Innovation and Skills (BIS) included a commitment to "re-launch an enhanced web-based UK Clinical Trials Gateway", which would "provide patients and the public with authoritative and accessible information" about clinical trials taking place in the UK.[153] The Gateway, operated by the NIHR, was re-launched in April 2012 and currently contains details of around 14,500 trials taking place in the UK, approximately 3,100 of which are listed as recruiting.[154]

46. Mr Denegri considered the Gateway to be a "good initiative" that had been "very much welcomed" by patients, and the AMRC agreed that it was a "valuable resource".[155] BioMed Central, an open-access scientific publisher, cited the Gateway as evidence that "increased participation in trials" remained "very much supported by the UK Government".[156] However, the Gateway does have several limitations. Mr Denegri stated that there were "two broad issues":

> First, knowledge of it is not great; and, secondly, from a patient perspective, it is a little clunky and does not quite do everything you need. At the moment, you can search generally and nationwide for trials in which you might be able to participate, but you cannot search for trials that are local to you—perhaps 20 or 30 miles down the road—which is a priority for someone with a busy life.[157]

BioMed Central summarised the Gateway's challenges slightly differently, as ones of "coverage" and "accessibility", explaining that additional trial databases would need to be searched to ensure full coverage and pointing out that "clinical trial descriptions are often not in plain English", reducing the resource's accessibility.[158] A 2012 patient survey found that 67% of respondents considered the information contained on the Gateway to be either very clear or fairly clear but there were also "many requests for information to be kept up to date, clear, simple and relevant to its purpose".[159] Some respondents also felt that "there

153 Department for Business, Innovation and Skills, Office for Life Sciences, *Strategy for UK Life Sciences*, December 2011, p 3

154 Based on a "return all" search of the Clinical Trials Gateway, performed in September 2013

155 Q 97; Ev w110, para 23

156 Ev w78, para 16

157 Q 97

158 Ev w78, para 16

159 National Institute for Health Research, *UK Clinical Trials Gateway: public and patient survey 2012*, January 2013, pp 16–17

was too much medical and technical information" and that lay summaries were used inconsistently across the Gateway.[160]

47. The same survey also found that 80% of respondents—primarily patients and carers, who are the most likely users of the resource—had not heard of the Clinical Trials Gateway.[161] When questioned about this, the Minister acknowledged that "knowledge of the Gateway is less than we would like" but added: "I understand that the NIHR is taking various steps to promote the existence of the Gateway, as indeed the NHS itself must do".[162] When asked to expand upon how this was being achieved, the Minister responded that the NIHR had ensured that all parts of the NHS were "made aware" of the Gateway's existence, so that "at relevant opportunities, clinicians and others are encouraged to draw attention to it when they have a patient sitting in front of them".[163] However, he acknowledged that efforts to "promulgate the existence of the Gateway" had had "limited success so far".[164] The Minister also stressed that the Gateway had "recently been updated and renewed and is in the process of being improved still further", for example by giving it a better geographical focus, as highlighted by Mr Denegri, "so that, if you are living in a certain part of the country, you can find out what trials are going on nearby".[165]

48. The CancerHelp UK clinical trials database, funded and operated by CR-UK, is an online resource dedicated to UK cancer trials. According to CR-UK, unlike other trial registries, which are typically clinician or researcher-focused, the trial summaries included on CancerHelp UK "are written specifically with patients in mind".[166] Professor Johnson, CR-UK's Chief Clinician, stated that "about six whole-time equivalent staff" were "continuously trawling the different databases" to identify new trials, following which they wrote bespoke trial information sheets, "usually in concert with the researchers".[167] He continued:

> we check the accuracy of what we are putting up with the researchers conducting the trials to make sure that we have got it absolutely right and that we put it in terms that are readily understandable to the people arriving on the website.[168]

In comparison, support and development of the Government's Clinical Trials Gateway is performed by contract staff, equating in total to "two whole time equivalents" and most of the information it contains is pulled from existing sources, such as regulatory trial registers, not specifically designed for a lay audience.[169] Box 2 contains a comparison of entries for a

160 National Institute for Health Research, *UK Clinical Trials Gateway: public and patient survey 2012*, January 2013, p 16

161 National Institute for Health Research, *UK Clinical Trials Gateway: public and patient survey 2012*, January 2013, p10; p 12

162 Q 186

163 Q 187

164 Q 188

165 Q 186

166 Ev 94, para 2

167 Q 55

168 Q 55

169 Ev 58; "What the UKCTG is", *National Institute of Health Research*, ukctg.nihr.ac.uk, accessed September 2013

current phase I/II cancer trial on the Clinical Trials Gateway and the CancerHelp UK trials database.

49. Dr Elliott, MRC, stated that CR-UK had done a "great job with CancerHelp" and Ms Perrin, Wellcome Trust, agreed that it was an "excellent" resource.[170] This is reflected in the level of traffic received by the site: according to CR-UK, each month, on average, 35,000 full trial summaries are viewed on the CancerHelp UK database—more than the number of people diagnosed with cancer each month.[171] In comparison, the Government stated that in May 2013 (a month that included International Clinical Trials Day[172] and the launch of the Government's OK to Ask campaign) 41,115 pages on the Clinical Trials Gateway—covering not just cancer, but all conditions—were viewed, although it did not specify whether all of these views were of trial summaries.[173] The Government told us that, since 2008, it had invested £611,000 in the Gateway, part of which related to "limited advertising and promotional materials" including leaflets, postcards and placards.[174]

Box 2: Comparison of information on the UK Clinical Trials Gateway and CancerHelp UK

The ARISTOTLE study is a phase III trial looking at the use of irinotecan, a chemotherapy drug, in treating rectal cancer. It is currently attempting to recruit patients in the UK and is detailed on both the CancerHelp UK trials database and the UK Clinical Trials Gateway.

The "lay summary" contained on the Clinical Trials Gateway was taken directly from the UK Clinical Research Network (UKCRN) portfolio database—a system designed for use by clinical researchers.[175] It stated that:

> ARISTOTLE is a randomised multi-centre phase III trial with a target accrual of 920 patients with MRI defined locally advanced non metastatic rectal cancer. [...]
>
> The trial aims to determine whether the addition of a second drug (irinotecan) to the standard treatment of oral chemotherapy using capecitabine and radiotherapy improves outcome.[176]

In contrast, the summary provided by CancerHelp UK was written specifically for a lay audience and described the trial as follows:

> This trial is looking at adding irinotecan to the standard treatment for cancer of the rectum that has spread into the surrounding tissues (locally advanced cancer). [...]

170 Q 45 [Dr Elliott]; Q 54 [Ms Perrin]

171 Ev 90; "Cancer Stats: Cancer incidence for all cancers combined", *Cancer Research UK*, cancerresearchuk.org, accessed September 2013

172 Monday 20 May 2013

173 In addition, there had been approximately 8,500 downloads of a mobile phone and tablet computer "app" version of the Gateway since its launch in 2011; Ev 58

174 Ev 58

175 "Aristotle", *UK Clinical Research Database*, ukcrn.org.uk, accessed September 2013

176 "ARISTOTLE: a phase III trial comparing standard versus novel chemoradiation treatment (CRT) as pre-operative treatment for magnetic resonance imaging (MRI)-defined locally advanced rectal cancer", *National Institute for Health Research Clinical Trials Gateway*, ukctg.nihr.ac.uk, accessed September 2013

Doctors usually treat locally advanced rectal cancer with chemotherapy and radiotherapy followed by surgery. Having both treatments together is called chemoradiotherapy. As well as killing cancer cells, some chemotherapy drugs can make cancer cells more sensitive to radiotherapy. Having chemotherapy with radiotherapy is often better at shrinking cancer than radiotherapy alone. The chemotherapy drug capecitabine with radiotherapy is standard treatment to shrink rectal cancer before having surgery to remove it.

In this trial, researchers are looking at adding another chemotherapy drug called irinotecan. They want to find out

- If adding irinotecan to standard treatment stops or helps to delay the cancer coming back following surgery
- More about the side effects

This is a randomised trial. It will recruit about 920 people in the UK. The people taking part are put into 2 groups by a computer. Neither you nor your doctor will be able to decide which group you are in.[177]

50. **We were impressed by the quality and accessibility of Cancer Research UK's trials database, which is reflected in the high volume of traffic that it receives. In contrast, while we are satisfied that the Government is working to improve and promote its own Clinical Trials Gateway, we were concerned to find that only 20% of its target users were aware of its existence as of mid-2012, and that the Minister was unable to give us a more detailed account of what was being done to improve this. *The Government must improve the Clinical Trials Gateway and raise its profile with patients, clinicians and the general public. We recommend that the Government provides details about how it will achieve this, together with indicative timelines and targets, in its response to our Report.***

51. **We consider it important that the information contained on the Clinical Trials Gateway is accessible to the lay person, which does not appear to be consistently the case at present. *The Government should ensure that all trials listed on the Gateway include a plain language summary written specifically for a lay audience. Where such summaries are not already in existence, the Government must be prepared to commit the time and effort needed to create them. Taking into account the Gateway's current resource levels, we recommend that, where possible, preparation of a lay summary should be included as a requirement for publicly-funded trials, but that the Government remain open to the option of increasing the level of resource dedicated to the Gateway if necessary.***

177 "A trial looking at standard treatment with or without irinotecan for cancer of the rectum (ARISTOTLE)", *Cancer Research UK*, cancerresearchuk.org, accessed September 2013

4 Clinical trial transparency

The need for trial transparency

52. Clinical trials generate large amounts of information, much of which is used by regulators when evaluating a drug for licensing. The term clinical trial transparency generally refers to the extent to which this data is made more widely available, to other scientists, clinicians and members of the public.[178] Witnesses to our inquiry broadly supported the notion of greater trial transparency and pointed out that this would be likely to bring about a number of benefits, including:

- **Improved patient outcomes:** several witnesses drew a connection between greater transparency and improved clinical decision-making—the AllTrials campaign[179] claimed that failures to register and publish trials led directly to "bad treatment decisions" and "missed opportunities for good medicine".[180] Dr Ben Goldacre, co-founder of the AllTrials campaign and a practising clinician and author, explained that "healthcare professionals and patients need the results of clinical trials to make informed choices about which treatment is best" and added that it was "not satisfactory to say that the results of trials should be reported only to regulators".[181] The Academy of Medical Sciences (AMS) agreed that if only a subset of clinical trials "with extreme, or favourable, results" reached the public domain, "a biased conclusion" could be drawn about a treatment's effectiveness, potentially leading to the wrong medical decisions being made.[182]

- **Enhanced scientific knowledge**: according to the AMS, "greater access to appropriately controlled data for valid scientific inquiry offers significant scientific benefits and helps ensure scientific validity" by opening research up to greater scrutiny.[183] Tracey Brown, Managing Director of Sense about Science, agreed that this ability to "self-correct" is essential to science, explaining that:

  > We do not have the modern scientific approach that we have today because everybody has secretly gone off and done things in the cupboard; we have it because people have tested each other's ideas, pulled them apart and asked if something could have been done better. That is a very important part of scientific medical advance.[184]

  Sense about Science also stated that greater transparency could provide "a richer research base for both industry and academia" by increasing the visibility of research

178 This inquiry has not focused on the level or type of data used by regulators such as the European Medicines Agency (EMA) or the UK Medicines and Healthcare products Regulatory Agency (MHRA) in making decisions about marketing authorisation. Rather, we have focused on the extent to which information relating to and generated by clinical trials is made available to the scientific community and the public.

179 The AllTrials campaign is discussed further in paras 114-116

180 "Home", *AllTrials*, alltrials.net, accessed September 2013

181 Ev 110, para 3, Q75

182 Ev 79, summary; see also Ev 110; Q87 [Dr Goldacre]

183 Ev 81, para 22

184 Ev 67, para 2.2; Q 116

and thereby expanding the potential for collaboration and could also prevent the same trial from being unknowingly conducted more than once.[185]

- **Increased public trust in research**: it was a common view that greater transparency of trial data would engender greater public trust in medical research. Dr Margaret McCartney, a General Practitioner and medical writer, told us that lack of transparency in the past meant that she could currently "have no faith that patients taking part in clinical trials are not doing themselves harm".[186] INVOLVE, the national advisory group for public involvement in research, agreed that there needed to be "far greater openness and transparency in the publishing and accessibility of research findings" if the public were to "trust and have confidence" in clinical trials.[187]

- **Fulfilment of basic ethical standards**: several witnesses felt that it was unethical not to make the results of clinical trials public. A group from the Cochrane Collaboration, an independent research organisation, stated that for "experiments conducted on human beings" the full reporting of results "should be a right, not a gift".[188] Dr Goldacre agreed, telling us that by failing to make trial data transparent researchers were "breaching the ethical pacts" forged with patients when they agreed to take part in a clinical trial.[189] A letter from 53 trial participants to the European Medicines Agency (EMA), provided to us by Sense about Science, stated that failure to publish the results of clinical trials was "a betrayal of our trust in clinical trial regulation, and the trust of the families of those patients who volunteer for trials having had a terminal diagnosis".[190]

53. While support for the notion of greater trial transparency was strong, witnesses acknowledged that there were challenges, including the need to:

- protect the privacy of patients participating in clinical trials and ensure that data disclosure did not go beyond the confines of patient consent;

- protect any intellectual property contained within clinical trial data and respect commercial sensitivities, and

- mitigate the risk that clinical trial data would be re-analysed in an inexpert or irresponsible way, potentially leading to regulatory decisions being undermined and misleading conclusions reaching the public domain.

54. The most significant of these concerns related to patient privacy. Clinical trials can use and generate a large quantity of personal data, many of which could serve in combination to identify the patient even if their name were removed (for example, the patient's age, weight, occupation, the condition that is being treated and the location of their local hospital). While the disclosure policies currently applied by most pharmaceutical companies may limit trial transparency, according to the Association of the British

185 Ev 67, para 2

186 Ev w13, para 3, see also Ev 81, para 22; Ev w110, para 23; Ev124, para 4.1; Ev 59, para 2.1; Ev 56, para 30

187 Ev 105

188 Ev w11, para 19

189 Q 88

190 Ev 62, appendix 2

Pharmaceutical Industry (ABPI) they also "protect patients' personal data" as "consent is not given for [patients'] data to be utilised by other third parties".[191] Roche also noted that "many of the trials of today's medicines were conducted many years ago when the imperative for transparency of patient-level data was somewhat less" and, as a result, "they were not always conducted in a way which supported easy disclosure of patient-level data".[192] In particular, according to Roche, in many cases "the wording of the patient consent forms" from past trials makes data-sharing "very difficult to achieve".[193] The ABPI, BioIndustry Association (BIA) and others also emphasised the need to protect commercial interests.[194] The BIA argued that regard must be given to the "considerable investment in intellectual effort, inventive skill, time and money" represented by a clinical trial, which could be put at risk if "trade secrets" were revealed through a requirement for increased data disclosure.[195] The concern that making trial data more widely available would make it vulnerable to inappropriate re-analysis was also widespread.[196] Sir John Bell, Regius Professor of Medicine at the University of Oxford and a non-executive Director of several life science companies, described the threat as follows:

> 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.[197]

Dr Keith Bragman, President of the Faculty of Pharmaceutical Medicine (FPM), agreed, arguing that "simply to open up these data resources to anybody, and for them to do anything that they wish and perhaps come up with claims that cannot be substantiated, could create a chaotic situation".[198]

55. Others, however, disputed the significance of each of these challenges. Dr Goldacre, for example, while acknowledging that there were "challenges in ensuring confidentiality for individual patients", felt that these challenges could "be overcome", and Sense about Science pointed out that many forms of trial data did not include individual patient-level information and suggested that, where they did, such data could be redacted.[199] There was also disagreement about the extent to which trial data should be treated as commercially confidential, with the *BMJ* asserting that many data did not include commercially sensitive information and arguing that, even where it did, "citizens' right to know should override commercial confidentiality".[200] Sir John's argument that the public was "ill-equipped" to deal with the conclusions drawn from secondary analysis was disputed by Dr Helen Jamison of the Science Media Centre, who argued that the mainstream media was now

191 Ev 68, appendix 1

192 Ev 88, para 5.3

193 *Ibid.*

194 Ev 98, para A.4; Ev w65, paras 38–39; Ev 109, para 18; Ev w92–93, paras 4.7–4.9

195 Ev w65, paras 36-37

196 Ev w44, para 4.4; Ev 91, para 3.9.1; Ev 88, para 5.1; Q 76 [Mr Burns]

197 Ev w44, para 4.4

198 Q 24

199 Ev 117, appendix para 57; Ev 60, para 3.6; Ev67, para 4

200 Ev 75, para 1.iii

more able to deal responsibly with medical "scare stories" than it was in the past, making it less likely that misleading and potentially harmful analyses would reach the public domain.[201] These arguments are considered further later in the Report.[202]

56. In bringing about greater transparency, several witnesses also emphasised the need to extend policies to trials that had occurred in the past, as well as those that will occur in the future.[203] In Dr Goldacre's words, since most of the drugs currently in use came onto the market as a result of trials conducted several years ago, efforts focused only on future trials will "do nothing to improve medicine until most of us are dead".[204] While acknowledging these calls for retrospective action, the AMS nevertheless considered that "the focus should be on developing mechanisms to ensure rapid prospective posting and publication of current and future trials as this can be practically addressed more swiftly".[205] It cautioned that resources, in particular, "could be a key constraint" when considering retrospective disclosure.[206]

57. It is not enough simply to release data; Professor Peter Johnson, Chief Clinician at Cancer Research UK, explained that greater transparency would be of limited value if it resulted in scientists and the public being "simply swamped in largely meaningless" information.[207] According to the Royal Society, in order to avoid this scenario and realise the benefits of open scientific data, data must be:

- accessible and readily located;
- intelligible to those who wish to scrutinise them;
- assessable so that judgments can be made about their reliability and the competence of those who created them; and
- usable by others.[208]

The AMS agreed that information from clinical trials should be shared in a way that was "intelligible, assessable, reliable and usable" and Ms Brown also considered that an "intelligent approach" to data sharing was needed, adding that "we do not want a situation where [...] people put things into the public domain in binary code [for example], or where there is data dumping".[209]

58. **Clinical trial transparency is important and greater transparency would be likely to provide a number of benefits, particularly if applied retrospectively. However, there are obstacles to achieving this and the drive for greater transparency must be balanced**

201 Q 140

202 See paras 76-77 and 81-84

203 Ev 97, para 22; Ev w120, para 6; Ev w9, para 4; Ev 60, para 3.1-3.2

204 Q 86

205 Ev 84, para 42

206 *Ibid.*

207 Q 57

208 Royal Society, *Science as an open enterprise,* June 2012, p 7

209 Ev 79, summary; Q 117

against other concerns, particularly the need to protect patient privacy. Greater disclosure does not necessarily equate to greater transparency if the information shared cannot easily be understood and *we therefore recommend that efforts to increase the availability of clinical trial data focus on providing information that is accessible, assessable, intelligible and usable.*

The four levels of clinical trial transparency

59. The costs and benefits of making clinical trials more transparent are closely linked to the types of information being discussed, which can range from high-level facts about the aims and planned methods of a trial, to the thousands of lines of raw data generated over its course. The AMS explained that "clarity about which aspect of transparency" was being discussed was important, "as each presents different issues" which could significantly affect the arguments for and against making a particular level of trial data more transparent.[210] We agree and have therefore differentiated between four levels of trial transparency in drawing our conclusions. These are:

- trial registration (level 1): a record that the trial has been conducted, from a clinical trial register detailing basic trial information;
- summary-level trial results (level 2): a brief summary of the trial's results, together with key conclusions, most commonly in an academic journal or trial register;
- clinical study report (level 3): a detailed report, usually prepared for regulatory purposes, of the method, conduct and outcome of a trial, often running to several hundred pages in length; and
- individual patient-level data (level 4): the raw patient data generated over the course of a trial, from which aggregate results and other conclusions are drawn.

Level 1: Trial registration

60. A registered trial is one whose details have been entered onto a publicly-accessible database in advance of its commencement. There are many trial registries currently in existence but, as of mid-2013, only 15 were recognised as "primary registries" by the World Health Organisation (WHO).[211] To be listed as a primary registry, registers must include details of:

- the trial sponsor and source of funding;
- countries of recruitment;
- a description of the intervention being tested;
- key inclusion and exclusion criteria for trial participants;

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210 Ev 82, para 28

211 "About registries: primary registries in the WHO registry network", *World Health Organisation International Clinical Trials Registry Platform,* who.int/ictrp, accessed September 2013

- target sample size (the number of participants the trial intends to enrol), and
- the outcomes that the trial is intended to test.[212]

Current WHO primary registries include several national trial registries, the EU Clinical Trials Register[213] and ISRCTN.org, a global database that accepts registration of any study designed to assess the efficacy of a health intervention in a human population.[214]

61. Witnesses were unanimous in their support of trial registration. The Wellcome Trust stated that registration was "the most important" way in which clinical trials could be made more open to scrutiny, while Dr Fiona Godlee, editor-in-chief of t*he British Medical Journal (BMJ)*, claimed to "only see benefits", explaining that "if prospective trial registration were working [...], it would ensure that we would have a full record of all the ongoing trials and, therefore, the potential to chase up and obtain the full results of those trials".[215] Tracey Brown, Sense about Science, agreed that, at present:

> We do not even have the contents list, if you like, of what has been done, never mind being able to track down some of the results. That is something that reviewers who are looking across a whole range of studies really struggle with; they spend a lot of time just trying to find out what has actually been done but been left in a cupboard somewhere. Registration is about knowing what the trial is for and registering the protocols.[216]

Dr Elizabeth Wager, a freelance writer and publications consultant, noted the particular importance of registering design details before a study began, in order to "help to reduce, or at least identify, the selective reporting of outcomes, or changes in study design occurring between initiation and publication".[217]

62. Although several attempts have been made to increase the level of trial registration,[218] evidence suggests that many trials remain unregistered. According to Dr Goldacre, a 2009 study found that "half of all trials published in major medical journals [...] had not been properly registered, and a quarter had not been registered at all".[219] In the UK, a 2013 sample audit conducted by the Medical Research Council (MRC) also found that a significant proportion of MRC-funded trials—14%—had not been registered, even though this was a condition of the grant.[220] The Minister, however, while agreeing that all trials should be registered "whatever their nature", appeared to believe that there was currently

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212 "About registries: WHO Registry Criteria (Version 2.1, April 2009)", *World Health Organisation International Clinical Trials Registry Platform,* who.int/ictrp, accessed September 2013

213 See paras 91–94

214 "About registries: primary registries in the WHO registry network", *World Health Organisation International Clinical Trials Registry Platform,* who.int/ictrp, accessed September 2013; Ev 107, para 5

215 Ev 120, para 22; Qq 14-15 [Dr Godlee]

216 Q 119 [Ms Brown]

217 Ev w29, para 4.1

218 See paras 90–101

219 Ev 114, appendix para 14

220 Q 48 [Dr Elliott]

"no problem" with this aspect of transparency since a number of publicly-accessible registers were already in existence.[221]

63. **We consider universal trial registration to be a crucial step in increasing clinical trial transparency and believe that all future trials should be included in a publicly-accessible register. This is clearly not the case at present, even for trials conducted in the UK.** ***We recommend that the Government take steps to ensure that, in future, all clinical trials conducted in the UK, and all trials related to treatments used by the NHS, are registered in a WHO-listed primary registry.***

64. **Since the trials of treatments currently in use often occurred many years ago, retrospective disclosure is important if the benefits of clinical trial transparency are to be realised in the short to medium-term. Although retrospective trial registration will incur some cost, we consider that this will be outweighed by the public health benefit of having a complete picture of the trials conducted on treatments currently available to patients.** ***The Government should support the retrospective registration of all trials conducted on treatments currently available through the NHS and should actively pursue policies to bring this about.***

Level 2: Summary-level trial results

65. The term "summary-level trial results" refers to the relatively basic information needed to understand the outcome and potential implications of a clinical trial. Such information is most often found in a scientific journal but can also be included in a variety of other media, such as trial registers, sponsor websites, regulatory documents and conference posters and presentations. Although summary-level results can come in many forms, there are some common standards, and such summaries usually include an exposition of the aims, methods, results and statistical findings of a trial.[222]

66. Most of those who submitted evidence to our inquiry agreed that summary-level results should be published for all trials, and the Government also stated that it was "fully supportive of transparency in the publication of clinical trial results".[223] However, there was some debate over the most appropriate mode of publication for this type of data. The AMS recommended the use of "peer-reviewed media such as scientific journals", as did the Cochrane Collaboration's meta-analysis methods group, which stated that formal publishing would be "preferable" to alternative models "because of the more permanent nature of journals and [the] advantage of peer review".[224] Dr Wager agreed that publication in the peer-reviewed literature had many benefits, including "permanence, the possibility for corrections or retractions, some measure of quality control via peer review, [and] the opportunity for post-publication commentary and discussion".[225] In 2011, we reached a similar conclusion in our Report on *Peer review in scientific publications*, which stated that

221 Q 224; Q 198

222 See for example "The CONSORT Statement", *CONSORT,* consort-statement.org, accessed September 2013

223 Ev 56, para 30

224 Ev 82, para 30; Ev w41, para 10.1

225 Ev w30, para 4.4

"peer review in scholarly publishing, in one form or another, is crucial to the reputation and reliability of scientific research".[226]

67. However, there are several limitations to academic journals as a source of summary-level trial results, the most significant of which, according to the advocacy groups Healthy Skepticism UK (HS-UK) and Health Action International (HAI), is the potential for journal articles to "not only misrepresent the actual results or conclusions of that study but also skew the larger body of evidence".[227] HS-UK and HAI stated that misrepresentation could come in the form of several types of reporting bias, which affect how, when and where a trial is published, based on the nature and direction of its results.[228] The most frequently highlighted bias was publication bias, whereby "positive" results—those which suggest that a treatment is effective—are placed in the public domain more frequently than "negative" results. Dr Wager, an ex-employee of the pharmaceutical industry, agreed that "under-reporting" was a problem, particularly for negative results, and put this down to a number of causes including:

- clinical investigators being uninterested in unexciting or unfavourable results;
- journal space constraints and the rejection of papers detailing "negative" results;
- deliberate omission of unfavourable or inexplicable outcomes; and
- resources being transferred away from drugs that were no longer being developed, making publication of the results of related trials a low priority.[229]

The Global Alliance of Publication Professionals (GAPP) agreed with Dr Wager that "publications do not write themselves" and suggested that many studies remained unpublished simply because researchers "lack the resources to write up their results".[230] Dr Godlee, *BMJ*, however, criticised researchers who kept trial results "in their bottom drawer" if they did not "come up with the results that they wish[ed] for".[231] Dr Godlee agreed that in the past journals had also been at fault in failing to publish "negative" results, but claimed that the introduction of "open access journals and online journals that have lots of space to publish negative and neutral results" meant that this was no longer the case.[232] BioMed Central, an academic publisher, concurred, suggesting that rejection by journals was no longer a valid reason for non-publication since "many peer-reviewed journals [...] strongly encourage publication of negative results" and "at least one journal makes publication of negative results its mission": the *Journal of Negative Results in Biomedicine*.[233]

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226 Science and Technology Committee, Eighth Report of Session 2010-12, *Peer review in scientific publications*, HC 856, para 277

227 Ev w80, para 3.1.2

228 Ev w80, para 3.1.1; See also Ev w52, para 12

229 Ev w29, para 3.4

230 Ev w7, para 19

231 Q 30

232 Q 30

233 Ev w77, para 7

68. **We consider that summary-level results should be made publicly available for all clinical trials and we welcome the many new media through which it is now possible to share this information. Nevertheless, peer review is vital to the reputation and reliability of scientific research and we deem it appropriate that journal articles remain the primary instrument for the publication of summary-level trial results.**

69. **Many historic trials remain unpublished, which is far from ideal. However, retrospective publication of all trials of all treatments currently in use, while desirable, would almost certainly be unachievable given the likely time and resources that this would require. We therefore emphasise again the importance of retrospective trial registration as a means of providing a vital "index" against which individual cases of non-publication can be identified and, where of particular importance, pursued on an ad hoc basis.**

70. **Given recent changes to academic publication models, we do not recognise as legitimate the argument that it is not possible to publish "negative" results in a peer-reviewed journal and we consider failure to publish on a timely basis to be poor scientific practice. However, we are sympathetic to the pressure that scientists are often working under and therefore *we urge the Government and other trial funders to ensure that researchers are provided with the time and resources needed to meet their publication obligations.***

71. In 1981, Franz Ingelfinger, editor of the *New England Journal of Medicine* (*NEJM*) stated that, in future, the *NEJM* would only accept papers on the understanding that "neither the substance of the article nor any of its pictures or tables have been published or will be submitted for publication elsewhere".[234] Many other medical journals followed suit, applying the "Ingelfinger Rule" to their own publications, with the result, according to Dr Wager, that "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".[235] CR-UK demonstrated the ongoing impact of the Ingelfinger rule, stating that in some cases, if trial results were due to be published in an academic journal, it could not add results to its own CancerHelp UK database until the publication date had passed.[236]

72. **We encourage academic publishers to remove "Ingelfinger" restrictions on the pre-publication of summary-level results through media such as trial registries, in order to facilitate greater openness and faster access to important scientific data.**

Level 3: Clinical study reports

73. A clinical study report (CSR) is a standardised account of the plan, conduct and outcome of a clinical trial. A CSR includes significantly more detail than summary-level trial results and contains in its appendices large amounts of information not usually found elsewhere, such as patient data listings, names and CVs of the investigators involved in a

234 "The Ingelfinger Rule", *New England Journal of Medicine*, October 1 1981, vol 305, pp 824-826

235 Ev w30, para 4.7

236 Ev 94

trial, documentation of statistical methods and case report forms.[237] The standard CSR format was designed by an international collaboration in 1995,[238] in the hope that "the compilation of a single core clinical study report acceptable to all regulatory authorities" would ease the burden on sponsors hoping to gain approval for a new product in multiple jurisdictions.[239] Today, CSRs—often running to several hundred pages in length—are primarily used as regulatory documents and are not generally prepared for non-commercial trials.[240]

74. We heard mixed evidence about the importance of CSRs and whether or not they should be placed in the public domain. According to GAPP, "making [CSRs] available would do considerably more for transparency than any attempt to increase rates of publication in peer-reviewed journals" because the level of detail included in a CSR "far exceeds" that of an academic paper.[241] The Cochrane Collaboration agreed that, while CSRs were "massively complex documents, containing hundreds or thousands of pages of information with minute details about trials, their planning and execution", they were nevertheless an important source of additional data because they allowed for scrutiny of what had been published about a trial in the academic literature.[242] Dr Goldacre drew on the example of Roche's drug Tamiflu to highlight this point:

> By comparing clinical study reports on Tamiflu against brief published reports, Cochrane has already found discrepancies. For example, things that were described as placebos in the academic journal article turned out to be, first, a different colour from the active treatment, and, secondly, not to be inert placebos at all; in fact they had active ingredients. [...] It is to resolve discrepancies like that that we need better access to clinical study reports.[243]

In light of their potential value, Oxford University's Centre for Evidence-based Medicine proposed that legislation be introduced "to make clinical study reports, of all completed trials, available within one year of trial completion".[244] Sense about Science's AllTrials campaign made a similar call for "the publication of the results (that is, full clinical study reports) from all clinical trials—past, present and future—on all treatments currently being used".[245]

75. In contrast, many other witnesses stressed the relative unimportance of CSRs when compared with other forms of disclosure, such as trial registration and the publication of summary-level results. When asked whether he would be in favour of publishing CSRs for

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237 A case report form is the document on which much of the information relevant to an individual's participation in a trial is recorded. It may include information such as the patient's age, sex and ethnicity, medical history, results of physical examinations and blood tests and hospital visit dates.

238 The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

239 "ICH harmonised tripartite guideline: structure and content of clinical study reports (E3)", *ICH*, November 1995, p 1

240 Ev 108, para 13

241 Ev w8, para 27

242 Ev w9, paras 3.4, 4.2-4.3

243 Q 80

244 Ev w47, para 31

245 "The AllTrials campaign", *AllTrials,* alltrials.net, accessed September 2013

all trials, Professor Sir Michael Rawlins, AMS, told us that he was "ambivalent" about whether it was worth publishing them, explaining that were "voluminous", sometimes running "to thousands of pages" and did not "add very much".[246] Professor Johnson, CR-UK, agreed that it was "important to dispel any misconception" about how useful a CSR was "in its unedited and unanalysed form", and warned us of the "opportunity cost" that would be associated with preparing them for non-commercial trials, telling us that "doing more trials and doing them faster" represented better use of limited resources.[247] Other non-commercial trial sponsors agreed that a "huge additional financial and time burden" would be introduced if they were to start producing CSRs, as was being discussed at EU-level as part of the revision of the Clinical Trials Directive in early 2013.[248] The MRC stated that mandatory CSR production for non-commercial trials would introduce "a significant burden on academic funders" with each CSR taking "about three months' additional work to produce".[249]

76. Even for commercial trials, for which CSRs are already produced as standard, there are potential problems associated with greater transparency. There were mixed views on whether or not CSRs contained commercially sensitive information, the disclosure of which could potentially harm industry. According to the ABPI:

> As clinical study reports, until now, have been written for a regulatory audience and assuming confidentiality, they may describe commercial plans of the company. For instance, the development strategy for future studies on new indications may be described to put the particular study in context. [...] Furthermore, study reports often include appendices with detailed information on analytical methods (chemical and physical) and on the manufacturing of the clinical trials material.[250]

Disputing this, however, Dr Goldacre pointed out that the European Medicines Agency (EMA) had already shared some of the CSRs that it held, suggesting that this information was not commercially sensitive.[251] According to the *BMJ*, the European ombudsman had also declared that there was "no commercially confidential information" in a CSR.[252]

77. There was greater consensus over the legitimacy of the issue of patient confidentiality, although there remained disagreement over how easy this might be to resolve. Sir Kent Woods, then Chief Executive of the MHRA and Chair of the EMA's Management Board, told us that "to ensure that one is not releasing personal, identifiable data", CSRs "need to be quite carefully scrutinised before release and may need to be redacted in places; and that is a very labour-intensive process".[253] He explained that the EMA had released 1.6 million pages of clinical trial data over two years, and that this had cost it "somewhere between €2

246 Q 24

247 Q 57

248 Q 59 [Ms Perrin]; European Parliament, Committee on the Environment, Public Health and Food Safety, *Draft report on the 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*, 31 January 2013, p 51

249 Ev 108, para 13; Q 57 [Dr Elliott]

250 Ev 68, appendix 1

251 Ev 112, para 33; P. C. Gøtzsche, "Opening up data at the European Medicines Agency", *BMJ,* 10 May 2011

252 Ev 75, para 1(iii)

253 Q 159

million and €3 million".[254] Dr Goldacre disputed this point, claiming that it was "easy to redact" patient confidential information from CSRs and that the European Ombudsman had agreed that "the administrative burden" of preparing CSRs for publication was "not significant".[255] Dr James Shannon, GSK's Chief Medical Officer, also believed that it could be "very difficult" to redact patient data included in historical CSRs because this information is "on paper" rather than in electronic databases.[256] Nevertheless, in February 2013, GSK committed to posting CSRs on its own dedicated clinical trials register for all approved medicines dating back to the company's formation in 2000, suggesting that while potentially difficult, comprehensive publication of redacted CSRs was not impossible.[257] (This and other industry-led initiatives to increase trial transparency are discussed later in the Report).

78. The Minister commended GSK for its "good work" in this area, although he stated that the Government considered "publication of summaries" rather than CSRs to represent "the right level" of trial transparency.[258] The Minister added that he considered it "unduly burdensome" to require publication of "a fully fledged CSR" for all trials, and told us that the Government had been "concerned" about EU discussions earlier in the year which had suggested that CSR preparation might become mandatory for all trials as part of the revised Clinical Trials Regulation.[259] Following further discussion, however, the current draft Regulation does not include this requirement.[260]

79. **It would be unduly burdensome to mandate that clinical study reports (CSRs) be produced for non-commercial trials. We also consider that issues concerning the reliability of the information contained in academic journal articles should be dealt with at source, for example by strengthening the peer review process as recommended in our 2011 Report, rather than by effectively bypassing academic publication through greater reliance on CSRs. We therefore do not support any move to make it mandatory for non-commercial trials to produce a CSR, or any other document of an equivalent level of detail. However, we recognise that CSRs can provide a useful contribution to the scientific literature and, once a regulatory decision has been reached, we see no compelling reason why CSRs should not be placed in the public domain, with identifiable patient data redacted.**

Level 4: Individual patient-level data

80. Individual patient-level data (IPD) are the underlying data collected from patients participating in a clinical trial. For example, IPD from a trial of a new diabetes drug might

254 Q 159

255 Q 86; Ev 112, para 33

256 Q 75

257 Ev 124, para 4.2

258 Q 215; Q 218

259 Q 218; European Parliament, Committee on the Environment, Public Health and Food Safety, *Draft report on the 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,* 31 January 2013, p 51

260 European Parliament, Committee on the Environment, Public Health and Food Safety, *Report on the 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,* 7 June 2013

include details of a participant's changing blood sugar levels over time, together with their age, gender, height, weight, dates and locations of hospital visits, and various other pieces of personal, clinical and administrative information.

81. At present, public disclosure of IDP is not mandatory for any type of trial, and the European Medicines Agency (EMA) does not regularly request access to IPD for the trials that it evaluates, unlike the US Food and Drug Administration (FDA).[261] However, several witnesses emphasised the potential scientific value of this data and advocated greater access to it. For example, the data-sharing company PatientsLikeMe considered that "society would benefit significantly" from the transition of trial results from "inaccessible records" to "an open repository of machine-readable data" and several witnesses pointed out the potential for such data to be reanalysed and combined to produce much more reliable and statistically significant results.[262] As a result, Michael Power, a clinical researcher, recommended that the Government commit to making all trial data, suitably anonymised, "publicly and freely available on the internet without unreasonable delay".[263] In an effort to increase the transparency of IPD, in January 2013 the *BMJ* announced that it would "no longer publish any trials of drugs or devices where the authors do not commit to making the relevant anonymised patient-level data available upon reasonable request".[264] In contrast, Professor Sir John Bell believed that "the extreme position of making all patient line data available to all comers" had not been "properly thought through", adding that, "if applied forcefully for early stage trials", such as position would "essentially eliminate the biotechnology sector in the UK".[265] He, and several other witnesses, cited three issues in particular in opening IPD up to wider scrutiny: the potential detrimental effect on industry, the risk of inappropriate reanalysis and reinterpretation of data, and the need to protect patient confidentiality.

82. In considering the costs and benefits of sharing IPD, the ABPI stressed the need to protect the "legitimate interests of companies".[266] Dr James Shannon, Chief Medical Officer of GSK, also acknowledged that "if companies make [individual patient-level] data available, other companies will access it", describing how, during four hours in which GSK's new IPD-sharing system prematurely went live by accident, "three other companies accessed the data, plus Johns Hopkins hospital in the United States", despite there being no announcement of the system's activation or guidance in accessing it.[267] However, Dr Shannon considered that "the more eyes that are put on data the better, and that is why GSK has taken the lead to commit both to patient level data transparency as well as clinical study reports".[268]

261 National Audit Office, Session 2013–14, "Access to clinical trial information and the stockpiling of Tamiflu", HC 125, para 7

262 Ev w101, para 25; Ev w44, para 4.6; Ev w81, para3.2.5; Q 24 [Professor Rawlins]

263 Ev w1, para 2a

264 Ev 77, para 4.6

265 Ev 43, para 4.1.1

266 Ev 98, para A3

267 Q 89

268 Q 76

83. On the topic of inappropriate reanalysis and reinterpretation of IPD, the co-convenors of the Cochrane Collaboration IPD meta-analysis methods group told us that:

> 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.[269]

The Ethical Medicines Industry Group, a trade body representing small and medium-sized biopharmaceutical companies, warned that "sub-optimal analyses" could "only inevitably lead to sub-optimal conclusions and sometimes these will be dangerous to public health", and Dr Jamison, SMC, agreed that there was "a risk that, if there is more information out there, there is an opportunity for groups and individuals to either misuse that information or for groups who have an agenda to seize on it".[270] Roche cited "the scares around MMR vaccines" as an example that highlighted "the importance of handling data in a responsible way".[271] However, Dr Jamison questioned whether this was a valid comparison, stating that she did not think that we were "in the situation that we were in when we had the MMR scandal in the 1990s", and pointing out that "if you do not put that data out there, it may equally lead to scare stories, mistrust and confusion".[272]

84. The most substantial barrier to the sharing of IPD is the risk that it would violate patient privacy. IPD contains large amounts of personal information, and although anonymisation can reduce the risk of trial participants being identified from their data, several witnesses pointed out that this risk could not be entirely eliminated.[273] William Burns, a Roche Board Member, told us that patient confidentiality was a particular issue for trials of rare ("orphan") diseases, and other trials involving small numbers of participants, since this made it "more difficult" to effectively anonymise patients.[274] For example:

> If you had cystic fibrosis but you give a postcode, there may be only one child in that postcode that has the disease. As you get down to the more orphan diseases, it needs a little more thoughtfulness about how to protect the interests of the patient.[275]

The Cochrane IPD meta-analysis methods group agreed that relying on anonymisation of IPD "would retain some risk of disclosure" and told us that this would also "render the data less useful for research purposes" because of the information necessarily removed in the process of anonymisation (for example, the conversion of dates of birth into age brackets, or the removal of information such as a participant's occupation).[276]

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269 Ev w42, para 17

270 Ev w91, para 3.9.1; Q 139

271 Ev 88, para 5.1

272 Q 140

273 Ev w39, summary; Ev 102, para 4.2a; Q 24 [Professor Rawlins]

274 Q 77

275 Q 77

276 Ev w39; Ev41 summary, paras 15.0–15.1

85. In March 2013, the Department of Health published a review looking at the balance between sharing personal information and protecting individuals' confidentiality. *The Information Governance Review*, led by Dame Fiona Caldicott—known as the Caldicott 2 Review—concluded that:

> while from a legal perspective, patient data exists in one of two forms—with patients either identified or anonymous, in reality, the situation is more complex. In particular, there is a 'grey area' of data that on its own does not identify individuals, but could potentially do so if it were to be linked to other information".[277]

Peter Knight, Deputy Director, Head of Research Information and Intelligence at the Department of Health, told us that the IPD generated from a clinical trial was likely to fall into this "grey area", for which anonymisation was "a starting point" but where there remained a risk that participants could be re-identified by "meshing [...] together" other datasets in the public domain.[278] The Caldicott 2 Review recommended that for such data there should always be "safeguards for limited access" comprised of two components, "a contractual agreement and a set of data stewardship functions", recommending that such data could be managed through secure environments known as safe havens.[279]

86. Dr Godlee considered that an alternative solution would be to simply obtain a patient's consent to share their data at the outset.[280] Mr Denegri, NIHR and INVOLVE, agreed that patient consent could provide part of the solution, explaining that:

> There will always be some people who are concerned about [making their data available], and some quite rightly because they have a stigmatised disease and have a life experience that is extremely arduous. But, generally speaking, if you enter into a dialogue with a group of patients, they readily get the idea about data and why data need to be shared, or why it is beneficial to do so, and they will readily buy into that, as long as the rules are clear, the risks are clear and they know where they can get further information.[281]

CR-UK pointed out, however, that when it comes to retrospective disclosure of IPD, lack of patient consent may be a more difficult problem to overcome, since "patients may have only provided consent for their data to be used in a certain way", which prevents it from being shared with other researchers, for example.[282] A possible solution to this problem would be to contact patients again retrospectively to request consent. However, Professor Karol Sikora, Medical Director of Cancer Partners UK and Dean of the University of Buckingham Medical School, told us that this would be a difficult exercise and one that might "rekindle unpleasant memories" for patients and their families, particularly if the trial had not been a success.[283]

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277 Department of Health, *The information governance review,* March 2013, p 63

278 Department of Health, *The information governance review,* March 2013, p 63; Q 166

279 Department of Health, *The information governance review,* March 2013, p 64

280 Q 24

281 Q 104

282 Ev 92, para 25

283 Q 106

87. Serious reservations were expressed about increasing the transparency of IPD. For example, Sir Michael Rawlins, AMS, questioned how useful this type of data would be to "anybody who was not an expert statistician" and even the Cochrane Collaboration's IPD meta-analysis methods group—a group dedicated to providing guidance to those wishing to use IPD—stated that it would "not support open public access to clinical trial IPD".[284] David Willetts, Minister for Universities and Science, also expressed doubts, telling us that allowing for greater transparency of IPD while protecting patient privacy was "not at all straightforward".[285] Dr Janet Wisely, Chief Executive of the HRA, stressed the importance of restricting access, explaining that a recent survey indicated that while the public was "very comfortable" with researchers having access to anonymised data, there was "caution" about allowing wider access, for example, by researchers working outside the NHS.[286] Nevertheless, according to Lord Howe, Parliamentary Under-Secretary of State for Quality, Department of Health, there are "ways in which we and the pharmaceutical industry see a way through this"; namely, through the use of accredited safe havens—secure environments within which datasets can be combined and analysed in a way that protects patient privacy.[287]

88. **We are not in favour of placing anonymised individual patient-level data (IPD) in the public domain in an unrestricted manner, as we consider that the risk to patient confidentiality is too great and, for many past and current trials, this level of disclosure would go beyond the confines of previously obtained patient consent. Nevertheless, we recognise the scientific value of IPD and consider these data to be currently underutilised.** ***We agree with the Caldicott 2 Review that providing specific individuals with controlled access to personal confidential data such as IPD through carefully managed and secure "safe havens", together with contractual agreements about how that data can be used, is the best way forward. We also consider that access should be facilitated by an independent "gatekeeper", responsible for evaluating research proposals and ensuring that data is handled responsibly and in a way that makes a useful contribution to scientific knowledge.***

89. **The UK could take the lead in shaping how a global system for sharing IPD for non-commercial trials might operate and a national system covering all non-commercial UK trials would be capable of delivering potentially significant benefits. We consider that the Health Research Authority (HRA) could act as developer, administrator and gatekeeper for a central repository of IPD for non-commercial UK trials. In order to achieve this,** ***template consent forms provided by the HRA should allow for and emphasise to trial participants the benefits of data sharing. Research Ethics Committees should also take into account any transparency restrictions imposed by patient consent forms when evaluating research proposals for clinical trials.***

284 Q 34; Ev w42, para 18

285 Q 204

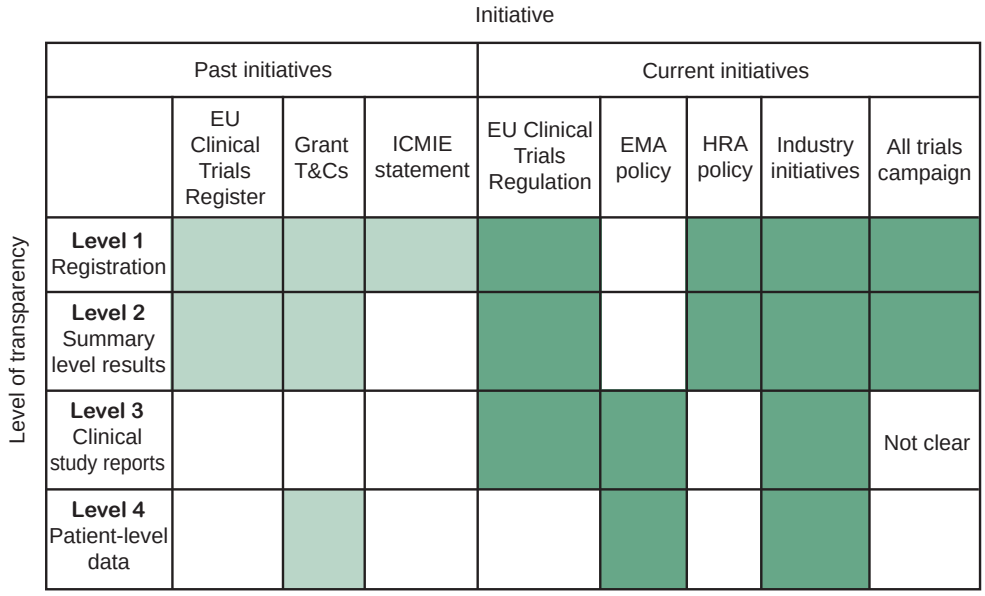
286 Q 171

287 Q 198

Past initiatives to increase clinical trial transparency

90. Over the last decade, several initiatives have attempted to bring about a greater level of transparency for trials conducted in the UK, Europe and the rest of the world. A brief overview of these initiatives is provided below and is summarised in Figure 2.

Figure 2: Past and current initiatives to increase trial transparency[288]



The EU Clinical Trials Register and ClinicalTrials.gov

91. In May 2004, the European Medicines Agency (EMA) established the EudraCT clinical trials database, a restricted-access record of all clinical trials of investigational medicinal products (CTIMPs) conducted in the EU.[289] Since March 2011, basic details of the trials contained within EudraCT (excluding phase I trials) have been made publicly available through the EU Clinical Trials Register (EU CTR), and from late 2013 it is planned that the EU CTR will also provide public access to summary-level trial results (although a previous pledge to include results on the register by 2012 was not met).[290] Since 2000, the ClinicalTrials.gov registry has fulfilled a similar role for US-based trials and is the currently the largest trials register globally.[291] Although largely US-focused, ClinicalTrials.gov also contains some UK-based trials and, since 2007, has included summary-level results.[292]

92. The EU CTR was described by the academic publisher BioMed Central as a "step towards increased transparency" and many other witnesses also referred positively to the

[288] Initiatives: EU Clinical Trials Register (paras 91–94); grant T&Cs = Public and charitable grant requirements (paras 95–100); ICMJE statement =International Committee of Medical Journal Editors (para 101); EU Clinical Trials Regulation (paras 103–104); EMA policy (paras 105–106); HRA policy (paras 107–110); industry initiatives (paras 111–113); AllTrials campaign (paras 114–116)

[289] Ev 57, para 32–33

[290] Ev 57, para 32–33; Ev 115, appendix para 22; Ev112, para 31

[291] Ev 95, para 19; Ev 80, para 6

[292] Under US legislation, results must be published on ClinicalTrials.Gov for: all trials that have at least one site in the United States; are of a drug, device, or biological agent; and are initiated or ongoing as of September 2007, excluding phase I studies and early feasibility trials of devices.

register in their evidence.[293] However, Dr Goldacre described the register as a "failed initiative" which was "incomplete by design" because it contained only "a small subset of all the trials that have been conducted" on a particular medicine.[294] Dr Goldacre explained that:

> The European Clinical Trials Register is a list of trials conducted within Europe over the past few years. It is not a list of all the trials that have been conducted on all the medicines currently available in Europe. It should be, or it should at least strive to be. Clinicaltrials.gov, similarly, is mostly trials conducted in the US, mostly from the past ten years, and with compulsory registration only since 2007.[295]

The Minister stated that the Government had "supported the work of the EMA" in developing EudraCT and described the EU CTR as "a public registry of all trials of medicines in the EU".[296]

93. We received mixed evidence regarding the level of compliance with regulatory registers, including both the EU CTR and its US equivalent, ClinicalTrials.gov. According to Dr Goldacre, a recent US law requiring trial results to be included on ClinicalTrials.gov "is widely cited as evidence that the problem of missing trials has been fixed. However there was no routine public audit of implementation, and when one was finally conducted [by Prayle *et al* in 2012] [...] it found that this law has been ignored by four trials out of five".[297] According to the ABPI, a representative of the US Food and Drug Administration has since "challenged the results of the above mentioned study, finding several flaws in the analysis":

> The US FDA's preliminary review of Prayle's results found that instead of 77.9% of trial summary results being overdue, 34.6% trial results were overdue by January 2011. Updating this analysis to May 31 2012, 21.1% of trial results were overdue, a compliance rate of 78.9%.[298]

The ABPI has since conducted its own research which suggested that for US trials of products approved by the European Medicines Agency between 2009 and 2011, 76% had published summary results within 12 months and 89% had published summary results as of January 2013—a far remove from the 22% compliance rate found by Prayle *et al.*[299] (We note that the ABPI's figures have not been subject to peer review and are based on a smaller and more recent sample of ClinicalTrials.gov data than the Prayle *et al* study.)

94. **We support the development of the EU Clinical Trials Register (EU CTR) and hope it will also include summary-level results, as promised, by the end of 2013. However, we do not consider the register to represent a complete solution to the problem of non-registration of clinical trials, as it does not include all the trials that have been**

293 For example, Ev w78, para 13; Ev 97, para 26-27; Ev 102, para 5.1

294 Ev 111, para 19; Ev 114–15 ,appendix para 10, paras 18–24

295 Ev 111, para 19

296 Q 215

297 Ev 110, para 6

298 Ev 100, para 3.4

299 Ev 103

conducted on all medicines currently available in Europe. ***The Government should encourage the EMA to further increase the scope of the EU CTR, for example by including phase I trials and trials conducted outside of the EU. We also recommend that the Government monitor the EMA's fulfilment of its pledge to include trial results on the register and obtain an explanation if the EMA fails to do so by the end of 2013.***

Public and charitable grant requirements

95. The UK Clinical Research Collaboration estimated that of approximately £8 billion spent each year in the UK on health-related research and development, £3.5 billion is spent by the public and not-for-profit sectors.[300] Two large public funders of UK trials are the MRC, which funds first-in-man and early phase studies[301] and the National Institute for Health Research (NIHR), which, since its formation in 2006, has had responsibility for funding later phase clinical trials.[302] The Government also provides indirect support to many trials funded by the charitable sector through its Charity Research Support Fund (CRSF).[303]

96. During our inquiry we discovered that, while the transparency requirements of the MRC and the NIHR were broadly similar, they varied in their detail. For example, while both required that the trials that they funded were registered and published, only the MRC set out a timescale for publication and only the NIHR stipulated that this must be in a "suitable peer-reviewed journal".[304] Compliance with these requirements, however, is mixed and is substantially below 100%. A 2013 audit of a sample of MRC-funded trials found that 11% had not yet been published and at least 14% had not been registered.[305] We were told that the rate of publication from NIHR-funded research was also variable, although the NIHR's Health Technology Assessment programme, which requires trial registration prior to monies being paid and which publishes research in its own dedicated journal, was unique in achieving "near total and complete publication for its research findings" (estimated to be around 98%).[306]

97. Sharmila Nebhrajani, Chief Executive of the Association of Medical Research Charities (AMRC), told us that 80% of AMRC member charities set out transparency requirements in the terms and conditions of their research grants.[307] Compliance, however, is mixed and not consistently monitored. Nicola Perrin, Head of Policy at the Wellcome Trust, stated that the organisation required all of its trials "to be registered and we expect publication as well", but admitted that "it is not an area that we have actively policed until now" and was

300 UK Clinical Research Collaboration, *UK health research analysis 2009/10*, 2012, p 10

301 First-in-man studies are studies in which a health intervention is tested in a human for the first time. Early phase studies are generally considered to comprise phase I and II trials (see para 9).

302 Ev 107, para 3

303 The CRSF came into existence in 2006–07 following changes to the dual-support system for research funding. It was designed to ensure that charities would not have to cover the indirect costs of the research that they funded. For further information see "AMRC guidance on the Charity Research Support Fund", *AMRC*, amrc.org.uk, accessed September 2013

304 Ev 107, para 8; Q 49 [Dr Elliott]; Ev w61, para 4.5

305 Q 48 [Dr Elliott]; Q 52 [Dr Elliott]

306 Ev w61, paras 4.4-4.7

307 Q 49 (Includes only those members that fund clinical research)

unable to provide a current figure for compliance.[308] In contrast, Professor Peter Johnson, Chief Clinician at CR-UK, was confident that his charity achieved a high level of compliance, explaining that:

> It is a condition of funding by Cancer Research UK that any trial is registered. The way we police that is to check at the first annual renewal of the grant that the trial is indeed registered, so we think we have 100% take-up rate for registration and very high rates of publication.[309]

98. When questioned, David Willetts, the Minister for Universities and Science, told us that the Government "would usually expect that publicly-funded research should be made publicly available" and Lord Howe referred to the fact that the NIHR and MRC already required all clinical trials to be published, adding that the Government "would expect compliance [with this requirement] to be 100%".[310] Acknowledging that this was not currently the case, the Government told us that "applicant-declared intentions to register and publish trial results" would be more closely monitored in the future through a software programme called Researchfish.[311] When asked whether current registration and publication policies should also be imposed retrospectively, the Minister pointed out that the Government was encouraging industry to publish the results of past trials, but made no comment on the retrospective disclosure of publicly-funded research.[312]

99. **As a major direct and indirect funder of clinical trials, the Government can influence behaviour across both the public and charitable sectors. This influence has not been wielded effectively to increase transparency, meaning that many publicly-funded trials remain unregistered and unpublished.** ***We recommend that registration in a WHO-listed registry and publication of summary-level results in a peer-reviewed journal be made contractual requirements for all publicly-funded trials, including research supported by the Charity Research Support Fund. The wording of these requirements should be standardised across all contracts to ensure consistency. We also recommend that public funders of research rapidly put in place mechanisms to monitor compliance with transparency policies and ask the Government to detail in its response to this Report how and when this will be done.***

100. **Since the Government has encouraged industry to disclose retrospectively the results of past trials, we think that it should be prepared to do the same for the major trials that it has funded.** ***We therefore recommend a retrospective audit of all public phase III trial grants awarded since 2000, followed by action to ensure that any failures to register or publish the summary-level results of these trials are rectified within 12 months. Any failures to correct these mistakes should be taken into account when considering future grant applications from principal investigators of previously unregistered or unpublished trials. In future, for grants awarded to fund phase III clinical trials we suggest that the MRC and the NIHR allocate a small proportion of funding to cover the***

308 Q 51

309 Q 49

310 Q 219 [Mr Willetts]; Q 198 [Lord Howe]; Q 225 [Lord Howe]

311 Ev 55, para 16; Q 198 [Lord Howe]

312 Q 199; Q 225

time and resource requirements of preparing a manuscript for publication, and withhold this funding until the results of the trial are ready to be published.

The International Committee of Medical Journal Editors

101. In 2004, the International Committee of Medical Journal Editors (ICMJE) issued a statement pledging that, in future, "ICMJE member journals will require, as a condition of consideration for publication in their journals, registration in a public trials registry" before recruitment of the first patient.[313] As a result, several leading medical journals, including the *BMJ, The Lancet* and the *New England Journal of Medicine*, agreed to require registration as a pre-requisite of publication for all trials initiated after July 2005, and according to PLOS, a not-for-profit academic publisher, since then "many [...] journals, including all the PLOS journals, have adopted this policy".[314] Dr Elizabeth Wager, a freelance writer, editor and publications consultant, claimed that this had brought about "a sharp increase" in trial registration.[315] However, according to Dr Goldacre, research conducted in 2009 showed that "half of all trials published in major medical journals [...] had not been properly registered, and a quarter had not been registered at all", despite the ICJME pledge.[316] PLOS agreed that trial registration was far from universal, stating that it too continued to receive "submissions of unregistered trials" for publication in its journals, which it rejected as a result.[317] **We suggest that the academic publishing industry put in place robust measures to ensure that unregistered trials are not just rejected, but that the trial sponsor(s) and funder(s) are notified that the trial has not been properly registered.**

Current initiatives to increase clinical trial transparency

102. Since we began taking evidence in early 2013, several developments have occurred at the European and national level which aim to increase the transparency of trials conducted across Europe and the UK.

The EU Clinical Trials Regulation

103. The new EU Clinical Trials Regulation contains several clauses related to trial transparency. According to the current draft, adopted by the European Parliament's Environment, Public Health and Food Safety (ENVI) Committee in May 2013, all trials within the Regulation's scope will need to be registered on a publicly accessible European database prior to initiation and sponsors will also be required to submit to this database summary results "together with a layperson's summary, and, where applicable, the clinical

313 "Uniform Requirements for Manuscripts Submitted to Biomedical Journals", *ICJME*, icmje.org, accessed September 2013; "Frequently Asked Questions: Questions about Clinical Trials Registration", *ICJME*, icmje.org, accessed September 2013

314 Ev w52, para 13

315 Ev w29, para 4.1

316 Ev 114, appendix, para 14

317 Ev w52, para 13

study report" within a year of the trial's completion or termination.[318] The most recent amendments to the draft Regulation were adopted towards the end of our inquiry and so we have limited evidence on their reception by stakeholders. However, when giving evidence a few days after the ENVI Committee's vote, the Minister stated that the Government was "supportive" of these amendments and felt that the ENVI Committee had reached "a sensible and proportionate decision".[319] When asked whether he would have liked to have seen any other changes made to the proposed Regulation, the Minister answered "no".[320] This legislation is scheduled to be debated by the European Parliament in plenary in March 2014 and, if passed, will likely come into effect in 2016.

104. **In mandating trial registration, publication of summary-level results and publication of CSRs for commercial trials, we consider that the European Parliament's ENVI Committee appears to have reached a reasonable decision regarding the transparency requirements of the proposed EU Clinical Trials Regulation.**

The European Medicines Agency

105. In June 2013, the EMA issued for consultation a proposed new policy on access to clinical trial data, in advance of a target implementation date of January 2014.[321] This proposed policy would split the trial data that it receives, including clinical study reports (CSRs) and individual patient-level data (IPD), into three distinct categories:

- Category one: trial data containing information deemed commercially confidential;
- Category two: trial data or documents where the protection of personal data is not a concern, either because the document does not contain personal data, or because personal data have been adequately de-identified, and
- Category three: individual patient-level data for which the protection of patient confidentiality is a concern.[322]

Under the terms of the EMA's revised policy, category one data would remain largely confidential, category two data would be downloadable from the EMA's website and category three data would be made available on request under a controlled-access model. According to the proposed mechanism for category three data, patient privacy would be protected through de-identification and a legally binding data-sharing agreement which would prohibit those accessing the data from using it for unauthorised purposes or sharing it with unauthorised persons, amongst other things.[323]

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318 European Parliament, Committee on the Environment, Public Health and Food Safety, *Report on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use,* 7 June 2013, p 26

319 Q 200; Q 217

320 Q 218

321 European Medicines Agency, *Draft policy 70: publication and access to clinical trial data*, EMA/240810/2013, June 2013

322 European Medicines Agency, *Draft policy 70: publication and access to clinical trial data*, EMA/240810/2013, June 2013, pp 4-5

323 This is a partial list of requirements. For full details see European Medicines Agency, *Draft policy 70: publication and access to clinical trial data*, EMA/240810/2013, June 2013, pp 5-6

106. The EMA's draft policy was issued after we had concluded taking evidence. However, we did get a sense from the Minister of the extent to which the Government had been involved in its development. The Government told us that, while Sir Kent Woods, MHRA Chief Executive, had attended the EMA workshop preceding the consultation in his capacity as Chair of its Management Board, "officials from the Department and the MHRA were not present" at subsequent discussions.[324] Government authorities and regulators of several other countries, including the US Food and Drug Administration, the Danish Health and Medicines Authority, the Norwegian Medicines Agency and the German Federal Institute for Drugs and Medical Devices, were represented during these discussions.[325] ***The Government should clarify why Department of Health or MHRA officials were not present at recent discussions relating to the EMA's revised transparency policy.*** **We hope that the Government will be more fully engaged in the next stages of the development of this policy.**

The Health Research Authority

107. Under both the EU Clinical Trials Directive and UK governance arrangements, in order to obtain clinical trial authorisation, all UK trials must first be evaluated and approved by an accredited Research Ethics Committee (REC), currently operated by the National Research Ethics Service, part of the Health Research Authority (HRA). According to the HRA, as part of the research application process "researchers are asked to provide information about the registration of their study [...] and their plans for dissemination of results" and "these aspects are reviewed by RECs".[326] However, in a 2013 HRA survey less than 50% of RECs confirmed that they actively reviewed the intentions of researchers to register and publish their results when assessing a research proposal and a 2013 audit revealed that of a sample of 115 studies, only "33 had done what they said they would do, in publishing, and two phase 1 studies had done likewise, in not publishing".[327]

108. In May 2013, the Health Research Authority (HRA) issued a paper setting out new plans for promoting clinical trial transparency. This included proposals to:

- make trial registration within an agreed timeframe a condition of Research Ethics Committee (REC) approval from September 2013;
- develop mechanisms to review actively plans for publication and include them specifically within the condition of the REC approval, and
- develop simple mechanisms to monitor compliance with REC-approved publication plans.[328]

Dr Wisely, Chief Executive of the HRA, explained that the HRA already had "simple mechanisms to check at the end of the study whether people have registered and published

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[324] Ev 58

[325] European Medicines Agency, *Clinical trials advisory groups: membership overview*, EMA/33488/2013, 20 February 2013

[326] Ev 104, para 12

[327] Health Research Authority, *Transparent Research*, May 2013, p 16; Q 151 [Dr Wisely]

[328] Health Research Authority, *Transparent Research*, May 2013, pp 4–5

as they should", but admitted that "a better framework" was needed.[329] Nevertheless, under its new policy Dr Wisely stated that for some research the HRA would continue to "rely on the sponsor" to ensure compliance.[330] For instance:

> when the NIHR funds research [...] it ensures that studies are registered and published, so we don't need to double-check. The MRC has got very good rates for publication registering, so it may be that for some we do a random audit within an overall assurance at a sponsor level and for others we do the audit on an application level.[331]

In July 2013, the HRA confirmed its plan of action for improving transparency in health research, but details of this plan do not appear to have been made publicly available.[332]

109. In March 2013, the Joint Committee responsible for scrutinising the Draft Care and Support Bill, through which the HRA will likely be established in legislation as a non-departmental public body in 2013/14, published its report.[333] The Committee recommended that the draft Bill be amended "so that promoting transparency in research and ensuring full publication of the results of research, consistently with preservation of patient confidentiality, becomes a statutory objective of the HRA".[334] The Committee also recommended that the HRA place on RECs "an obligation to include provisions on the publication of research when granting approval for the conduct of research, and an obligation to ensure that such provisions are complied with".[335] In its May 2013 response to the Joint Committee's report, the Government reiterated that it fully supported the principle of transparency in research and would want to take account of the findings of our Report on clinical trials before "determining the HRA's future role in relation to transparency of research".[336] ***We agree with the Joint Committee that the Care and Support Bill should make the promotion of research transparency a statutory objective of the HRA and we recommend that the Government includes the necessary provision.***

110. **Research Ethics Committees should have a role in considering and monitoring compliance with transparency policies. As such, we welcome the HRA's new transparency policy and support, in principle, the proposals made in its May 2013 paper.** ***We recommend that the HRA initially retains full responsibility for policing its own policies and ensures that all trials have been registered and published according to an agreed timeline, rather than performing checks on a sample basis. In addition, there must be penalties for non-compliance. We recommend that the HRA provides us with a progress update on implementation of its new transparency policy by the end of 2013.***

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329 Q 153

330 Q 153

331 Q 153

332 "HRA confirms its action plan on transparent research", *Health Research Authority press release*, 16 July 2013

333 Joint Committee on the Draft Care and Support Bill, Session 2012–13, *Draft Care and Support Bill*, HC 822

334 Joint Committee on the Draft Care and Support Bill, Session 2012–13, *Draft Care and Support Bill*, HC 822, para 335

335 Joint Committee on the Draft Care and Support Bill, Session 2012–13, *Draft Care and Support Bill*, HC 822, para 336

336 Department of Health, *The Care Bill explained: including a response to consultation and pre-legislative scrutiny on the Draft Care and Support Bill*, Cm 8627, May 2013, para 201

Industry-led initiatives

111. In recent years, select members of the pharmaceutical industry, led by GSK, have taken steps to increase the transparency of the clinical trials that they sponsor.[337] In 2004, GSK became the first company to launch its own dedicated trials register and was quickly followed by other companies including Roche, AstraZeneca and Novartis.[338] In February 2013, GSK stated that it would supplement this register by posting clinical study reports (CSRs) for all future trials and for past trials of approved medicines, and in May 2013 it became the first major pharmaceutical company to put in place a dedicated system aimed at providing researchers with access to the anonymised individual patient-level data (IPD) generated by its trials.[339] According to GSK, requests for access to this data are considered by "an independent panel of experts" conducting "a high-level review of proposals to help ensure that data is used in a scientific and responsible manner".[340] Once a request has been approved, access is provided via a "secure IT environment" akin to the type of safe haven recommended by the Caldicott 2 Review, although this prevents researchers from combining GSK's data with data from other sources, thereby effectively preventing the data from being used for the purpose of meta-analysis.[341] In February 2012, Roche announced that it would implement a similar system to complement its existing clinical trials registry and results database, although it has not announced any plans to provide systematic access to CSRs.[342]

112. In July 2013, the trade bodies the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA) published their joint *Principles for responsible clinical trial data sharing*.[343] According to these principles, pharmaceutical companies will make the synopsis section[344] of clinical study reports of many trials publicly available, and will "commit to sharing upon request from qualified scientific and medical researchers" individual patient-level data (IPD), provided that such requests are approved through a "scientific review board" established by the company.[345] Companies will not be required to provide access to IPD if there is "a reasonable likelihood that individual patients could be re-identified", or where this goes beyond the limits of signed patient consent forms.[346] Dr Goldacre described these commitments as "weak and filled with loopholes", but Trish Groves, Deputy Editor of the *BMJ*, considered that these principles demonstrated that transparency campaigners had "won a battle, if not the war" over greater trial transparency.[347]

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337 See paras 77 and 82

338 Ev 122, introduction, para 3; See also, for example, the trials registers available at roche-trials.com, novctrd.com and astrazenecaclinicaltrials.com

339 Ev 124, paras 4.2–4.4; Nisen, P. and Rockhold, F., "Access to Patient-Level Data from GlaxoSmithKline Clinical Trials", *New England Journal of Medicine*, vol 369, 1 August 2013, pp 475–478

340 Ev 124, para 4.4

341 Meta-analysis is a statistical technique in which the results of several independent studies are combined.

342 "Roche launches new process for accessing clinical trial data", *Roche press release*, 26 February 2013

343 "EFPIA and PhRMA Release Joint Principles for Responsible Clinical Trial Data Sharing to Benefit Patients", *EFPIA press release,* 24 July 2013

344 The synopsis section of a clinical study report (CSR), usually limited to no more than three pages of text, summarises the objectives, methodology, results and conclusions of a trial.

345 EFPIA/PhRMA, *Principles for responsible clinical trial data sharing*, July 2013, p 1

346 EFPIA/PhRMA, *Principles for responsible clinical trial data sharing*, July 2013, p 4

Implementation of these commitments by EFPIA/PhRMA members will begin on 1 January 2014.

113. **We recognise the efforts of some members of the pharmaceutical industry, particularly GSK, to increase clinical trial transparency and hope that other companies will act in the same spirit in implementing industry-wide principles for responsible clinical trial data sharing. We suggest that all companies endorsing such principles agree and report on a common set of clinical trial transparency metrics each year in their annual reports.**

The AllTrials campaign

114. The AllTrials campaign is an initiative co-founded by Sense about Science, Dr Ben Goldacre, the *BMJ,* the James Lind Initiative and Oxford University's Centre for Evidence-based Medicine.[348] It was launched in January 2013 and called for "all clinical trials to be registered and results to be reported, from both industry and academia".[349] According to Dr Goldacre, the campaign has "now got the support of 50,000 individuals, more than 100 patient groups and most of the medical and academic professional bodies in the UK".[350]

115. The campaign's website states that AllTrials is calling for the publication of results—"that is, full clinical study reports"—from all clinical trials of treatments currently in use.[351] Similarly, Sense about Science recommended to us in its written evidence that "for all trials (phase 2 and above) conducted since 1990 [...] full clinical study reports, or equivalent, should be made publicly available".[352] Applying the terminology used in this Report,[353] Sense about Science and the AllTrials campaign therefore appeared to be calling for the first three levels of trial transparency: trial registration (level 1), publication of summary-level results (level 2) and publication of clinical study reports (CSRs), or their equivalent (level 3). In oral evidence, Tracey Brown, Managing Director of Sense about Science, stated that "the aim of the AllTrials campaign is to ensure that levels 1 and 2 are published" but admitted that the requirements for level 3 still needed to be "ironed out and worked on".[354] Ms Brown later confirmed in supplementary evidence that the AllTrials campaign was only specifically "calling for levels 1 and 2".[355] In August 2013, however, AllTrials published "a detailed plan" of the campaign's objectives in which it stated that the campaign was concerned with the "first three" levels of trial transparency.[356] This document called for all those producing a CSR (or equivalent) for regulatory reasons or "any other purpose" to make the report publicly available.[357] The plan did not set out what information the

347 "EFPIA and PhRMA publish principles on clinical trial data sharing", *AllTrials*, alltrials.net, accessed September 2013

348 Ev 59, para 1.1

349 "AllTrials campaign launch", *Sense about Science press release*, 9th January 2013; Ev 59, para 1.1

350 Uncorrected transcript of oral evidence taken before the Public Accounts Committee on 17 June 2013, HC 295–i, Q 6

351 "The AllTrials campaign", *AllTrials*, alltrials.net, accessed September 2013

352 Ev 60, para 3.3

353 Level 1 = trial registration, level 2 = publication of summary-level results, level 3 = publication of clinical study reports and level 4 = sharing of individual patient-level data

354 Q 120

355 Ev 74

356 "All trials registered and results reported", *AllTrials*, alltrials.net, accessed September 2013

357 "All trials registered and results reported", *AllTrials,* alltrials.net, accessed September 2013

campaign expected to be included in a non-commercial full trial report or in what circumstances such a report might be prepared.

116. **We are supportive of the broad aims of the AllTrials campaign and agree that all clinical trials should be registered and their results reported. We suggest that the AllTrials campaign clearly set out what it considers a full trial report to contain, particularly when prepared for non-commercial purposes, so that its supporters can work together to achieve a specific set of common goals.**

Value-based pricing and the renegotiation of the PPRS

117. For most branded medicines, the price that the NHS pays is agreed through a voluntary agreement with the pharmaceutical industry known as the pharmaceutical price regulation scheme (PPRS).[358] The current PPRS, agreed in January 2009, is due to expire at the end of 2013 and negotiations for the 2014 successor scheme are currently underway.[359] Alongside the PPRS, from January 2014 the Government will operate a parallel scheme for establishing the price of newly-licensed branded medicines. Value-based pricing (VBP), according to the Government, will "ensure [that] NHS funds are used to gain the greatest possible value for patients" by more closely aligning the price paid for a drug with the value that it delivers to the NHS and to society.[360] According to the Government, VBP will help to "recognise and reward innovation" and will give industry "clear signals about priority areas, so that research efforts are directed to maximum effect".[361] In light of this argument, we wanted to understand how the Government might be able to use its influence as a customer to encourage other forms of good behaviour, such as increased transparency. When we questioned the Minister about the Government's ability to influence industry, he acknowledged that the NHS was "an important customer for drug companies", and added that "if you speak to the pharmaceutical companies, you may hear them say that the pricing arrangements do have an influence on their decision-making".[362]

118. **Value-based pricing (VBP) is predicated on the idea that the Government is able to influence industry's behaviour through its spending power. We therefore consider VBP—and to a lesser extent the PPRS—to be tools that could also be used to encourage and reward industry for making its clinical trial data more transparent. *The Government should consider ways in which clinical trial transparency could be incentivised in the future through VBP and the current renegotiation of the Pharmaceutical Price Regulation Scheme (PPRS).***

358 The 10% of branded drugs not covered by the PPRS fall within the scope of the statutory pharmaceutical pricing scheme, which was also open for consultation when this Report was published; See "ABPI response to Department of Health's consultation on medicines pricing", *ABPI press release*, 26 June 2013

359 "Understanding the pharmaceutical price regulation scheme", *ABPI*, abpi.org.uk, accessed September 2013

360 Department of Health, *A new value-based approach to the pricing of branded medicines: a consultation*, December 2010, p 5; p 12

361 Department of Health, *A new value-based approach to the pricing of branded medicines: a consultation*, December 2010, para 2.16

362 Q 211

Incorporating emerging evidence into clinical practice

119. Throughout this inquiry, we heard that a key motivation for making clinical trial data more transparent was to improve the evidence-base for treatments currently used by the NHS.[363] If this is to happen, the emerging evidence generated by increased transparency must be taken into consideration in clinical decision-making. We have considered one mechanism for achieving this—the National Institute for Health and Care Excellence (NICE).

120. NICE is an "independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health".[364] It produces several forms of advice designed to help health professionals make decisions that support "effective, good value healthcare" on the basis of the best available evidence.[365] While it is not currently mandatory for health professionals to follow all types of NICE guidance,[366] Bill Davidson, Acting Deputy Director and Head of Research Standards and Support at the Department of Health, told us that NICE guidance was a "key mechanism" through which emerging evidence reached the "front line".[367] Professor Sikora, Cancer Partners UK and the University of Buckingham Medical School, agreed that doctors "could not deviate" from NICE guidance "because the pharmacy will reject if you prescribe a drug" not recommended by NICE.[368]

121. Fortunately, given its apparent influence, Professor Sikora considered NICE's advice to be high quality and "very well thought out", although he considered guidance to be "too slow" in some cases.[369] The time taken to develop NICE's advice is varied, typically ranging from 9-24 months and "to keep pace with the changes" in medical knowledge NICE stated that its guidance was "regularly reviewed [...] to take into account any new evidence that may influence our recommendations".[370] When asked whether he was satisfied with the timeline for development of NICE guidance, the Minister replied that "if it were the case that it took two years for NICE to do everything, I would not be satisfied".[371] However, he added, "I do not believe that is so", and "over the last few years NICE has significantly accelerated the rate at which it is able to produce results".[372] The Minister told us that "NICE routinely reviews clinical guidelines every three or four years to consider whether they should be updated and can take into account any new evidence" and assured us that

363 See for example Ev 116, appendix, paras 47–51; Ev67, para 1

364 Ev w98, para 2

365 "What we do", *NICE,* nice.org.uk, accessed September 2013

366 See "What we do", *NICE*, nice.org.uk for further information on the various types of NICE guidance.

367 Qq 172–173; We were not able to identify any data indicating overall take-up of NICE guidance, although information at the level of individual items of guidance is available online at "Search the uptake database", *NICE*, nice.org.uk, accessed September 2013

368 Q 107

369 Q 107

370 "How we work", *NICE*, nice.org.uk, accessed September 2013

371 Q 191

372 Q 191

"it also has processes in place to bring forward updates if significant new evidence emerges before the scheduled review point".[373]

122. **Increased transparency is unlikely to lead to improved medical outcomes unless mechanisms are in place to ensure that emerging evidence is quickly and effectively incorporated into clinical practice. Given the high degree of reliance placed on NICE's guidance by health professionals, we consider it essential that this advice remains fully up to date and that processes are in place to ensure that emerging evidence is rapidly incorporated.** ***The Government should ensure that, as improved transparency leads to ever greater volumes of trial data becoming available, NICE continues to receive the resources it needs to assimilate emerging evidence into its guidance in a timely manner.***

[373] Q 193

5 Conclusions

123. For several years the Government has been aware of the key barriers to conducting clinical trials in the UK, and some progress has been made in eliminating them. We are satisfied that the introduction of the new European Clinical Trials Regulation will, if implemented as currently envisaged, make it easier to conduct trials across the EU, and we also consider the creation of the HRA to be a potentially significant step forward. **Nevertheless, we consider that more can and should be done to make the UK a more attractive location to conduct clinical trials.**

124. The UK regulatory and governance landscape for clinical trials remains complex, and not all researchers are yet aware of the ways in which the HRA can help them to navigate a path through this environment. The Government has also failed, so far, to eliminate the biggest barrier to initiating a clinical trial in the UK—the requirement for multiple NHS R&D approvals. In addition, despite positive public attitudes towards medical research, it is disappointingly difficult for the public to find out about potential research opportunities, and while we welcome the re-launch of the Clinical Trials Gateway, we consider that it has not yet reached its full potential. **We are confident that the Government is aware of these problems and the need to resolve them, but its promises have yet to be matched by effective action. We strongly urge the Government to act on our recommendations and put an end to these long-standing issues, so that the UK can continue to make progress towards being the location of choice for the global life sciences industry.**

125. Today, many of the clinical trials taking place in the UK remain unregistered and unpublished and their data continue to be unavailable to both the general public and the scientific community. This is unacceptable and we have not been impressed by the Government's efforts to resolve this important issue. Until recently, the Government has apparently been content to leave it to other groups at the national, European and global level to lead the way in tackling the problem of trial transparency and, while UK initiatives alone cannot solve what is a global problem, we do not accept limited jurisdiction as a legitimate excuse for Government inaction. **We call on the Government to take decisive steps, as outlined in this Report, to ensure greater transparency in all future trials conducted in the UK, in order to demonstrate to the rest of the world how effective solutions might one day be applied at a global level.**

Conclusions and recommendations

What are clinical trials?

1. Clarity in use of the term “clinical trial" is essential. The establishment of consistent terminology would be an important first step towards making the UK an easier place to conduct clinical research. We recommend that the Government agrees a set of simple definitions for the terms “clinical trial”, “clinical study” and “clinical research” and ensures their consistent use across the Health Research Authority, Medicines and Healthcare Products Regulatory Agency, Medical Research Council, National Institute of Health Research and the NHS. (Paragraph 11)

The European Clinical Trials Directive

2. We recognise the significant barrier to research posed by the European Clinical Trials Directive and welcome proposals for a new European Clinical Trials Regulation. However, we are concerned that a lack of clarity in the detail of the Regulation could lead to inconsistencies in its implementation across Member States, and we are not persuaded that proposals go far enough in ensuring that low-risk trials are regulated in a proportionate way. We urge the Government and MHRA to continue engaging at a European level to resolve these issues and to work together to ensure that, when the resulting legislation is introduced, the administration of clinical trials in the UK will be pragmatic and proportionate. (Paragraph 24)

UK regulatory and governance complexity

3. We commend the establishment of the Health Research Authority (HRA) and note that feedback on the HRA’s performance to date has been largely positive. However, we are unable to judge whether the HRA has so far been effective in achieving its objectives, as the necessary performance indicators are not currently in place. We recommend that the HRA establishes and publishes a suite of relevant key performance metrics and targets in its 2014/15 Business Plan, and monitors performance against these targets annually. We further recommend that a triennial review of the HRA takes place no later than December 2014, three years after its creation as a Strategic Health Authority. (Paragraph 31)

4. Over a year after its creation, some stakeholders (including an academic health science centre, intended to be a centre of excellence for UK health research) remained unaware of the function, or even the existence, of the HRA. Although these stakeholders also bear some responsibility for their own awareness of such developments, we consider that the HRA should now place greater emphasis on engaging with the clinical research community and raising the profile of its work. The HRA should detail in its response to this Report how it intends to do this. (Paragraph 32)

5. We welcome moves by the HRA to streamline NHS governance arrangements and stress the importance of this initiative, which, in our view, should be given the highest priority. Following completion of the feasibility study, we recommend that a

timeline detailing the next steps be published as part of the HRA's response to this Report. The Government should assist the HRA in its efforts to meet this priority, including making additional resources available if necessary. (Paragraph 35)

6. We are disappointed that the Government has failed to meet its own 2012 deadline for measuring NHS Trust performance against a 70-day benchmark for clinical trial initiation and we query whether this target is realistic in the short-term. We recommend that the Government updates us on current performance and on how many NHS Trust contracts now include this benchmark in its response to this Report. (Paragraph 37)

Patient recruitment

7. We welcome changes designed to make the NHS Constitution more research-focused and the launch of the Government's OK to Ask campaign. However, we are cautious of any suggestion that the system, as a result of this new onus, will automatically act to promote the existence of and encourage involvement in clinical trials. We recommend that the Government provides details of how changes to the NHS Constitution and the OK to Ask campaign have been communicated and promoted, both within the NHS and to the general public. In twelve months' time it should publish evidence on how the measures have affected both public and professional attitudes to, and participation in, clinical trials. (Paragraph 43)

8. We note the apparent lack of public confidence in the pharmaceutical industry and are concerned that this may increasingly pose a barrier to conducting trials in the NHS. Industry should act to regain trust lost through past examples of poor behaviour by engaging more effectively and transparently with the public in the future. In addition, Trusts need to do far more to educate patients about the benefits, both to them and to the wider community, of participating in research and allowing properly controlled sharing of patient data. (Paragraph 44)

9. We were impressed by the quality and accessibility of Cancer Research UK's trials database, which is reflected in the high volume of traffic that it receives. In contrast, while we are satisfied that the Government is working to improve and promote its own Clinical Trials Gateway, we were concerned to find that only 20% of its target users were aware of its existence as of mid-2012, and that the Minister was unable to give us a more detailed account of what was being done to improve this. The Government must improve the Clinical Trials Gateway and raise its profile with patients, clinicians and the general public. We recommend that the Government provides details about how it will achieve this, together with indicative timelines and targets, in its response to our Report. (Paragraph 50)

10. We consider it important that the information contained on the Clinical Trials Gateway is accessible to the lay person, which does not appear to be consistently the case at present. The Government should ensure that all trials listed on the Gateway include a plain language summary written specifically for a lay audience. Where such summaries are not already in existence, the Government must be prepared to commit the time and effort needed to create them. Taking into account the Gateway's current resource levels, we recommend that, where possible, preparation

of a lay summary should be included as a requirement for publicly-funded trials, but that the Government remain open to the option of increasing the level of resource dedicated to the Gateway if necessary. (Paragraph 51)

Clinical trial transparency

11. Clinical trial transparency is important and greater transparency would be likely to provide a number of benefits, particularly if applied retrospectively. However, there are obstacles to achieving this and the drive for greater transparency must be balanced against other concerns, particularly the need to protect patient privacy. Greater disclosure does not necessarily equate to greater transparency if the information shared cannot easily be understood and we therefore recommend that efforts to increase the availability of clinical trial data focus on providing information that is accessible, assessable, intelligible and usable. (Paragraph 58)

Level 1: Trial registration

12. We consider universal trial registration to be a crucial step in increasing clinical trial transparency and believe that all future trials should be included in a publicly-accessible register. This is clearly not the case at present, even for trials conducted in the UK. We recommend that the Government take steps to ensure that, in future, all clinical trials conducted in the UK, and all trials related to treatments used by the NHS, are registered in a WHO-listed primary registry. (Paragraph 63)

13. Since the trials of treatments currently in use often occurred many years ago, retrospective disclosure is important if the benefits of clinical trial transparency are to be realised in the short to medium-term. Although retrospective trial registration will incur some cost, we consider that this will be outweighed by the public health benefit of having a complete picture of the trials conducted on treatments currently available to patients. The Government should support the retrospective registration of all trials conducted on treatments currently available through the NHS and should actively pursue policies to bring this about. (Paragraph 64)

Level 2: Summary-level trial results

14. We consider that summary-level results should be made publicly available for all clinical trials and we welcome the many new media through which it is now possible to share this information. Nevertheless, peer review is vital to the reputation and reliability of scientific research and we deem it appropriate that journal articles remain the primary instrument for the publication of summary-level trial results. (Paragraph 68)

15. Many historic trials remain unpublished, which is far from ideal. However, retrospective publication of all trials of all treatments currently in use, while desirable, would almost certainly be unachievable given the likely time and resources that this would require. We therefore emphasise again the importance of retrospective trial registration as a means of providing a vital "index" against which individual cases of non-publication can be identified and, where of particular importance, pursued on an ad hoc basis. (Paragraph 69)

16. Given recent changes to academic publication models, we do not recognise as legitimate the argument that it is not possible to publish "negative" results in a peer-reviewed journal and we consider failure to publish on a timely basis to be poor scientific practice. However, we are sympathetic to the pressure that scientists are often working under and therefore we urge the Government and other trial funders to ensure that researchers are provided with the time and resources needed to meet their publication obligations. (Paragraph 70)

17. We encourage academic publishers to remove "Ingelfinger" restrictions on the pre-publication of summary-level results through media such as trial registries, in order to facilitate greater openness and faster access to important scientific data. (Paragraph 72)

Level 3: Clinical study reports

18. It would be unduly burdensome to mandate that clinical study reports (CSRs) be produced for non-commercial trials. We also consider that issues concerning the reliability of the information contained in academic journal articles should be dealt with at source, for example by strengthening the peer review process as recommended in our 2011 Report, rather than by effectively bypassing academic publication through greater reliance on CSRs. We therefore do not support any move to make it mandatory for non-commercial trials to produce a CSR, or any other document of an equivalent level of detail. However, we recognise that CSRs can provide a useful contribution to the scientific literature and, once a regulatory decision has been reached, we see no compelling reason why CSRs should not be placed in the public domain, with identifiable patient data redacted. (Paragraph 79)

Level 4: Individual patient-level data

19. We are not in favour of placing anonymised individual patient-level data (IPD) in the public domain in an unrestricted manner, as we consider that the risk to patient confidentiality is too great and, for many past and current trials, this level of disclosure would go beyond the confines of previously obtained patient consent. Nevertheless, we recognise the scientific value of IPD and consider these data to be currently underutilised. We agree with the Caldicott 2 Review that providing specific individuals with controlled access to personal confidential data such as IPD through carefully managed and secure "safe havens", together with contractual agreements about how that data can be used, is the best way forward. We also consider that access should be facilitated by an independent "gatekeeper", responsible for evaluating research proposals and ensuring that data is handled responsibly and in a way that makes a useful contribution to scientific knowledge. (Paragraph 88)

20. The UK could take the lead in shaping how a global system for sharing IPD for non-commercial trials might operate and a national system covering all non-commercial UK trials would be capable of delivering potentially significant benefits. We consider that the Health Research Authority (HRA) could act as developer, administrator and gatekeeper for a central repository of IPD for non-commercial UK trials. In order to achieve this, template consent forms provided by the HRA should allow for and emphasise to trial participants the benefits of data sharing. Research Ethics

Committees should also take into account any transparency restrictions imposed by patient consent forms when evaluating research proposals for clinical trials. (Paragraph 89)

Past initiatives to increase clinical trial transparency

21. We support the development of the EU Clinical Trials Register (EU CTR) and hope it will also include summary-level results, as promised, by the end of 2013. However, we do not consider the register to represent a complete solution to the problem of non-registration of clinical trials, as it does not include all the trials that have been conducted on all medicines currently available in Europe. The Government should encourage the EMA to further increase the scope of the EU CTR, for example by including phase I trials and trials conducted outside of the EU. We also recommend that the Government monitor the EMA's fulfilment of its pledge to include trial results on the register and obtain an explanation if the EMA fails to do so by the end of 2013. (Paragraph 94)

22. As a major direct and indirect funder of clinical trials, the Government can influence behaviour across both the public and charitable sectors. This influence has not been wielded effectively to increase transparency, meaning that many publicly-funded trials remain unregistered and unpublished. We recommend that registration in a WHO-listed registry and publication of summary-level results in a peer-reviewed journal be made contractual requirements for all publicly-funded trials, including research supported by the Charity Research Support Fund. The wording of these requirements should be standardised across all contracts to ensure consistency. We also recommend that public funders of research rapidly put in place mechanisms to monitor compliance with transparency policies and ask the Government to detail in its response to this Report how and when this will be done. (Paragraph 99)

23. Since the Government has encouraged industry to disclose retrospectively the results of past trials, we think that it should be prepared to do the same for the major trials that it has funded. We therefore recommend a retrospective audit of all public phase III trial grants awarded since 2000, followed by action to ensure that any failures to register or publish the summary-level results of these trials are rectified within 12 months. Any failures to correct these mistakes should be taken into account when considering future grant applications from principal investigators of previously unregistered or unpublished trials. In future, for grants awarded to fund phase III clinical trials we suggest that the MRC and the NIHR allocate a small proportion of funding to cover the time and resource requirements of preparing a manuscript for publication, and withhold this funding until the results of the trial are ready to be published. (Paragraph 100)

24. We suggest that the academic publishing industry put in place robust measures to ensure that unregistered trials are not just rejected, but that the trial sponsor(s) and funder(s) are notified that the trial has not been properly registered. (Paragraph 101)

Current initiatives to increase clinical trial transparency

25. In mandating trial registration, publication of summary-level results and publication of CSRs for commercial trials, we consider that the European Parliament's ENVI Committee appears to have reached a reasonable decision regarding the transparency requirements of the proposed EU Clinical Trials Regulation. (Paragraph 104)

26. The Government should clarify why Department of Health or MHRA officials were not present at recent discussions relating to the EMA's revised transparency policy. We hope that the Government will be more fully engaged in the next stages of the development of this policy. (Paragraph 106)

27. We agree with the Joint Committee that the Care and Support Bill should make the promotion of research transparency a statutory objective of the HRA and we recommend that the Government includes the necessary provision. (Paragraph 109)

28. Research Ethics Committees should have a role in considering and monitoring compliance with transparency policies. As such, we welcome the HRA's new transparency policy and support, in principle, the proposals made in its May 2013 paper. We recommend that the HRA initially retains full responsibility for policing its own policies and ensures that all trials have been registered and published according to an agreed timeline, rather than performing checks on a sample basis. In addition, there must be penalties for non-compliance. We recommend that the HRA provides us with a progress update on implementation of its new transparency policy by the end of 2013. (Paragraph 110)

29. We recognise the efforts of some members of the pharmaceutical industry, particularly GSK, to increase clinical trial transparency and hope that other companies will act in the same spirit in implementing industry-wide principles for responsible clinical trial data sharing. We suggest that all companies endorsing such principles agree and report on a common set of clinical trial transparency metrics each year in their annual reports. (Paragraph 113)

30. We are supportive of the broad aims of the AllTrials campaign and agree that all clinical trials should be registered and their results reported. We suggest that the AllTrials campaign clearly set out what it considers a full trial report to contain, particularly when prepared for non-commercial purposes, so that its supporters can work together to achieve a specific set of common goals. (Paragraph 116)

Value-based pricing and the renegotiation of the PPRS

31. Value-based pricing (VBP) is predicated on the idea that the Government is able to influence industry's behaviour through its spending power. We therefore consider VBP—and to a lesser extent the PPRS—to be tools that could also be used to encourage and reward industry for making its clinical trial data more transparent. The Government should consider ways in which clinical trial transparency could be incentivised in the future through VBP and the current renegotiation of the Pharmaceutical Price Regulation Scheme (PPRS). (Paragraph 118)

Incorporating emerging evidence into clinical practice

32. Increased transparency is unlikely to lead to improved medical outcomes unless mechanisms are in place to ensure that emerging evidence is quickly and effectively incorporated into clinical practice. Given the high degree of reliance placed on NICE's guidance by health professionals, we consider it essential that this advice remains fully up to date and that processes are in place to ensure that emerging evidence is rapidly incorporated. The Government should ensure that, as improved transparency leads to ever greater volumes of trial data becoming available, NICE continues to receive the resources it needs to assimilate emerging evidence into its guidance in a timely manner. (Paragraph 122)

Conclusions

33. We consider that more can and should be done to make the UK a more attractive location to conduct clinical trials. (Paragraph 123)

34. We are confident that the Government is aware of these problems and the need to resolve them, but its promises have yet to be matched by effective action. We strongly urge the Government to act on our recommendations and put an end to these long-standing issues, so that the UK can continue to make progress towards being the location of choice for the global life sciences industry. (Paragraph 124)

35. We call on the Government to take decisive steps, as outlined in this Report, to ensure greater transparency in all future trials conducted in the UK, in order to demonstrate to the rest of the world how effective solutions might one day be applied at a global level. (Paragraph 125)

Formal Minutes

Monday 9 September 2013

Members present:

Andrew Miller, in the Chair

Mr Stephen Metcalfe	Sarah Newton
Stephen Mosley	Graham Stringer

Draft Report (*Clinical trials*), proposed by the Chair, brought up and read.

Ordered, That the draft Report be read a second time, paragraph by paragraph.

Paragraphs 1 to 125 read and agreed to.

Annexes and Summary agreed to.

Resolved, That the Report be the Third Report of the Committee to the House.

Ordered, That the Chair make the Report to the House.

Ordered, That embargoed copies of the Report be made available, in accordance with the provisions of Standing Order No. 134.

Written evidence was ordered to be reported to the House for printing with the Report

[Adjourned till Wednesday 11 September at 9.00 am

Witnesses

Wednesday 13 March 2013

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Monday 22 April 2013

Wednesday 15 May 2013

Monday 3 June 2013

List of printed written evidence

List of additional written evidence

(published in Volume II on the Committee's website www.parliament.uk/science)

List of Reports from the Committee during the current Parliament

The reference number of the Government's response to each Report is printed in brackets after the HC printing number.

Session 2013–14

First Special Report	Educating tomorrow's engineers: the impact of Government reforms on 14–19 education: Government Response to the Committee's Seventh Report of Session 2012–13	HC 102
First Report	Water quality: priority substances	HC 272–I
Second Special Report	Marine science: Government Response to the Committee's Ninth Report of Session 2012–13	HC 443
Third Special Report	Bridging the valley of death: improving the commercialisation of research: Government response to the Committee's Eighth Report of Session 2012–13	HC 559
Second Report	Forensic science	HC 610

Session 2012–13

First Special Report	Science in the Met Office: Government Response to the Committee's Thirteenth Report of Session 2010–12	HC 162
First Report	Devil's bargain? Energy risks and the public	HC 428 (HC 677)
Second Report	Pre-appointment hearing with the Government's preferred candidate for Chair of the Medical Research Council	HC 510–I
Second Special Report	Engineering in government: follow-up to the 2009 report on Engineering: turning ideas into reality: Government Response to the Committee's Fifteenth Report of Session 2010–12	HC 511
Third Report	The Census and social science	HC 322 (HC 1053)
Fourth Report	Building scientific capacity for development	HC 377 (HC 907)
Fifth Report	Regulation of medical implants in the EU and UK	HC 163 (Cm 8496)
Sixth Report	Proposed merger of British Antarctic Survey and National Oceanography Centre	HC 699 (HC 906)
Third Special Report	Devil's bargain? Energy risks and the public: Government Response to the Committee's First Report of Session 2012–13	HC 677
Fourth Special Report	Building scientific capacity for development: Government and UK Collaborative on Development Sciences Response to the Committee's Fourth Report of Session 2012–13	HC 907
Fifth Special Report	Proposed merger of British Antarctic Survey and National Oceanography Centre: Natural Environment Research Council Response to the Committee's Sixth Report of Session 2012–13	HC 906

Seventh Report	Educating tomorrow's engineers: the impact of Government reforms on 14–19 education	HC 665 (HC 102, Session 2013–14)
Eighth Report	Bridging the valley of death: improving the commercialisation of research	HC 348 (HC 559, Session 2013–14)
Sixth Special Report	The Census and social science: Government and Economic and Social Research Council (ESRC) Responses to the Committee's Third Report of Session 2012–13	HC 1053

Session 2010–12

First Special Report	The Legacy Report: Government Response to the Committee's Ninth Report of Session 2009–10	HC 370
First Report	The Reviews into the University of East Anglia's Climatic Research Unit's E-mails	HC 444 (HC 496)
Second Report	Technology and Innovation Centres	HC 618 (HC 1041)
Third Report	Scientific advice and evidence in emergencies	HC 498 (HC 1042 and HC 1139)
Second Special Report	The Reviews into the University of East Anglia's Climatic Research Unit's E-mails: Government Response to the Committee's First Report of Session 2010–12	HC 496
Fourth Report	Astronomy and Particle Physics	HC 806 (HC 1425)
Fifth Report	Strategically important metals	HC 726 (HC 1479)
Third Special Report	Technology and Innovation Centres: Government Response to the Committee's Second Report of Session 2010–12	HC 1041
Fourth Special Report	Scientific advice and evidence in emergencies: Government Response to the Committee's Third Report of Session 2010–12	HC 1042
Sixth Report	UK Centre for Medical Research and Innovation (UKCMRI)	HC 727 (HC 1475)
Fifth Special Report	Bioengineering: Government Response to the Committee's Seventh Report of 2009–10	HC 1138
Sixth Special Report	Scientific advice and evidence in emergencies: Supplementary Government Response to the Committee's Third Report of Session 2010–12	HC 1139
Seventh Report	The Forensic Science Service	HC 855 (Cm 8215)
Seventh Special Report	Astronomy and Particle Physics: Government and Science and Technology Facilities Council Response to the Committee's Fourth Report of Session 2010–12	HC 1425
Eighth Report	Peer review in scientific publications	HC 856 (HC 1535)
Eighth Special Report	UK Centre for Medical Research and Innovation (UKCMRI): Government Response to the Committee's Sixth Report of session 2010–12	HC 1475
Ninth Report	Practical experiments in school science lessons and science field trips	HC 1060–I (HC 1655)
Ninth Special Report	Strategically important metals: Government Response to the Committee's Fifth Report of Session 2010–12	HC 1479
Tenth Special Report	Peer review in scientific publications: Government and Research Councils UK Responses to the	HC 1535

	Committee's Eighth Report of Session 2010–12	
Tenth Report	Pre-appointment hearing with the Government's preferred candidate for Chair of the Technology Strategy Board	HC 1539–I
Eleventh Special Report	Practical experiments in school science lessons and science field trips: Government and Ofqual Responses to the Committee's Ninth Report of Session 2010–12	HC 1655
Eleventh Report	Alcohol guidelines	HC 1536 (Cm 8329)
Twelfth Report	Malware and cyber crime	HC 1537 (Cm 8328)
Thirteenth Report	Science in the Met Office	HC 1538
Fourteenth Report	Pre-appointment hearing with the Government's preferred candidate for Chair of the Engineering and Physical Sciences Research Council	HC 1871–I
Fifteenth Report	Engineering in government: follow-up to the 2009 report on Engineering: turning ideas into reality	HC 1667 (HC 511, Session 2012–13)

Oral evidence

Taken before the Science and Technology Committee

on Wednesday 13 March 2013

Members present:

Andrew Miller (Chair)

Stephen Metcalfe	Sarah Newton
David Morris	Graham Stringer
Stephen Mosley	David Tredinnick
Pamela Nash	Hywel Williams

Examination of Witnesses

Witnesses: **Professor Sir Michael Rawlins**, Chair of the Academy of Medical Sciences Working Group on the Regulation and Governance of Health Research, **Dr Keith Bragman**, President of the Faculty of Pharmaceutical Medicine, and **Dr Fiona Godlee**, Editor in Chief of the *British Medical Journal*, gave evidence.

Q1 Chair: Thank you for coming this morning. I apologise for the delay, especially to you, Professor Rawlins, as I think you were rushing to get here on time and then we started late. We had a lively session, let us say, with a Minister on another subject just now. We will keep it as brief as possible because we realise that people have travel arrangements and so on.
For the record, may I ask the three of you to introduce yourselves?
Sir Michael Rawlins: I am Michael Rawlins. I am here representing the Academy of Medical Sciences, but I am also the chairman of NICE, and, if you want to throw questions at me that are more related to NICE, that is fine.
Dr Godlee: I am Fiona Godlee. I am editor in chief of the *BMJ*.
Dr Bragman: I am Keith Bragman. I am president of the Faculty of Pharmaceutical Medicine.

Q2 Chair: So that we understand the position that the three of you are in, what experience do you have of conducting or working with those who conduct clinical trials in the UK?
Sir Michael Rawlins: In my career, I have published the results of 19 clinical trials. I was chairman of the Committee on Safety of Medicines, so I have reviewed hundreds and hundreds of clinical trials, and it is the same at NICE.
Dr Godlee: As editor of the *BMJ*, I have reviewed many, many trials, and published some of them.
Dr Bragman: In my second career—this is my third one—I was working for a number of pharmaceutical companies where I have been responsible for the clinical development across a wide range of therapeutic areas, covering clinical cancer, immunology, virology and the rest of infectious diseases, inflammation and even some CNS disorders. That covers the best part of 20 to 25 years of work.

Q3 Chair: Aside from the regulatory landscape, what are currently the main barriers in conducting clinical trials in the UK?
Sir Michael Rawlins: Apart from the clinical trials directive, which is generally regarded as very flawed, hence the clinical trials regulations coming forward, there are two main barriers. This was from a review that I led on behalf of the Academy of Medical Sciences. First was the plethora of ethics approvals that sometimes needed to be garnered in order to embark on a clinical trial. The National Research Ethics Service, which has now been integrated into the Health Research Authority, was good, but, unfortunately, many other ethics arrangements had to be put in place.
By far the greatest impediment to doing clinical trials in Britain has been the fact that each single individual trust, if you are doing a multi-centre trial—and most trials are—takes on itself its own governance arrangements, with all of them looking at things like criminal records reviews and patient consent forms. The contracts go to their lawyers, and you do not send a contract to a lawyer without him commenting on it—and they all make different comments. We met one woman who had been a principal investigator in a study that involved 62 hospitals because it was a rare disease, and she had 62 CRB checks.

Q4 Chair: You are shaking your head for obvious reasons.
Sir Michael Rawlins: It is dreadful.
Dr Bragman: May I add to Professor Rawlins' remarks? I fully endorse what he is saying. When I talk to the people who practise pharmaceutical medicine, members of the faculty who work not just in the pharmaceutical industry but also in regulatory agencies, academia, clinical practices and so on, they do not complain about problems, for example, in terms of getting ethics approval or getting approval to conduct a trial, for example, through the MHRA. The problems are very much focused on issues of governance, problems with getting contracts negotiated with many different area health authorities and with bureaucracy. These sorts of things are making clinical research increasingly unattractive here in the UK. It is very much governance-focused.

Q5 Stephen Metcalfe: You have just given us a flavour of some of the barriers. Would you explain how those relate to the clinical trials directive, or is

that what you were doing? I did not quite follow whether that was so.

Sir Michael Rawlins: The clinical trials directive is the arrangement whereby the regulatory authority gives approval for a particular trial to be undertaken. The clinical trials directive—the one that is still in place—is over-burdensome, brings into its scope studies that probably should never be there and lacks proportionality. If I want, as an experiment, to give a patient a dose of paracetamol, which is pretty harmless stuff, I would still have to go through the whole business, and there would not be any distinction made between paracetamol and some rather more toxic agents.

To be fair, the MHRA has tried to take a proportional approach, but, broadly speaking, the clinical trials directive does not have a proportionality about it. That is one of the things that we criticise about it. It is one of the things that the clinical trials regulation is trying to address.

Q6 Stephen Metcalfe: On the over-burdensome aspect of the clinical trials directive, are you saying that proportionality is the biggest barrier?

Sir Michael Rawlins: It is a major barrier. There are some studies that probably should not be in it at all, and there are—

Q7 Stephen Metcalfe: I am sorry to interrupt, but could you give us an example of what should be in it and what should not?

Sir Michael Rawlins: Yes. A group of palliative care doctors wanted to see whether high-dose morphine, which is commonly used in end-stage cancer—late-stage cancer—affected cognitive thinking. That could be quite important, actually, if somebody wanted to remake a will or something like that. It was not a placebo trial for patients: they wanted to test their cognitive function. This fell within the scope of the European clinical trials directive, which meant that they had to get insurance. This was normal treatment. When they were told that the indemnity would have to be £6,000, they decided to give up and do something else. This is the sort of problem that we have.

Q8 Stephen Metcalfe: Do you think that the clinical trials regulation will help to address it?

Sir Michael Rawlins: It will help considerably, yes. There are problems; we sent in evidence about where they are, and I would not want to go over that, but it does help a lot, yes.

Q9 Stephen Metcalfe: Does anyone want to add to that?

Dr Bragman: Yes, very briefly. The quality of science and ethics should not be set at a different level irrespective of whether we are talking about a study being sponsored by a pharmaceutical company or one that is being sponsored by a university institution. Academic clinical research has greatly suffered from one-size-fits-all, and it came as a real shock to many clinical academics when they found the amount of bureaucracy that was being imposed upon them by the translation of the European clinical trials directive when it was transposed into national law. That brings us back to proportionality.

Stephen Metcalfe: There is a bit of gold plating going on.

Dr Bragman: Yes.

Q10 Graham Stringer: Sir Michael, you said a very interesting thing in answer to the Chair's first question about having to get authority for 62 different health bodies for rare diseases. Is it more difficult when dealing with orphan diseases and orphan drugs than it is for more common issues? I have a specific example in mind, where drugs have been shown to be effective for Duchenne muscular dystrophy. How would you speed up the process? Is it more difficult in cases like that?

Sir Michael Rawlins: It depends. With Duchenne muscular dystrophy, the patients very often attend one centre so you have a pool of patients. I spent many years in Newcastle, where they have a special interest in Duchenne dystrophy, so they have a lot of patients. In a way, it is sometimes a little easier. It depends on the circumstances. But there was a second part to your question.

Q11 Graham Stringer: Is it more difficult generally with rare diseases to deal with clinical trials? That was the implication of your first answer.

Sir Michael Rawlins: Yes; if they are the sorts of diseases that do not coalesce on specific centres, it can be. There is another condition called Bell's palsy, where the nerve to your face gets paralysed, and that comes on just like that. There aren't centres that specialise in Bell's palsy, so you might need to have 15 or 20 hospitals looking for cases to join a trial. It depends on the circumstances.

Q12 Graham Stringer: How effective has the Health Research Authority been in simplifying the process of getting to a clinical trial?

Sir Michael Rawlins: It has made a good start. It has obviously brought in the National Research Ethics Service, which has served well. It is bringing together other ethical approvals, so it has made a good start there. It is also looking at the feasibility and, hopefully, piloting a single sign-off, or at least a single arrangement, for governance so that the business of having to go round and get all these checks from 62 different hospitals disappears.

It is making good progress, and I don't want to gainsay its efforts. It is also consulting with stakeholders and patient organisations.

Q13 Graham Stringer: The HRA did not take up the recommendations of the Academy of Medical Sciences in its recent report, did it?

Sir Michael Rawlins: It is the governance area that it is pursuing. It is bringing together the research ethics functions, and that is what we wanted. We also wanted it to take responsibility for doing the checks for the research governance arrangements. It is now looking into that and doing a feasibility study.

There is another way in which this might happen. In some areas, one trust is taking the lead on behalf of a group of trusts, and the academic health science

networks may well also take on that sort of responsibility. I, for example, am going to chair the eastern academic health science network when I finish at NICE at the end of this month. We hope to have a single sign-off for all of the 20-odd hospital trusts in the network. That is another way of doing it.

Q14 David Tredinnick: I want to ask some questions about prospective trial registration to begin with. How important do you consider prospective trial registration to be in the move towards the increased transparency and scrutiny of clinical trials, and why do you hold those views?

Dr Godlee: It is a very important initiative. It is something that has been suggested for many years, but only recently, since about 2005, has it become something that is more widespread. Even now, it is by no means all trials; in fact, a large proportion of trials remain unregistered.

The reason why it is important is because of the problem of positive publication bias, which is well known to affect the whole of medical literature. It is optimism bias about the effectiveness of treatments being greater than it is and the safety being better. If you have a situation where more positive trials are published and we don't know about the negative trials, people would assume that that is the truth about the treatments.

If prospective trial registration were working—at present, it is only partially working—it would ensure that we would have a full record of all the ongoing trials and, therefore, the potential to chase up and obtain the full results of those trials.

Q15 David Tredinnick: What would be the potential problems if it were to become mandatory to pre-register all clinical trials, including those unrelated to drugs? You touched on this in an earlier reply but perhaps you could expand on it.

Dr Godlee: I can see no problem with that. I can only see benefits.

Q16 David Tredinnick: Dr Godlee, this is a question for you. The *BMJ* has committed to publish research papers only on clinical trials that have been prospectively registered. How is compliance to this policy monitored, and how successful has the policy been in encouraging trial registration?

Dr Godlee: When the major journals first said in 2005 that they would not only publish but only peer review and consider randomised trials that had been prospectively registered, it sent a strong message. If you look at the data, it is from that point onwards that the acceleration in registration has occurred.

As you will know, there is evidence that the policy has by no means been 100% successful. Since the study was done that found that some trials that were still not registered were published in major journals, not to mention those trials that were unregistered that are published in the multiplicity of many other journals across the literature, the major journals have tightened up their processes. Certainly, the *BMJ* has, and, as far as we are aware, in the last two years we have not published any trial that has not been prospectively registered.

Q17 David Tredinnick: Sir Michael, this question is for you, as you generously offered to speak as chairman of NICE. You recently approved the use of acupuncture for lower back pain. I suggest to you and to other doctors that we need to broaden our analysis of available treatments. One area where a lot more could be done is with traditional Chinese medicine. Acupuncture has a 3,000-year history, and when I looked recently there were 50,000 hospitals in the People's Republic of China using acupuncture.

I wonder, Sir Michael, if you would not agree with me that there is a great opportunity for NICE to broaden its research and to get more of these treatments approved. I myself used acupuncture for carpal tunnel syndrome to save having an operation.

Sir Michael Rawlins: We were attacked in some quarters for recommending acupuncture for lower back pain, but my colleagues who developed the guideline were convinced about the evidence for its efficacy. There are other areas, however, where acupuncture is ineffective. It is probably ineffective for migraine, where comparable trials have been done. Although we do not really understand the mechanism, in a way I do not mind if I don't understand it. It is nice to know the mechanism by which things work, but what I am really interested in is whether they work for the benefit of patients even if I do not understand why.

Q18 David Tredinnick: That brings me on to my next point. In American institutes, trials tend to compare treatments against each other rather than against a placebo. This is a new trend. Is this not a significant development?

Sir Michael Rawlins: Well, yes, comparative trials like that are very helpful, but they are very difficult to do because of the choice of the comparator. The comparator differs in different countries. What is standard care varies, even within a country like the United Kingdom. Comparative trials are quite difficult to do if you want to generalise broadly from them.

Q19 David Tredinnick: Finally, with your indulgence, Chair, when Professor George Lewith of Southampton presented to another House Committee, the Integrated Healthcare All-Party Group, a week ago, he was talking about trials that are now being conducted to see whether herbal medicine is capable of replacing antibiotics because of the problem of antibiotics being ineffective. I wonder whether that is an area that you think should be taken more seriously.

Sir Michael Rawlins: Of course, many modern drugs are based on herbal products, such as digoxin and so on. Artemisinin, which is a herbal medicine in China used for the treatment of malaria, has now become widespread. We should take compounds wherever they come from, whether they are herbal or whatever. All I want to know is that they work.

Q20 Stephen Mosley: Going back to the regulation and regulatory reporting of clinical trials, before a medicine can be sold in the EU it needs approval. As part of that approval, you are meant to submit all clinical trial data, whether it is successful or not. Is there any evidence to suggest that all clinical trial data

is being submitted, or is there any evidence that some clinical trial results are being withheld?

Dr Godlee: Shall I go first?

Sir Michael Rawlins: You go first.

Dr Godlee: As long as you follow up. It is fair to say that there is a great deal of evidence. Some cases that have been very well investigated and looked into suggest that evidence is withheld, whether on purpose or as a result of the system that we currently use. You will be aware from the written evidence that was submitted, which summarised a number of well-known cases, that drugs have been approved based on incomplete information, and that when information was provided subsequently the drug has been found either to be ineffective or even harmful.

In a famous recent case, the German regulator required the drug manufacturer Pfizer to give all the evidence on its antidepressant Reboxetine. It had not been widely used but was being used in practice. When the 75% of the evidence that had remained unpublished was finally provided, at the threat of not allowing the drug to be made available in Germany, it was found that the drug was ineffective and harmful. That is one case, but I could quote you many others that are in the written evidence. It is important to say that we are talking not only about hidden data in commercial trials but also in academic research. We recognise that there is a problem across the research enterprise.

As for whether the regulator gets all the information, this is something that is still rather murky. The industry will claim—Keith may be able to say more on this—that it does provide all the information that it is asked to provide, but I would like to hear Sir Michael tell us about his view of the current situation at NICE, how NICE relies on the EMA, and what it is that the EMA is provided with. We have good evidence on a number of drugs that the EMA is by no means provided with all the information that it would require to make a proper regulatory decision. The EMA and the FDA in America make different decisions because they get different quantities and quality of information.

Q21 Stephen Mosley: Professor Rawlins, while you are answering that, perhaps you would explain what the loophole is and how we go about filling it.

Sir Michael Rawlins: When looking at a new product at NICE, we do two things. First, we require the medical director to confirm that all relevant information has been provided to us. Secondly, we look at the scientific summary evaluation of the EMA, the European regulator, to see whether we have indeed seen all the clinical trials.

The problem is that, if things are being concealed from us, and particularly if they have been concealed from the medical director in Britain, we will not know about it. It is no good pretending that one can make a law, because the law will only influence the activities of the subsidiary company within the United Kingdom. Much as you might not like it, your writ does not go further than the English channel, as Stephen Dorrell said not long ago in a session of the Health Select Committee. If a medical director lied to us and knowingly withheld information, we would formally make a complaint to the General Medical Council.

Q22 Stephen Mosley: What would happen to that complaint?

Sir Michael Rawlins: Almost certainly the person would be struck off. Medical directors have in the past been struck off for that sort of behaviour, although not that in particular. Keith would probably throw him out of the faculty, too.

Dr Bragman: I am sure we would, Michael. Clearly there is a problem, and Fiona Godlee and Michael Rawlins have just summarised it. We need remedies. Most people who are practising pharmaceutical medicine and developing novel medicines are doing the right thing. Unfortunately, a number of individuals—I hope a small minority—need to be compelled to do the right thing. That means that we need registration of all clinical trials, we need results and we need access to data so that people can validate observations.

We are talking about the pharma industry, although I am not here to represent that industry, but it eventually comes back to the patient. We are eroding belief in medicines because people cannot trust the results that are published. I hope that it is a very small minority, but I think, Fiona, that you may have a different perspective in terms of the amount of data that you see that is potentially flawed. If we do not know what we can believe, the whole system suffers. Belief in medicines suffers, patients do not take their medicines properly, the benefits that can be derived from medicines suffer, and it costs the NHS more money at the end of the day. This is something that we need to put right.

Dr Godlee: I pick up on the point about the limits of your jurisdiction. We heard recently from the Chief Medical Officer about the need to see antibiotic resistance as a global problem and that we must act globally; we must act at the European and international level. This is another of those examples where we absolutely have to see this as an international problem. It is an international challenge, and the solutions have to be international. We look to Europe, and recent events suggest that the EMA is taking this seriously, but whether it will be able to do what it now wants to do is obviously something that we are watching with great concern. It may in some way be prevented from achieving the transparency that it wants.

Dr Bragman: May I add that the UK, whatever it does, needs to feed into the international scene so that we do not create a more bureaucratic problem or expand upon the problem, or make it more difficult for people to come and do research in the UK? We want international solutions.

Q23 Stephen Mosley: I was going to ask a question about whether the research ethics committees have a role, but from the sound of it, maybe, given your previous answer, that might not be the ideal way to go then.

Sir Michael Rawlins: I think it would only help a little bit. You have to remember that the big pharma

companies are in Switzerland, North America and Japan, and your writ does not run there.

Q24 Sarah Newton: I would like to stay within this area of the reporting of information and clinical trials in relation to doctors, patients and the public and push you a little on that. Quite a few of our witnesses have said that the full publication of clinical study reports would be the way to go, but others have said that that would be quite an expensive thing to do and could add to the whole cost of the trials and therefore some things might not happen. Do you think that that would be a good route to go, and, if you do, how do you think that information should be presented? Obviously, doctors will have a degree of training to be able to understand it, but what about patients and the public?

Sir Michael Rawlins: May I start? Dr Godlee probably does not agree with me entirely.

The business about transparency has three components. The first is publishing what are often called the summary results of the trial in a conventional journal such as the *BMJ*. When I say conventional, I mean superb.

Dr Godlee: Superb.

Sir Michael Rawlins: It will never publish anything of mine again now. Somehow, every single trial should be placed in the public domain. The negative trials and the positive trials should all be in the public domain. That is the first thing.

The study reports are voluminous. They sometimes run to thousands of pages, and I do not think that they add very much, except to the cognoscenti. I am ambivalent about whether it is worth it. I looked at many of them in the days when I was chairman of the Committee on Safety of Medicines. They are huge, and they do not really add anything very much.

The third thing is about looking at individual patient data from clinical trials. That can potentially be very important and helpful, either to reanalyse them in a different way or to merge the results of different trials so that, instead of a trial of 10,000 patients, you have 10 trials of 100,000 patients. These individual patient meta-analyses can be extremely helpful. My big worry is ensuring the privacy of the patients. However well you anonymise it, particularly if you are talking about the rarer diseases, you can de-anonymise it and identify them. That is my big worry.

Because these meta-analyses or this single patient data are so valuable, we need to develop a mechanism whereby there is some sort of safe haven to ensure that the people who have access to the data are going to use it responsibly, particularly when it comes to the privacy of the participants. We owe it to them to protect them at all costs.

Dr Godlee: I agree with a lot of that. We have talked about the prospective registration of trials and the protocol being published and made available. Summary results should be given in a timely fashion—within a year is the figure used—but we know that that is not happening despite FDA legislation in the States. A lot of trials are still not published after a year.

We are only just discovering what is in a CSR. It is all a bit new to the academic and meta-analytical community, partly because of the Tamiflu case. The Cochrane group has been looking at that Roche drug and understanding more and more as, by painful means and very slowly, it obtains additional information. Its understanding, despite what Michael says, is that the CSR is providing information that increases discrepancies and raises more questions. It makes people realise that the basis on which we have been stockpiling this drug is probably rather more dubious than may have been understood.

The value of the CSR is something that is being explored at the moment. The alltrials.net campaign is calling for the registration of all trials, with the summary results of all trials and the CSRs to be made available. The extent to which that involves individual patient data is still very much being explored, some CSRs having patient data and others not to the same extent. I would agree that individual patient data is crucial for proper meta-analysis in certain fields, and that will require very careful management.

On the idea of having a protocol before a request is agreed to, and releases to researchers for research purposes, we are going to have to find a way to achieve that level of oversight. My basic view is that the more transparency the better. We could create a level playing field for industry on this. If we asked patients' consent at the outset when they joined a trial, you will find that patients not only will give their consent but will start saying, "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." Consenting a patient right at the outset would be our answer to patient confidentiality problems.

Dr Bragman: May I quickly add to that? These are extremely valuable resources in terms of the raw data content. I do not want to repeat everything that has been said but simply to say that we need to know who is accessing this data. What are the questions that people want answers to? What are they going to do with the data, and what is their protocol going to be? Simply to open up these data resources to anybody, and for them to do anything that they wish and perhaps come up with claims that cannot be substantiated, could create a chaotic situation. To be able to validate claims and to be able to answer novel and new questions relating to meta-analysis is extremely important, but we need to have some form of control—not to prevent it from happening, but simply to facilitate it and know that it is being used responsibly.

Dr Godlee: Just to add to that, and I think Keith would agree, there is the question of who oversees it. Who takes the decisions is very crucial. It has to be independent. The idea that industry or manufacturers should in some way decide who sees the data and for what purpose is entirely wrong. It has to be an independent decision-making process that looks at the science and not the commercial implications.

Dr Bragman: I fully agree with that. Again, the preface is that I am not here to represent the pharmaceutical industry, but I do not think industry—some of it has, but much of it has not—has really woken up to the fact that it has so much to gain from having its data and claims validated, and that will

create much more trust in the whole process and in the medicines that people take.

Q25 Sarah Newton: In your discussion you answered a lot of the questions that I was going put to you, but there are the who and how questions. Who the independent person would be who was to make these decisions and how that is all going to be done are two very important questions. Would you share with us at least your initial thoughts on the who and how?

Sir Michael Rawlins: The Academy of Medical Sciences is planning to have discussions with the Institute of Medicine in the United States about this, because these are transnational issues. It is no good one country trying to do its own thing without involving others.

Saying that patient consent is okay and satisfied is not enough. Some of these things are very complicated. Just to be a bit anecdotal, my little grandson was in a clinical trial. He is fine; it was a trial in London funded by the National Institutes of Health, and they wanted to collect his DNA in case a genetic change could account for the allergies that he was getting. That was fine, but then they asked at the end of the study for the DNA to go over to the United States. I said to my daughter—the lad was only a year old—that she had not got the right to give his DNA away. My daughter had not thought about this; she thought that she could do anything she liked with her little son. This patient business and getting patients' agreement can be very complicated, but it is not fair on patients to opt out by saying that we have patient consent. It is more complicated than that.

Q26 Chair: Is not the reverse also a problem? I personally had to sign a consent form for myself recently on whether the results of a particular test could go into a dataset. Instead of the hospital explaining first the positive benefits of me engaging in that large group piece of research, it started the other way around by telling me how to opt out. Is that not an unwise way for hospitals to operate?

Sir Michael Rawlins: It is; it is not being fair to people.

Chair: It is not a good way of conducting science, either, is it?

Q27 Sarah Newton: Are there any more comments on the who and the how?

Dr Godlee: We have two examples in front of us about the who. One is GSK, which has said that it will set up an independent body to look at requests to reanalyse its data. We have not yet seen the detail on that—I think that they are still working on it—but there is a commitment that it will be independent, which is obviously to be applauded. However, there are many details to be hashed out. On the other hand, we have Roche, with the Tamiflu example, which suggested a group of people, who are paid experts of Roche, but there is a sense among those that I talk to that this is clearly inadequate and it will not serve the purpose.

You then have the question, if it becomes scalable, at what level it should take place. Should it take place at the European Medicines Agency or some sort of super-terrestrial body that could look across global boundaries? I expect that we will experiment and have a number of approaches to this, but it overwhelmingly has to be independent, with science at its heart and patients at its heart. We hope that things will move forward fast on this.

Q28 Sarah Newton: A lot of the conversation has been around information that will be used by other scientists to advance the body of knowledge. When it comes to explaining the results of trials to patients and the public in order to build up confidence in the system and transparency, who should be doing it and how should it be done, assuming that we can get the sorts of improvements that you have all mentioned?

Sir Michael Rawlins: Increasingly now, triallists themselves are writing to the participants to tell them the results of the trials, and we ought to encourage that.

I add to what I said before. A lot of trials are done by academics, and we need to bring them into the fold, as it were, and make sure that, whatever the arrangements, they apply appropriately to academic types of trial, which is important. We also need to remember that clinical study reports are not produced by academics. Academic triallists do not submit things to the regulatory authorities. They rely on publications in excellent journals such as the *BMJ*.

Dr Godlee: Your point is very important. If patients are to take part in trials and if patients and doctors are to make best use of the results, we need to know that we have all the results, and that is a big part of what you are looking at; but, assuming, in a magical world, that we reach that stage, we have to have the ability to explain why the trial was done, what it found and what comes next. The HRA may have a role in that. Certainly, we have written in the *BMJ* about the need for patient-friendly information at every stage in the process, in terms of when they may participate and when they are trying to interpret the results.

The education of the public and the provision of information is another challenge. At every stage, we have to avoid patronising the public. They are brilliant and bright people, and they have a lot of information already, but there is often a tendency to say, "Don't scare patients. Don't scare the public. We mustn't tell them about the potential risk of this drug." I look forward to a time when we have a much more grown-up conversation with patients and the public about the risks of drugs. All treatments carry risk, and the pharmaceutical industry would do itself a lot more of a service if it allowed us to have that public conversation.

There are some drugs that have been taken off the market. Vioxx is one; it was a good drug but it had some adverse effects, and those adverse effects were hidden in all the ways that we have described in the journal that it was published in. As a result, over a period of time the drug has been withdrawn. I do not know if others would agree, but that seems to be a lost medicine of a certain sort, which a proper grown-up conversation at an earlier stage would have avoided.

Dr Bragman: I think that there is room for improvement in terms of how we communicate trial results to patients. It should be done in ways that, as you say, are not patronising, but also use a language that people can understand and relate to. I would extend this not just through clinical trials but all the way through to when the drug is approved and ready for prescription purposes. The information that accompanies the medicine—the patient information leaflet—needs to be written in a way that is appropriate and that people can relate to and understand, and that is not uniformly the case at the moment.

Q29 Chair: There is a message here for the whole of the medical profession about how to communicate with patients on things like risk. Not everyone is a statistician, but explaining risk by using analogues that people can understand—you are more likely to be run over by a bus on your way home than this procedure is likely to fail—finding some such analogue, where it is appropriate, is a much better way of engaging in a conversation than throwing numbers at people who have not been trained in statistics.
Sir Michael Rawlins: Absolutely.
Dr Bragman: Absolutely, yes.

Q30 Chair: Whose fault is it that clinical trials are not always published in peer review journals?
Dr Bragman: I think that is one for you.
Dr Godlee: In the past, journals have been at fault, although never entirely to blame. There is evidence going back 10 years that suggests that authors also keep trial or research results in their bottom drawer if they do not come up with the results that they wish for, or they move on to another project and lose interest.
More recently, there have been studies suggesting that journals are much less at fault than they ever were, with open access journals and online journals that have lots of space to publish negative and neutral results. The majority of the fault, if that is the right word, rests with authors and the sponsors of trials, who are failing to publish all of their results. As I say, it is not only full trials that are not being published but also all the results from an individual trial.
In case I don't get the chance to say this, in the long run the solution to publishing clinical trials does not rest with journals. Journals have a role in publishing summary results, in educating doctors and patients about what the results mean, and in reviewing them and summarising them, but, with regard to the actual data, increasingly, in a timely fashion, we should be looking to see those on open access databases rather than waiting for journal publication to provide that accreditation.

Q31 Chair: That is fine, but, going back to Dr Bragman's comments about some of the metadata, some of the datasets are getting almost impossible to publish in that form, aren't they?
Dr Godlee: Journals don't currently publish datasets.

Q32 Chair: I realise that, but you are inviting everyone to put their data in some public space.
Dr Godlee: Such spaces do exist. We work closely with a database called Dryad, which publishes research data, and we encourage and will increasingly mandate our authors to deposit their data in research databases of that sort. Again, it is new and developing, and these things will need funding. A piece of research will require money, not only to publish the research but to make sure that the data are available in a form that will make it re-analysable by others.

Q33 David Tredinnick: I have a quick question about Tamiflu. How significant do you think the Tamiflu incident was? This is something that the Health Committee looked at too, being concerned that the Government bought a product without having the information that they needed to assess it properly. Dr Godlee, you touched on this earlier.
Dr Godlee: The Tamiflu incident is iconic increasingly on a number of levels. It is helping us to understand the relationship between the regulator and the information that is made available by the drug company. Michael may be able to give us more on that. It has shown how much a drug—in this case a public drug—was being prescribed and made widely available, and vast sums of money were being spent both in the UK and internationally, based on information that was only available to the manufacturer.
In that case there were 10 trials, only two of which were ever published, and those two were to some extent ghost-written by paid employees of the company. The other eight trials were only published in abstract form, including the largest trial ever of Tamiflu, in terms of its effect on complications. You have a picture there, but beyond that the Cochrane group has discovered that for 123 trials, of which the vast majority if not all were Roche-funded and Roche-performed, the data were not available to anyone other than the manufacturer.
We know that NICE had some data, and we know that EMA had some data. I gather that the EMA has provided information on 16 trials. That may be all that it had. The public are being asked to believe in this drug. I don't know if it works or not. I have no view on whether it works or not, or whether if my child was ill I would want to obtain it for my child. We are just left not knowing. The public have a right to be rather surprised that that was the basis on which the Government spent £500 million in stockpiling the drug.
The reason that it is iconic is that it may be an individual case. We are convinced by other evidence that it is not an individual case; there are other examples that suggest an endemic problem across the system. To some extent, the three of us here represent three failed groups who have tried to tackle this. They are the regulator, the medical literature and pharmaceutical researchers.
Dr Bragman: I have not given up.
Chair: There are no accusations from us.
Dr Godlee: We may be failing, and we hope that you will help us to come up with a better solution.

Q34 Graham Stringer: You answered the question that I was going to ask about whether all raw data

relating to clinical trials should be made available to the public, but having listened to all three of you I am not sure that I understood the answer. You seem to say that all the raw data should be made available, but you then put fairly heavy restrictions on it—that it should be made available to accredited or credible academics. Is that the right interpretation of what you were saying?

Sir Michael Rawlins: I really want to protect the confidentiality and privacy of the participants. That is my real goal. With regard to putting it out into the world so that individual people could look at it, I am not sure whether it would help anybody if you had 10,000 patients in a trial, as you could have line listings going on and on. Whether anybody who was not an expert statistician and had a huge amount of time to spare could devise anything, I am not sure, but I regard that sort of individual patient data as very important. As I said, I am very concerned about ensuring the privacy of the participants.

Q35 Graham Stringer: May I take you back to when you asked me what was the second part of my question? The question was in three parts, but I asked only two of them. The final part is this.

When you have a drug that might be effective for Duchenne or other diseases, how do you speed up the process of getting it to the patient?

Sir Michael Rawlins: Ah, isn't that the subject of another inquiry, almost? I have been critical of the linear way in which we traditionally develop drugs, with phases 1, 2 and 3. We need to start producing swifter and sometimes leaner ways of doing it. For example, with Duchenne dystrophy, if an early stage trial had suggested benefit, I would allow it on the market subject to very close observation of those people during the first year, or two or three. That is sometimes known as adaptive licensing. We need to be much sharper about how we develop drugs. It takes such a long time, it is hugely expensive, it erodes the patent life, and at the end of the day it becomes increasingly costly.

Q36 Chair: That requires a slightly better form of informed consent, coming back to an earlier question.

Sir Michael Rawlins: Yes. This might be the subject of a separate inquiry on adaptive licensing or something like that.

Dr Bragman: May I quickly add to what Professor Rawlins is saying? We have to look at diseases like Duchenne very differently from those such as hypertension—high blood pressure. People who are developing medicines need also to understand that they can use the regulator; they can use experts to gain much more insight and discuss how to speed up the drug development process than many currently do. That is why we have this self-fulfilling prophesy in terms of the linear approach to drug development simply because that is the way that it was done in the past. It need not be so.

Chair: The medical profession has this morning succeeded 100%, because the average blood pressure of the Committee dropped down following our previous session.

May I thank you for the clarity of your evidence? We were given a lot of information in just over three quarters of an hour. Thank you very much indeed.

Monday 22 April 2013

Members present:

Andrew Miller (Chair)

Stephen Metcalfe	David Tredinnick
Stephen Mosley	Roger Williams

Examination of Witnesses

Witnesses: **Dr Catherine Elliott**, Director, Clinical Research Interests, Medical Research Council, **Sharmila Nebhrajani**, Chief Executive, Association of Medical Research Charities, **Professor Peter Johnson**, Chief Clinician, Cancer Research UK, and **Nicola Perrin**, Head of Policy, Wellcome Trust, gave evidence.

Q37 Chair: Welcome, everyone. I apologise to those who are standing for the proceedings. We will try to cope and make it as comfortable as possible for everyone. Can I welcome the witnesses? Thank you for coming this afternoon. For the record, I would be grateful if you would introduce yourselves.

Nicola Perrin: I am Nicola Perrin, head of policy at the Wellcome Trust.

Dr Elliott: I am Catherine Elliott, director of clinical research interests at the Medical Research Council.

Professor Johnson: I am Peter Johnson, the chief clinician at Cancer Research UK.

Sharmila Nebhrajani: I am Sharmila Nebhrajani, chief executive of the Association of Medical Research Charities.

Q38 Chair: Thank you. We have got quite a lot to get through in a fairly tight time frame, so I am going to try to rattle through some questions. First, how much medical research do you fund annually? What proportion of this relates directly to clinical trials of drugs, devices or other types of therapies?

Professor Johnson: Cancer Research UK funds at any one time a portfolio of more than 240 clinical trials, of which about a third are recruiting internationally as well as within the UK. Around 80% of those involve an investigational medicinal product of one description or another, and around 5% involve testing novel techniques, such as radio therapy or surgery. We have a large portfolio of trials, which gives us a unique insight into the process and the regulatory impediments to it.

Q39 Chair: About a third are non-UK-based.

Professor Johnson: A third recruit internationally as well as in the UK. They all recruit in the UK.

Sharmila Nebhrajani: Perhaps I should go next representing the medical research charities, some of whom are also at the table. Medical research charities fund about £1 billion of medical research each year. I am here representing 125 members. About a third of those—41 of our 125 members—fund clinical research of some description, including clinical trials but also non-medicinal interventions, new diagnostics and so on. AMRC members funded 32% of all studies taking place in the NIHR. That is about 2,600 studies, which are by their definition clinical studies. Of those, 14%—or about 360 studies—are clinical trials in phase I to phase IV of investigational medicinal products, so that is the scale of it across the charitable sector.

Dr Elliott: The Medical Research Council currently has about 120 live clinical trials. As with CRUK, those are both in the UK and are also part of our global health portfolio. Our current commitment is around £105 million. Our annual spend over the past five years has been, on average, about £20 million on that specified portfolio of trials. We also spend about £50 million every five years on intramural units that deal with clinical trials, methodology and statistics. Our portfolio has changed due to NIHR taking over the larger phase III studies in UK through their health technology assessment scheme, and we now fund more in the early phase trials, and also phase II trials, which are administered by NIHR through their EME scheme.

As with other funders, the majority of the trials would be of medicinal products, but we also have a large portfolio dealing with surgery or interventions. Through the NPRI initiative, we also fund prevention initiatives, such as interventions for weight loss or stopping smoking.

Nicola Perrin: The Wellcome Trust funds approximately £600 million a year of biomedical research. Of that, a relatively small proportion of our funding involves clinical trials; it is less than 5% of the total funding that we provide each year. Within the UK, most of the trials that we fund are not for medicinal products; they are more often for behavioural interventions and psychological therapies—for example, cognitive behavioural therapies. A significant proportion of the clinical trials that we fund are global. For example, we fund in partnership with MRC and DFID the global health trial scheme. We also fund a number of earlier stage trials in low and middle income countries, including, for example, the recent trial of a new vaccine for TB. We do not run a dedicated trials unit or programme and we are not a sponsor of trials; we are a funder.

Q40 Chair: In your case, there are some crossover cases where you are funding projects here that are working in parallel elsewhere. Are the data a little complicated in the case of Wellcome?

Nicola Perrin: The data are, as you say, very complicated, particularly since a number of the awards that we fund are large strategic awards, or for our major overseas programmes we give a block grant and a number of different trials take place as part of that. We are now trying to improve our reporting systems to have a better figure of the number of the

actual trials that we are funding, so it is not as easy as we would like.

Q41 Stephen Metcalfe: In your opinion, what is the greatest barrier to conducting a larger number of trials here in the UK? Is it EU legislation, or are there specific issues that are challenges here in Britain?

Dr Elliott: We have produced statements across the funders; maybe we have similar views. There is no doubt that the European regulations have added complexities and delays to conducting clinical trials in the UK. However, in the UK, the trials regulations are overlaid on to an already complex regulatory framework. The report of the Academy of Medical Sciences and our own experience would be that that home-grown complex framework contributes to the complexity. Probably the most difficult bit relates to conduct across multiple NHS sites and the requirements for that, and, even more particularly, probably issues relating to patient data, access to data from health records and the longer-term follow-up of records.

Sharmila Nebhrajani: I will not repeat the points that Catherine has already made, but in addition there are two other issues, one of which is the capacity in the UK to conduct clinical research. We know of members—for example, Action on Hearing Loss—who would like to fund UK trials but cannot find the capacity to do so and are funding about £1 million worth of research overseas for that reason.

The other issue is access and knowledge. For example, we know that almost three quarters of people surveyed want to be involved in research. We also know there is a demand for that opportunity but there is a supply problem. There was recently an NIHR mystery shopper survey that went around trusts to ask, "Where are the opportunities to fund research?" Patients want to do it, but they have no idea how to get on it. There is definitely a knowledge and access barrier also.

Professor Johnson: I have personal experience because I conduct trials, both first-in-man and large randomised trials, and have been involved with both academic and pharma company-sponsored studies. My general view is that we have a very vibrant clinical research environment in the UK and have made enormous progress over the last 10 years with concerted investment in this area. Moves such as the embedding of research into the NHS constitution have been extremely positive and helped to move things forward and build capacity. The regulatory hurdles are well documented, and certainly when the European Clinical Trials Directive was first implemented it was a major impediment. We have made a lot of efforts collectively as a research community since then to improve things. Looking at our data and the information we have about the length of time it takes us to get trials started, there is evidence of success, but I have a sense that that has plateaued recently. We still need to put continuous emphasis on improvement, and, very importantly, also to be careful of avoiding the unintended consequences of additional legislation and regulations.

Nicola Perrin: As well as agreeing with the previous comments, the creation of the Health Research Authority has been a very important step forward. We particularly welcome its feasibility study to try to simplify assessments and have a single assessment that all NHS Trusts can accept and trust. We look forward to seeing its pilot study, which is coming shortly.

Q42 Stephen Metcalfe: Do you see the EU clinical trials regulations draft proposals that are coming forward adding a greater degree of complexity, or are you hopeful that they will build on the progress you have already made?

Dr Elliott: I am hopeful that they will build on the progress. The UK—particularly the MHRA, which is now working with the HRA—has led a lot of the work on reducing this complexity in the regulations. We strongly welcomed the initial draft adopting a more risk-proportionate approach and allowing greater harmonisation.

Sharmila Nebhrajani: It is a development in terms of trying to find a regulatory framework that is both a bit more agile as well as more proportionate, but we must not forget that science is advancing more quickly than that. You have to look at things like stratified medicine. Doing work on smaller sample sizes is going to require a greater degree of cross-working across boundaries, so, in a way, our clinical trials regulatory framework needs to be even more agile ahead of the way in which science is advancing.

Q43 Stephen Metcalfe: Do you feel those particular issues are being listened to by those drafting the regulations? Who is driving this process? Is it being put in place to help conduct safe and proportionate clinical trials, or do you get the sense that it is there to control you? Who is driving this?

Sharmila Nebhrajani: Others may comment. It is clear that the philosophical basis is correct. It is trying to be properly regulatory and protective, but, if the unintended consequence is that these new scientific advances cannot be developed into meaningful trials, then we have a problem.

Professor Johnson: The way the regulation was initially drafted looks very promising in terms of harmonising the establishment of trials—for example, across the different countries of the European Union—to make it much easier to get trials up and running. There is a good deal of detail that we need to see to know how it is going to work in practice. In general, the shape of the thing and the proposal to take a risk-adapted approach, for example, to the regulation of trials is very positive, but we need to be mindful of the detail that is going to come through.

Nicola Perrin: One of the problems with the previous directive is that it had a disproportionately negative effect on academic clinical trials, and we have been very pleased to see that, in the new draft regulations, that is one of the things that has, hopefully, been addressed. There are still some questions about scope and we would welcome greater clarity about some of the key definitions, but it is moving in the right direction.

Q44 Stephen Metcalfe: The other side of conducting clinical trials is recruiting patients, which you have

touched upon. Is there a particular challenge in recruiting patients in this country? Is there something we can do through better use of NHS data, and, if so, what would that look like?

Nicola Perrin: The biggest problem with recruiting patients in respect of using patient data is the so-called consent for consent issue. To identify whether or not people are approved for trials, researchers may need access to identifiable information—for example, date of birth, postcode and so on. Initially, they would not have a legal basis to access that information, so either you have to rely on the clinicians, who clearly have other understandable priorities and do not have time to do it, or you have to contact everyone to ask if it would be okay to look through their information to re-contact them to ask them to consent. That is a hugely complicated process for something that everyone wants to happen—and patients want it to happen.

We have been talking about this as a barrier for a number of years. We are hopeful that we are beginning to see improvements in it. The recent revisions to the NHS constitution, hopefully, will be very helpful but need to be accompanied by much better information to patients to help them understand what it means and to explain it better. The Caldicott review will be reporting shortly and we hope it will address this issue to some extent.

The other way it could be improved is through the CPRD—the Clinical Practice Research Datalink. It has some very exciting technologies that make use of non-identifiable information; there are identitiers behind the scenes that are looked at only by computers. If that provides the solution that it promises, it will be enormously exciting.

Q45 Stephen Metcalfe: Does anyone want to add to that?

Dr Elliott: I completely agree with all that Nicola said. The steps in the NHS constitution are very helpful, but we probably could go still further in helping patients to be aware of clinical research—and for those patients who would like to take part to know what is available. CRUK has done a great job with CancerHelp in terms of making that available, and the UK Clinical Trials Gateway has also taken us down that line, but we could do more.

Sharmila Nebhrajani: I agree; I think there is more to do. There are a lot of resources out there, but they are not necessarily well found by patients. There is definitely a marketing and access point. The UK Clinical Trials Gateway is great, but in a recent survey 80% of people had not heard of it. So you have demand for trials but no way that people can understand how to get on to them. The NHS constitution is also a good development here. There is something about, culturally, clinicians being trial-friendly and understanding their obligations to make opportunities available to patients, and patients having a right to be informed about trials, particularly vulnerable groups. The elderly and ethnic minorities are much more poorly represented in those populations than the norm. There is also something about the kind of practical help that the NHS or charities can give to facilitate access to trials. We have good examples of some of the charities working with Alzheimer's and Parkinson's trying to make the practical logistics of access to research work for patient groups.

Q46 Stephen Metcalfe: It strikes me that there is not very much public awareness of the whole issue of clinical trials until you arrive at a point where you might need to be involved. Do you think we should do more to raise general awareness among the well, not just among the sick, that clinical trials are things in which they may take part some time in their lives, similar to the way we have raised the profile of organ donation to the point where people now are much more accepting of it, so that it does not come as a shock when perhaps they are invited to take part in a clinical trial? Is there some way we could do that?

Professor Johnson: That is a very important point. Different groups of people have different levels of enthusiasm to take part in research. In general, people diagnosed with cancer have a very high level of motivation to take part in research. More than 37,000 people a year take part in one of Cancer Research UK's trials, which is about one in five of people diagnosed with cancer. People with a diagnosis find it easier, but it is a very difficult time to be making those kinds of decisions and to get on the internet to try to find the information. A much higher level of awareness among the general population would be enormously helpful and it is something on which we have been doing a lot of work. Our CancerHelp website is a means by which we promote the clinical trials both to the well and people with cancer.

Dr Elliott: That would apply particularly to clinical trials in this context but also, as has been alluded to, the use of tissue for research as well as organ donation and lawful use of data. Again, more awareness might make this research easier.

Q47 Chair: In some cases where trials are conducted, the patient is told about what is going on but in a fairly negative way. I have seen a document that says, "We are carrying out this procedure on you. This is how to opt out of participating in sharing that data," rather than first explaining why the data is being collated. Is that a managerial or regulatory issue?

Professor Johnson: There is an art to the construction of a properly put patient information sheet. Increasingly, we draw on help from patients and carers to help us write information sheets in a way that is readily comprehensible. Unfortunately, in investigational medicinal product-type trials, the volume of information required is quite high.

Chair: I am afraid there is a division just now. I am going to suspend the sitting for 15 minutes, assuming it is only one division; if there are two, with apologies to the witnesses, I will suspend it for 25 minutes.

Sitting suspended for Divisions in the House.

On resuming—

Chair: Can we resume, ladies and gentlemen? Apologies for the delay. There were two votes. We will go straight on, and I ask David Tredinnick to ask a question.

Q48 David Tredinnick: What proportion of the trials that you fund are pre-registered and published in peer-reviewed journals?

Dr Elliott: We looked at our portfolio of trials from 2006 to 2012. Of the studies that we identified correctly as trials—it sounds a bit long-winded, but doing that has been slightly complicated—and those funded before 2012, 94% have been confirmed to be registered. Of the total portfolio, 86% are either registered or are soon to be registered, because some of them have been funded quite recently.

Q49 David Tredinnick: Are you happy with those levels?

Dr Elliott: Our requirement is that all trials that we fund are registered, but we are looking at the gap of the trials that are not registered. We know that for some of them it is because they have only quite recently been funded. We are doing further work to look at the reasons why trials might not be registered from that group. The most common reason seems to be a difference in definition of trials—whether we consider them as trials in our portfolio or whether the researchers considered them as trials—because these are all trials, not just investigational medicinal products. So the definitions can be quite variable. We would like all of those that we consider to be trials to be registered, so that should be 100%.

Professor Johnson: It is a condition of funding by Cancer Research UK that any trial is registered. The way we police that is to check at the first annual renewal of the grant that the trial is indeed registered, so we think we have 100% take-up rate for registration and very high rates of publication. Inevitably, especially large international trials may take some years to complete and analyse the data. Of the rather more than 300 trials that we think have been completed over the last five years, we know that somewhat over 200 have already been published and the remainder are in the process of being analysed.

Sharmila Nebhrajani: From the perspective of charities that do not have their own clinical trials but are funding them, which is the point of your question, 80% that we know are funding clinical research have a requirement in the terms and conditions of their grant that the output must be published, and it is long-standing advice and guidance from the association that all charities should do that.

Q50 David Tredinnick: Does it worry you that some of the drugs that are approved go on to be prescribed as packages that have never been assessed? You get three or four drugs being used at the same time.

Professor Johnson: Do you mean combinations of drugs? Certainly, in cancer treatment, combination chemotherapy is very much the standard approach to treatment. So, often, we will have three or four drugs in combination routinely being used, and it is those combinations that are subjected to clinical trials as a general rule. I think we are comfortable with the data that we have on those combinations.

Q51 David Tredinnick: How do you monitor and enforce compliance with your stated transparency policy?

Nicola Perrin: From the Trust's perspective, we require all our funded trials to be registered and we expect publication as well. It is not an area that we have actively policed until now, but we have just updated our policy and, as a result of that, we are giving it greater attention and priority. We are implementing new reporting systems so that we can track trials through our e-val mechanism, but at the moment we do not have a figure of compliance.

Q52 David Tredinnick: The National Institute for Health Research health technology appraisal programme has achieved an extremely high level of transparency by withholding funds prior to trial registration and maintaining its own dedicated log. Do you see potential for this approach to be more widely used across the non-commercial research community?

Dr Elliott: Like Wellcome Trust, we have also implemented new systems to monitor outcomes in publications from research, so we also require that the results are published and that data is shared with other researchers. From the sample we have looked at, about 89% of the trials have been published to date and there is an ongoing trail of publication. We do need systems—which we call Researchfish, which is a very similar system to e-val—to monitor annually the outcomes of research and the publication rates.

Sharmila Nebhrajani: There is collaboration between the MRC and the AMRC to roll out that Researchfish project across charities so that you start to have a common language among non-commercial funders to track impact, not least because a lot of charity funders are funding in partnership with others. That will be a helpful process.

Q53 Roger Williams: Could I ask your views on whether trial registration should be limited to randomised control trials for investigational medicinal products, or should all forms of trials for all sorts of interventions be registered?

Dr Elliott: From the preliminary review we have made, we have seen the difficulty of defining trials and tracking them through these systems. Clearly, the RCTs of IMPs that you mention have to be registered under statutory requirements, but we would agree that all clinical trials should be registered. It is probably more difficult sometimes for researchers to do that and find the appropriate registry, and we could do more to help identify the appropriate registries and simplify that registration process.

Professor Johnson: In general terms, it is a sound principle that all trials should be registered if patients are giving informed consent to take part in them and the data is being collected. CancerHelp UK, which is our information database, collects and puts up information with good lay summaries, not just for the trials that Cancer UK funds but for as many cancer trials as we can find. We continue to update that on a rolling six-monthly basis so that the information is as current as we can possibly make it and, furthermore, so that we capture the outputs of trials as they are either presented at international meetings or get published in the literature. That is the way in which we maintain a high level of transparency and visibility of both the trials activity and also the results.

Nicola Perrin: Registering trials is an essential first step towards transparency, so we would certainly agree that it should be much wider than just CTIMPs; it should be all clinical trials, and that is why we have that as our policy. As I mentioned before, a lot of the trials that we fund are not for new medicinal products.
Sharmila Nebhrajani: It has been said before that transparency is a bigger agenda than just registration of trials. There are some trials that do not lend themselves to randomised placebos—for example, surgical interventions.

Q54 Roger Williams: What trial registries do you recommend that your grant-holders use, and how well suited are these registries to non-IMP studies?
Dr Elliott: Our grant-holders could use any of the range of trials registries. The trials that come under the European directive will be on the EUdraCT database, and the American US trials have to be on the ClinicalTrials.gov dataset. We also have the ISRCTN register. Under the WHO Clinical Trials Registry Platform there are 14 other registries. There is a plethora of registries, and it may add to the complexity that there are these different resources. We do not mandate or stipulate that a particular one must be used, but one must be used.
Nicola Perrin: On the other hand, we do specify that our researchers should use a subset of the metaRegister of Controlled Trials. The benefit of it is that it covers all types of clinical trials, not just medicinal products. It also means that they get a unique identifier—the ISRCTN. There are benefits to it. We are looking at whether it is still fit for purpose. It is not a user-friendly register by any means. If you know what you are looking for, you can just about find it; if you are a patient looking for a trial, you would not go to that site to find it. The CancerHelp registry is excellent; it is a really good resource; our current one is not. We have provided extra resource to help them improve the lay summaries. We need to do much better to make it more accessible, and we are very keen to work with other funders and users of registries to try to develop a broader and more accessible approach.
Sharmila Nebhrajani: I would support that.

Q55 Roger Williams: Professor Johnson, where do you get your information from for the CancerHelp UK register?
Professor Johnson: The information that we put out there is written in-house by a dedicated team. We invest a certain amount of the resource that we collect to make that available. About six whole-time equivalent staff are continuously trawling the different databases looking for trials and the information, and then we write the information sheets for the trials that we put up there, usually in concert with the researchers. We check the accuracy of what we are putting up with the researchers conducting the trials to make sure that we have got it absolutely right and that we put it in terms that are readily understandable to the people arriving on the website.

Q56 Stephen Mosley: In response to earlier questions, you said that you produced reports and published 89%—in some cases all—of the results from clinical trials. Are the reports you produce full ICH-compliant clinical study reports, or are they of a different format?
Dr Elliott: When we refer to "publication", that would normally be peer reviewed in an academic journal. That would not normally be in the full ICH CSR format, because that is a very specific format required for marketing authorisations. We require that authors and researchers follow the CONSORT guidance. MRC and others fund groups to provide guidance as to what should be in a publication so that other researchers and the public can see the protocol being followed, and there is a set format in which a trial should be published. We mandate that our trial should be published in that format, but it would not include all of the information that would necessarily be in the very tight definition of the CSR in the ICH.

Q57 Stephen Mosley: It is that tight definition in which I am specifically interested here.
Dr Elliott: A lot of academic trials are not directed towards a new marketing authorisation for a drug, so that would not be produced as a matter of course. Our MRC clinical trials unit, which does a lot of trials and sponsors on MRC's behalf, estimates that it takes about three months' additional work to produce one of those reports, over and above all of the statistical analysis and data that it will produce for an academic publication.
Professor Johnson: It is also important to dispel any misconception about how useful this data is. This data in its unedited and unanalysed form is not necessarily particularly useful. Despite the fact that it may take a lot of time and resource to produce, there is a risk of an adverse consequence of putting out a lot of that kind of data, which is that we are simply swamped in largely meaningless data. In general terms, our clinical trials units, of which Cancer Research UK core funds eight, has not felt that this would be a good use of its time. There is an opportunity cost to deploying resources to produce this data, which is difficult to interpret and analyse, versus doing more trials and doing them faster.
Sharmila Nebhrajani: I wanted to make the link back to the access point we were discussing earlier. From a charity funder's perspective, they require the outputs of their research to be published in peer review journals and, in many cases, also require that they are in open access models, like UK and Europe PubMed, which is very important, because that information is then freely available to researchers and the public. Alongside that, on the point about access, many charities also publish a lay summary of the research on their own website. That is not a report for the hard of thinking or the stupid—but an insightful lay indication of what the research says, why it is important and what its shortcomings are, not least because charity funders are funded by the public. So it is a kind of feedback loop that says, "This is what your money funded; this is what we did with it; and this is the next iteration of research that it will fund."

Q58 Stephen Mosley: It would be standard practice for you to produce this lay report.

Sharmila Nebhrajani: It is our guidance that this may be a helpful way of ensuring the outcomes of research are accessible to patients and the public.
Nicola Perrin: We do not specifically require CSRs to be produced unless they are needed for marketing authorisation. We require our researchers to make their research findings freely available through open access—both positive and negative findings.

Q59 Stephen Mosley: No doubt you will be aware of the January 2013 report on the draft EU clinical trials regulation and the proposed amendment that, within one year from the end of a clinical trial, the sponsor must submit to the EU database a clinical study report, including a lay summary of the clinical trial. I guess from your previous answers that there is some scepticism about that, but could you just put your thoughts on that on the record, please?
Nicola Perrin: Where a CSR has already been produced, we see no reason why it should not be made available, although we would clarify that by saying that, if the EU database is publicly available, we would have to redact any patient-identifiable information, which means that, potentially, you lose some of the value of the CSR. In any event, it would introduce a huge additional financial and time burden on non-commercial researchers, so from that perspective we certainly do not agree with that amendment. The other important point is what you are trying to achieve by it. If you are trying to increase access to underlying research data for the purposes of validation and scrutiny, the CSR is not the best way of doing that. You need the data in a reusable form that can be fully analysed, and a PDF is not the way of doing that.
Dr Elliott: We completely agree with that. We have been having some discussions about what would be the purpose of publishing a CSR or making that a blanket requirement across all trials, and not just those that already have a CSR produced. We would agree with Wellcome's position on where CSRs are already produced. The key thing is: what is the end purpose? The academic trials will also have statistical analysis, plans and details of the analysis conducted, and the datasets that have been used, for those that could be made available. Again, we would have concerns about the individual level data being made available, but there are ways that the same information could be made available and the ends could be met, both to allow the researchers to do further work or to allow the public greater insight into what has happened in a trial without mandating CSRs to be produced for all trials.
Professor Johnson: Our feelings are very similar. Proportionality here is very important. There is a sense of history repeating itself. The original Clinical Trials Directive set out to improve safety reporting and quality, but because it did not take a proportionate approach there were enormous difficulties with the running of trials, and safety and quality were not greatly changed. We run the risk of doing the same thing with this requirement for blanket data publication in this way. This is not to say that individual patient data is not already being used in analyses, and all our clinical trials units are continuously making individual patient data available for meta-analysis for further studies by different groups, so the data can be obtained. The question is how much resource one would want to divert into doing that for every single trial to no particular benefit in many cases.
Sharmila Nebhrajani: I would echo the comments made by others. There are already good examples of data sharing between researchers. Tissue banks are a good example of where those things are made available freely. So we do have models that work. The philosophy of sharing data is a good one, but one does not want to do that without regard to the overhead and the cost to research funders, because the opportunity costs of that are significant.

Q60 Chair: Is cost the only downside risk, if you like, associated with creating better anonymised datasets?
Dr Elliott: Cost is certainly one issue, and, particularly when we are talking about producing a clinical study report, that is probably one of the key concerns. Perhaps you are talking more about releasing the identifiable or individual datasets, even if they are anonymised. There is, again, an issue of cost in there. There are also the concerns that appropriately to anonymise that dataset would take a lot of resource and may not achieve the end of ensuring that there is appropriate privacy. In order to do that, the data may become much less useful for other researchers by the time the measures have been taken to ensure privacy. We think there are better ways to ensure that data is shared between researchers. We mandate that data should be shared from MRC studies, but there may be better ways to do that than releasing datasets in a publicly-available situation, where they have to be very stringently de-identified.
Nicola Perrin: We would agree with that. We would prefer more limited controlled access to a fuller dataset. In particular, if you are doing research into rare diseases, it is very difficult not to have the identifiable data or data that could potentially be identifiable. We would suggest it would be much more appropriate to have a tiered access model, where researchers can access the full dataset, but with independent review and a sort of access committee to approve that research first.

Q61 Chair: Who provides the independent review? Is there a sort of gatekeeper role to be played here? If so, who is that?
Nicola Perrin: There needs to be a gatekeeper role. We need to explore models to deliver that. There is not a solution at the moment, but we need to look at a consortium that involves industry, academia, funders, Government and regulators. We held a workshop at Wellcome Trust last week with a cross-sector group of stakeholders, including all those different parties. There was agreement that we need to explore workable, practical solutions to this, but the key conclusion was that whatever is decided needs to be a global approach. The UK could and should take a leadership role, but we cannot go it alone. Whatever is the mechanism for accessing data needs to be a global solution.

Dr Elliott: I completely agree with the gatekeeping role, but, if this is done properly, it is facilitating research and in some ways it is also a gate opening, because it is making sure that the research teams requesting data get the right data in the form they need, appropriately annotated and linked back to the original research, while maintaining patients' privacy and their additional consent requirements. It is not simply to delay access and scrutinise it—but also to make sure the right and most informative datasets are released.

Professor Johnson: I entirely concur with that. We would support a requirement to make the data available on suitable request, provided that request is accompanied by a protocol of what is going to be done with the data, how the analyses are going to be conducted and, very importantly, how those results will subsequently be made public by the people conducting the analyses.

Chair: Finally, is there anything else you want to add before we close this session, as we were slightly disrupted? No—silence all round. Can I thank you very much for your attendance? I apologise again for the disruption.

Examination of Witnesses

Witnesses: **Dr Bina Rawal**, Director of Research, Medical and Innovation, Association of the British Pharmaceutical Industry, **Dr James Shannon**, Chief Medical Officer, GlaxoSmithKline, **William M Burns**, Member of the Board of Directors, Hoffmann-La Roche, and **Dr Ben Goldacre**, Wellcome Research Fellow in Epidemiology, London School of Hygiene and Tropical Medicine, gave evidence.

Q62 Chair: Can I ask the second panel formally to introduce themselves?

Dr Rawal: I am Bina Rawal. I am research, medical and innovation director at the Association of the British Pharmaceutical Industry.

Dr Shannon: I am James Shannon. I am chief medical officer at GlaxoSmithKline.

William Burns: I am Bill Burns. I am a non-executive director on the board of Hoffmann-La Roche in Switzerland, and for the years 2000 to 2009 I was the CEO of the pharmaceutical division of that company.

Dr Goldacre: I am Ben Goldacre. I am a doctor and academic. I write about problems in science, and I am the co-founder of AllTrials.

Q63 Chair: I thank all four of you for coming. First, I put a couple of specific questions to Dr Rawal. Could you provide us with a brief overview of the current state of the health of the pharmaceutical industry in this country, focusing on the UK's position as a location for clinical trials?

Dr Rawal: I will certainly give it a try. The UK has suffered in recent years as a choice destination for clinical trials. A number of factors fed into that, one of which was the implementation of the EU Clinical Trials Directive, with the increase in bureaucracy and complexity that that brought. Overlaid upon that over the last decade or so were bureaucratic issues specific to the UK. The UK, being devolved in terms of NHS trusts, each having its own processes for getting clinical trials started and off the ground and contracts negotiated, meant there were perhaps increased hurdles here compared with some other countries.

Having said that, over the last two or three years, particularly with the investment put in by the National Institute for Health Research and the Office for Clinical Research Infrastructure that has been active, and also with the creation of the Health Research Authority, there now appears to be an upturn. The factors that are feeding into this are not only the excellent scientific base here in the UK; there is now a lot of impetus both at the level of early stage translational research but also in terms of moving forward with late stage clinical trials. Investment in the Clinical Practice Research Datalink and other initiatives to draw on the richness of NHS data and diversity of the population in the UK, and to facilitate that by putting in place mechanisms to do so, has helped enormously.

The NIHR NOCRI office, as well as HRA, have worked very closely with the industry, and the ABPI has helped streamline on several fronts, including the development of model clinical trial agreements and so forth.

Q64 Chair: The second question is to Dr Shannon and Mr Burns. In each of your companies, what proportion of your company's global clinical trials is conducted in the EU and the UK?

Dr Shannon: For GlaxoSmithKline, I cannot specifically answer the proportion in the EU as a whole, but, as far as the number of patients is concerned, overall about 4% of our global patient population comes from the UK. A lot of that is driven heavily by a single study using electronic health records and the health system in Salford. If you exclude that single study, it comes to about 1% in total of our patients.

As to what drives us in the location of trials, all of our trials are run globally. Approximately 25% of our trials in total have UK representative centres. As to those things that drive us in the location of trials, the first is quality of the data and the science, where the UK scores highly. Secondly, it is the ability to compare against the most modern medicines available and the best medicines of standard of care, where sometimes the UK does not score highly. Thirdly, it is the complexity and time to initiate the study, where other countries may be faster to initiate and less bureaucratic and complex—and, hopefully, the new legislation will help with that. Fourthly, we come to the cost of running the clinical study.

William Burns: It is remarkably similar from the Roche window. The majority of trials are run globally. As an order of magnitude, but not a precision, roughly 40% US, 40% Europe and 20% rest of world would

be a rather typical profile to run a major clinical trial. The one thing that one always admires within the United Kingdom is intellectual curiosity, and that seems to play particularly to translational medicine and some of the early medicine. It is probably a real strength of the UK, and it is certainly where I know many of the people in OSCHR have put a particular focus.

For Roche, the proportion actually within the United Kingdom is 2% to 3% of patients. This is strongly influenced by many of the points that Dr Shannon has mentioned, particularly the very large proportion of the work of the company in the cancer field, the complexity of cancer itself and the cocktails required as a standard of care. The adoption rate of new treatments in the UK in the cancer field particularly has lagged behind. With Mike Richards' help and a number of other initiatives, that has improved, but there is still a difficulty if you are looking at an investigational drug and a tougher standard of care. If standard of care is not widely used in that country, it becomes more difficult, more costly and slower to conduct the clinical research.

Q65 Chair: Can we try to home in a little more on the UK? How many clinical trials have you got going today in the UK, and what are the main therapeutic areas?

William Burns: For Roche at the moment, to frame it from a global perspective, there are over 320,000 patients actively involved within a clinical trial programme of 2,280 trials, in 35,720 health centres around the world. I do not have the equivalent numbers for the UK, but, out of a global research and development expenditure of approximately 8 billion Swiss francs, 400 million is spent through the UK.

Dr Shannon: For GSK, the overall total patient numbers and number of centres would be roughly similar. We have 59 active trials ongoing in the UK, which represents about 25% of our trials in centres worldwide and 1% of the patients or 4% of the patients.[1]

Q66 Stephen Metcalfe: You have covered some of what I wanted to talk about. Can I talk about what would make the UK a more attractive place to conduct clinical trials? In the opening gambit, we heard about the fact that there is a slightly toxic mix of EU legislation and UK bureaucracy that has put people off. What could we do to improve that situation to be able to attract more trials here?

Dr Shannon: As we look at starting a clinical trial, in many cases speed is of the essence in the ability to get a trial from the point of deciding to do a trial to the first patient being enrolled, and then patient enrolment at a rapid rate. We have to step through a number of hoops. In the UK, in the past, we had to go through the EU Clinical Trials Directive for the individual country, followed by the MHRA, ethics committees and individual trusts, and those individual trust discussions took a long time. I believe the HRA has started to help on the complexity as far as ethics committees and the initial portal are concerned but really has not dealt with the individual trust contract negotiations, which sometimes remain longsome and difficult.

William Burns: Interestingly, the European Clinical Trials Directive has been implemented in a variety of different ways, depending upon which country you are in. For example, the Dutch took the directive and implemented it with a complete lightness of touch because they felt that much of the prevailing legal framework, predominantly Roman law, addressed all the principles. The view of the Belgian authorities was that the current legal framework met the need and they did not feel the need for an additional framework. We, with our Anglo-Saxon legal system, try to cover every eventuality—positive or negative—and outcomes, and that does result in a more complex legal framework. If something is not covered, you can get some freezing in the system as to, "Can we navigate our way through here?"

The new directive coming from Europe is probably an opportunity with the new portal. Offline with Dr Goldacre there was some discussion. I agree it is somewhat vague at the moment, but it is an opportunity for a simplification and streamlining as we bring it from a directive into UK national law. That would be one area where we could get improvement. A second area would be a great initiative through the review that has led to the HRA being established. I hear back from colleagues as to whether they have the resources to do the task that we have empowered them to do—and it is probably the same with NIHR—to make sure that we do not start something well but the logical follow-through is not there. Probably one of the practical consequences of the question would be that I would look at whether the HRA has the resource to help simplify the trial framework for the United Kingdom.

Dr Rawal: I understand that the HRA is currently undertaking a feasibility exercise to look at a single process for getting ethics review and R and D approvals, with only the specifics having to be determined at the local trust level—for instance, whether there is a fridge in the pharmacy. But, for other matters and certainly a lot of the contractual matters, they are trying to undertake a feasibility study and will have some idea of how best to streamline the whole process by about the summer time frame.

Just in terms of putting numbers on it, from the previous question, in 2011 and 2012 there were approximately 500 clinical trial approvals issued by the MHRA, with industry-sponsors. The total number was about 200 higher

Q67 Stephen Metcalfe: Is patient recruitment an issue in the UK?

Dr Rawal: The first focus for the HRA will be on time to start. They have made it clear that they are going to aim for a 70-day target from receipt of a validated application. That will be their primary focus. In terms of recruiting to time and target efficiently and smoothly, yes, it will be important that they can demonstrate that and collect the metrics that can carry

[1] The witness later clarified that, these data cover pharmaceutical studies in patients. The percentage of patients recruited from the UK in 2012 was 4%. This falls to 1% if one large single-country COPD study in Salford is removed from the analysis.

some weight in terms of UK affiliates talking to their global colleagues with the metrics to show that it is being achieved. In terms of the outlook being good, at our conference last November, a big CRO was able to present information that supported that there was now an upturn.

Dr Shannon: Patient recruitment depends on many factors, including the interest or novelty of the active agent under investigation. The more interesting, novel or greater patient benefit that may be derived, frequently patient recruitment is better. If we look at how clinical research is conducted around the world—for example, in the United States—the process of clinical research is heavily driven almost by a business within the clinical site, where there are administrative staff focused on driving patient recruitment, managing those patients' records and so on. In the UK, it tends to be an add-on to a regular clinical job and it is less professional in the way it is conducted compared with some other countries.

William Burns: I do not sense from my colleagues any hesitancy from patients themselves. It is much more to do with the timeline for ethics committee clearances. Is the infrastructure there to facilitate the process for a patient? People are people, and any of us as citizens would want access to what we believe is the best standard of care we can get. I do not think there is any hesitancy from the British public; it is an issue of process.

Q68 Stephen Metcalfe: To what extent is the culture of the NHS a barrier to conducting more trials? I know you have covered some of that, but do you see anything else?

Dr Rawal: As has been alluded to earlier, clinical research is not embedded sufficiently as part of the work of NHS trusts in general, although there are increasing signs that it is changing, with the creation of the Academic Health Science Networks and the onus on them to undertake research and collaborate across the sectors to do clinical research. Testament to the fact that it is changing is the information that Dame Sally Davies, chief medical officer, presented at our conference last year that 99% of NHS trusts had entered a single patient into a clinical trial last year, and approximately two thirds or 60%—I do not know the exact figure—had entered a patient into a commercial trial. It will take time for the culture to change, but it is evolving and the outlook is good.

Q69 Chair: To push you a little further on that, since Sally Davies made those comments, we have a new structure in the system. Does that strengthen or worsen the engagement of people in the trials?

Dr Rawal: Optimistically, it ought to strengthen it. I have mentioned the Academic Health Science Networks, but the focus on information, sharing of data and the open data platforms that are being created—the HSCIC and CPRD, to name just a couple of sources of large datasets—will also facilitate more clinical research happening.

William Burns: To be eminently practical, this is not driven from the national health service, but, in running an organisation, if you make structural changes to it, you disrupt the natural rhythm of the place, and it takes a while for the rhythm to re-establish itself. Until it is clear what the rhythm is of the new world, given that trials are not a mainstream activity, undoubtedly I believe it will take a little while for this to show through in numbers that we can all quote to you.

Q70 Chair: I thought you were indicating you had something to say.

Dr Goldacre: The General Medical Council has recently revised its guidelines for best clinical practice and removed the obligation for doctors to work to reduce uncertainties about the effects of treatments wherever possible, which is a concerning backward step, especially since at the moment there is such a huge amount to be gained in the UK from using the electronic health records of 60 million patients and only a minority of general practices participate in the Primary Care Research Network. In the trial that I am involved in, which is a low intervention trial comparing two statins, we have been able to recruit only about 10% of the general practices that we have approached.

Q71 Stephen Mosley: Can I move on to regulatory reporting? We saw a study last year in the US that suggested that only 22% of clinical trials had been properly and fully reported after 12 months. I know that the ABPI has also done a study that suggests it is a lot better in Europe. Even so, I think you suggested that 79% had fully complied, which still means that 21% had not. In terms of your companies, ABPI—and then I will come on to Dr Goldacre—in what proportion of your clinical trials in the recent past, let's say five years, have you reported in advance and reported the results within 12 months?

William Burns: We are in a similar bandwidth. You have different datasets coming through at different times. The first priority that we give to the dataset is to satisfy a dossier for the regulators, which will include all the data. For that data, which goes down to individual patient data, as far as the United States is concerned, the FDA wants to see all the patient records, having previously discussed the prospect of statistics that will be applied to the study. Other Governments want to see only summary reports, so there is a major effort. That is our first obligation, if you like. That data has been given to us and generated to try to see whether this should or should not be a medicine. Does it pass first licensure, or not? Hot on the heels of that is the translation of that into publications, reportage at medical congresses and so forth. We are within that bandwidth of reportage. I have seen the figures getting better in recent years. This year it is about 90%. I am still not satisfied. We would want to strive towards 100%.

Dr Shannon: We report at a number of different levels. If we start with clinical trial registration, we require that all trials where we require informed consent are registered on a registry, namely the GSK Clinical Trials Register or ClinicalTrials.gov and/or the EUdraCT database. We are close to 99% to 100%. You may ask how I know these numbers. I monitor this on a monthly basis. We have a transparency council. I have a transparency report, and I watch it

on a monthly basis personally. On registry, I know we do that.

As soon as a trial of a medicine is complete, we require that within eight months of the end of it we will publish a result summary on the GSK clinical trials results database. We are 95% to 97% compliant with that. We require that all studies are published or submitted for publication within 18 months, and I know, again, that at the end of 2012 we were at 97% compliance on that record.

As far as concerns submitting clinical study reports to health authorities, that depends on whether we have so far submitted an application for a product licence. We supply all safety data as part of the clinical study reports, and all serious adverse events are reported within 15 days,[2] if they are unexpected, or again within the clinical study report. That is where we stand.

Dr Rawal: To clarify, reporting within the *BMJ*, of 22%—only a fifth—of trials reporting their results as per the FDA's mandatory reporting requirements. At a conference last November, the FDA presented a re-analysis of the information that related to those trials that completed in 2009 that were the subject of publication in the *BMJ*. Their preliminary review suggested that, instead of four out of five trials being overdue, more like 21% were overdue.

At the moment there has not been widespread, complete and comprehensive monitoring of compliance with either the FDA Amendments Act, which requires certain applicable trials to be posted and the results filed on ClinicalTrials.gov, or with the joint positions of the international and European trade industries and the ABPI. The ABPI commissioned a piece of research to look at all the new active substances approved by the EMA in 2009, 2010 and 2011. These are all new products, excluding vaccines and combination products, which are 53 new active substances. We looked to track all the trials that were part of the development of those drugs, from European public assessment reports and publicly accessible registries, international as well as the companies' own registries, and tracked the results either to a publication in scientific literature or a publicly accessible database.

Our preliminary review of the aggregated information for all three years' products—we are talking of approximately 1,000 trials—shows that about 87% of those trials had their results disclosed as of January this year. If a strict 12-month line was drawn at the time of completion of the study, about three quarters would have been reported within that time frame either in the scientific literature or on a database.

This review, which examines the evidence base for the medicine, takes into account all the trials that were done. So, for products approved in 2009, the clinical development would have been started perhaps in 2002, 2003 or 2004. Those trials were not necessarily subject to any requirements—mandatory or otherwise—for reporting, so it is a complete evidence base.

[2] The witness later clarified that, for fatal or life-threatening serious unexpected serious adverse reactions (SUSARS) the timeframe is 7 days.

Q72 Stephen Mosley: On that point, does it include trials conducted outside of Europe in the US as well?

Dr Rawal: Yes. It includes all the trials that we could locate on the companies' registries, on European public assessment reports and ClinicalTrials.gov, because the companies are mandated to file there. As far as we could tell, it included the trials that formed part of the submission for marketing authorisation and any subsequent applications for extended indications. So what we were looking at were only industry-sponsored trials, and we were also looking at any trials in patients—not the healthy volunteer trials.

Q73 Stephen Mosley: If a trial is not submitted when they apply for marketing authorisation and it is not one that they choose to put forward, who makes the decision whether or not it goes forward? Is it the case that all the trials go forward, or is there an element of choice? Who makes that choice, and for what reasons would they be omitted?

Dr Rawal: All trials that are relevant to the assessment of a medicine must be submitted to the regulator. The regulator is entirely able to ask for any trials. You have a clinical trial approval when you first want to embark on a trial. The regulator knows that you have asked for approval for those trials. They can request those, but, in essence, when you want to submit for marketing authorisation, all trials that are relevant to that authorisation—even if it is in a different indication and the trial failed—have to be submitted.

Dr Shannon: If a phase III trial—the end stage or any part of the programme—were to fail and there was no evidence or no evidence of efficacy versus a comparator, most likely we would not submit an application for a product licence; we would terminate that programme. The clinical study reports in those cases would not necessarily be submitted to a regulator because we were not applying for a product licence. However, all of those studies would be submitted for publication in a peer review journal.

Dr Goldacre: That may be true for GSK, but I am not sure it is universally true that trials that were not part of a marketing authorisation package would be made publicly available. I think, quite commonly, they would be withheld.

Q74 Stephen Mosley: Dr Goldacre, I know you have made the comment that, even if compliance is 100%, many times these registries would be incomplete by design. Could you expand on that and explain why?

Dr Goldacre: To practise medicine in a safe, informed fashion, we need the results of all of the trials for all of the uses and treatments that we are currently prescribing, and we do not have that at the moment. There is no legal requirement for all results of all trials to be shared with doctors, researchers, the public and commissioners of health services. Similarly, there is no legal way we can identify all of the trials that have been conducted on a treatment.

When it comes to recent figures on better compliance, the devil is in the detail. We need to know exactly what list of trials you are looking for publication of. It is ironic, in a sense, that the figures we get from Dr Rawal are for unpublished analyses of the extent of

missing data, because we need a fuller description of where the trials came from, how they were looked for in the public domain and what was and was not missing. Even if we had complete reporting of all trials starting from today—2013—or from 2008 under the FDA Amendments Act, that still would not improve the evidence base very significantly for medicine today, because about 85% of the medicines prescribed are generic, which means they came on the market more than 10 years ago. We need the results of clinical trials that completed in 2006, 2003, 1999 and 1994 in order to practise medicine safely, because those are the trials that inform the decisions for the treatments we are giving today.

Q75 Stephen Mosley: That sounds fair enough. What would you two guys say about that?

Dr Shannon: What Dr Goldacre says is absolutely true. Most of the data that originates from medicines on the market today are from the early 2000s, or even 1900s. There are two ways to look at this. One is that clinical trials as such are a rather small piece of the data once a product becomes available, and most of the data on a medicine that has been available for 10, 15 or 20 years would have been captured on the marketplace. One of the things that we miss—I think Dr Goldacre would agree with this—is to look at electronic healthcare records and try to maintain records of the products and product performance on the market. I know that was one of the ambitions of Sally Davies in trying to drive electronic health records and make sure that every patient who was on a clinical study was on electronic health records.

As far as we are concerned, we are trying to go back to the year 2000 from the formation of GSK to make all of those trials available,[3] which will capture many of the clinical trials of our medicines that are on the market today. But, before that, it becomes very difficult when we get into a situation where most of those reports could have been produced by a typewriter on paper. It is very difficult to make those available. Electronic databases prior to that time were in different data standards and are difficult to combine, and the usefulness of that data is difficult to ascertain and get hold of. As we have looked at it, we have tried to deliver what it is possible to deliver, even with difficulty, and for us even before 2000 it is very difficult to do.

William Burns: The bit of the jigsaw that comes to mind here that, maybe, we are missing is that this is a highly regulated industry, and the rules and regulations are predominantly put in place by society through an established regulatory authority. What seems to be happening is that, in recent years, there are more questions about whether the regulatory authorities are doing their job properly as well. It is not just whether the data is available and in what form, but also how we empower as a society our regulatory authorities.

We have seen an increasing requirement over recent years for more stakeholders to have more access to the data. If society wants that to happen, we have to respond; indeed, that is one of the reasons why James and I are here, because we believe this is a correct response to what society is looking for. But we should not underestimate that we should be working with a multiplicity of regulatory authorities. Any significant international pharma company is dealing with probably 80 different principal country authorities, and it goes from individual patient data with the Food and Drug Administration through to summary reportage in Europe. But do not underestimate that FDA and the European, Australian and Canadian authorities are themselves in a network and swapping notes about data and dossiers; they are also networking.

We are seeing here a requirement that is not just new today; it probably started 10 or 15 years ago. You saw more use of ClinicalTrials.gov and the reportage mechanisms that are there. Clearly, society wants us to go further, and probably the two companies sitting here are the first two out of the gate saying, "We will have a new policy going forward, with greater disclosure than we have ever had in the past." That is one of the reasons we are with you, because you tell us how far society wants to go.

Interestingly, sitting from a perspective outside the UK but being a UK citizen, one point I have heard James make is that, in different societies like Scandinavia, the societal benefit outweighs the rights of the individual, all the way through to the United States where the individual's privacy outweighs the relevance to society. As international companies, we see different countries drawing a dividing line between the individual and society. We need to find our way here, with guidance from various countries, as to how you want us to go, because our natural partner in a highly regulated world is the regulatory authority.

Dr Goldacre: It is not satisfactory to say that the results of trials should be reported only to regulators. We are talking about very difficult problems. What are the true benefits of a drug? What are the risks of a drug? If we look at some of the biggest problems that have been spotted in the evidence base for medicines over the past few years—Vioxx, Rosiglitazone/Avandia and Tamiflu—those were not spotted by regulators but by independent doctors and academics reviewing data, and their fight to get hold of that was often hard won. Those problematic signals were not missed by regulators because they are not clever. They are very clever people indeed, but these are difficult scientific questions and they benefit from having many eyes on them. It is a central tenet of science that we are open about our data, methods and results. It is odd that, in medicine, there should ever have been a presumption that it was enough only for regulators to see this information.

[3] The witness later clarified that, GSK will make available Clinical Study Reports (with personal information removed) from published studies of approved or terminated medicines. CSRs for all clinical outcome trials going back to the formation of GSK in Dec 2000 will also be made available in a stepwise manner, with priority given to the most commonly prescribed medicines. For GSK's initiative to provide access to patient level data, studies are listed after the medicine studied has been approved by regulators or terminated from development and the study has been accepted for publication. Global studies conducted since 2007 will also be included and over the next two years global studies going back to the formation of GSK will be added. All studies (including local studies) started in and after 2013 will also be included.

It is also important to be clear that we have known about the problem of publication bias since 1986, and people have been calling for complete registration and publication since then. We still do not have it today.
Lastly, we are not demanding individual patient datasets to be posted recklessly online. We are talking about very brief summary results in some cases. We cannot get hold of the simplest results about a trial from the 1990s saying that drug x was 22% better than a placebo, or drug x was 15% better than drug y. I cannot see any legitimate reason why doctors, patients and academics should not have access to the results of those clinical trials in order to make fully informed decisions about which treatment is best.

Q76 David Tredinnick: Would Dr Shannon or Mr Burns like to comment on what they have just heard?
Dr Shannon: We agree with Dr Goldacre 100%. The more eyes that are put on data the better, and that is why GSK has taken the lead to commit both to patient level data transparency as well as clinical study reports. We believe that, in a world of very complex, data the more eyes we can put on it will benefit patients, science and medicine, so we are 100% aligned in that objective.
William Burns: The same is true for Roche. We have come out publicly with a revised incrementalism in the policy, which will take the study reports to the level being looked for. If that is what society wants to deliver, that is fine. We just need to be mindful of the prospect of analyses of the data and that it is in the interests of patients and healthcare. Are there ways in which we can avoid measles outbreaks with a whole generation of children who were not given the measles vaccine because of a wrong piece of science?

Q77 David Tredinnick: That leads me neatly to the question that I had prepared, which again is for Dr Shannon and Mr Burns. Could you summarise your internal policies across all trial phases regarding trial registration, publication of clinical study reports, academic publication and the provision of third-party access to patient level data? I am aware that you have covered some of this ground already.
Dr Shannon: GSK has a requirement that all studies will be registered on the GSK Clinical Study Register, US ClinicalTrials.gov and/or the European Clinical Trials Register. We monitor that and follow it up. As a study is complete and finished, we require that within eight months of the last patient's last visit a summary of the results is published on the GSK clinical results registry, and that is a short summary of the information. We will write a clinical study report on all trials that are conducted as per the ICH guidelines. Within 18 months of the last patient's last visit, we require that all studies are written up and submitted to a peer review journal for publication. How long it takes to get published is not always in our hands, but all must be submitted within 18 months of that time.
At the end of last year we have taken one step further, which is to say that we will make anonymised patient level data available for all trials that have been conducted globally post-2007 within a clinical database. Scientists externally can request that data to be made available to them, subject to review by an independent panel as to the validity of the research. Initially, we started using trials post-2007 because we standardised the data at that point. It is easier for us to anonymise the data and we used standardised informed consent, so we know that. We will go back and make the data available for all trials since the formation of GSK. In February 2013, we went further and signed up to the AllTrials initiative, which said that we will make clinical study reports available for all studies since the formation of GSK in 2000.
For clinical study reports, it is somewhat more difficult to make sure that we anonymise the patient level data and the patient's identity, because those are on paper. While we can do that in a database by changing the patient code, we either have to redact the patient code in the study report or change it in some way, and we need to work out how to do that.
William Burns: There are some small differences, but in general principles we are on a similar journey. The use of ClinicalTrials.gov is the principal instrument that we use for the announcement of all the trials that are running. We have a similar policy towards publication and the time periods after completion of the studies within which they should be met. We have also announced this year moving to clinical study reports that will give redacted information on patients. It gets more difficult the smaller the patient numbers, or the more unique the disease. If you had cystic fibrosis but you give a postcode, there may be only one child in that postcode that has the disease. As you get down to the more orphan diseases, it needs a little more thoughtfulness about how to protect the interests of the patient.
We have not yet signed up to AllTrials, but you will find that our policy as written meets all the principles in AllTrials that Dr Goldacre has initiated. We are still working on the roadmap that we want to undertake to implement this. Once we have got through that, and also had discussions at European level—because there is a similar initiative on data transparency at that level—we will be publishing our roadmap. But, in terms of the principles as such and transparency, there is nothing to test between two independently worked-up proposals.

Q78 David Tredinnick: Do your policies vary from country to country or region to region?
William Burns: No. We want to have a policy that would apply to the corporation and which is there worldwide.

Q79 David Tredinnick: How will you monitor and ensure compliance with your new policies going forward?
William Burns: That will also be part of the implementation roadmap. We recognise, as Dr Rawal showed, that performance has not been as good as we might have liked it. Speaking on behalf of my company, it has not been as great as we would have wanted. However, we have seen the performance move dramatically over recent years. We want it to move further.

Q80 Roger Williams: We have heard tonight that GSK and Roche have very broadly similar approaches to trial registration, access, publication of results and proposed access to patient level data, and yet Dr Goldacre is critical of one company and congratulates another. Perhaps you can explain how you come to that conclusion.

Dr Goldacre: Certainly. GSK has been on a very long journey from being rather badly behaved, I suppose. It was the subject of a $3 billion fine last year for criminal and civil acts of fraud in the US, coming up to as recently as 2007. However, for many years it has made a series of commitments to greater transparency on which it has begun to deliver, whereas, for Roche, particularly in the case of Cochrane's attempts to get clinical study reports on the drug Tamiflu, on which the UK Government spent £500 million in 2008 alone—that is 5% of the total NHS drugs budget in one year—the experience of Cochrane has been very different from the aspirations described here today. They were blocked at every turn, and there is a very long and troublesome story, which I understand the Public Accounts Committee—or at least the National Audit Office—is looking into in some detail. If you wish to call Cochrane, it would be very happy to go into that in detail, but it was asked to sign non-disclosure agreements that also had clauses in them that said it was not even allowed to discuss the existence of those.

In December 2009, Roche made a commitment to share all the clinical study reports on Tamiflu, and that promise has still not been paid out on as yet. My concern is that Roche is certainly making exactly the right kind of noises that we would like to hear about sharing clinical study reports, but in its specific interactions with Cochrane so far it has fallen well short of those aspirations, albeit those may be very novel and announced only recently and only in press releases.

It is important to be clear about what we want and why. Clinical study reports contain much more information about the methods and results of a trial than a brief report in a publication, or a brief summary report on a clinical trials database. By comparing clinical study reports on Tamiflu against brief published reports, Cochrane has already found discrepancies. For example, things that were described as placebos in the academic journal article turned out to be, first, a different colour from the active treatment, and, secondly, not to be inert placebos at all; in fact they had active ingredients. It has also found episodes where the case mix was not as described and was flawed in a way that might be expected to over-exaggerate the benefits of Tamiflu, and that was clear only from the full clinical study report, not the brief trial report. Lastly, they found at least one case where in an academic journal article describing a trial there were no adverse events, but in the clinical study report describing the same trial there were adverse events. It is to resolve discrepancies like that that we need better access to clinical study reports.

The second question is about what to do with individual patient data that is in these full clinical study reports. That poses some very interesting questions. That is the only area where there is any reasonable area for disagreement about how much sharing there should be, and to what extent that should be behind an approval committee. It is important to be realistic here. You find bits of individual patient information even in academic journal articles. For example, you might find a sentence that says one patient developed pneumonia and was admitted to hospital, but it should be borne in mind that the patient was immuno-compromised and had HIV. That is the sort of sentence that one might expect to read in a published academic journal article as much as in a clinical study report. A lot of what you see in narrative descriptions of adverse events in CSRs is not the kind of information that people would necessarily be very worried about protecting, but at individual patient data level, when it comes to very long and complete databases with postcodes, dates of birth and so on, we have to be thoughtful about how we control that.

You asked—and I will finish in a moment—about the difference between GSK and Roche. One concern that I and many others have about both companies is that they say there is an independent review panel that will look at the analytic strategies being proposed by independent researchers to be conducted on the datasets that the companies have collected. First, I am concerned that there should be pre-approval. It is reasonable to ask for pre-registration in order to prevent people going on a statistical fishing trip. For pre-approval, if that is to be acceptable at all, it would have to be with a very low bar. Secondly, there is the matter of who is on these independent panels. As I understand it, we do not yet know who is on the GSK one, but for the panel called MUGAS by Roche there are four independent researchers. As I understand it, three of those have been paid consultants for Roche and one has had a trial research grant from Roche. We need to be cautious about whether it is okay for individual companies to set up their own boards.

It is not surprising that those disagreements will arise very early on in society's negotiations about what should be shared and how we should do it. We need to look at having standard protocols perhaps nationwide across both independent academics and also industry, and ideally internationally, setting down standards on what it is reasonable to ask, who should be on the review panels and also making sure that all the processes are transparent so that everybody can see what has been rejected.

Q81 Chair: Right of reply.

William Burns: Right of reply, but I will try to keep it short in the interests of your time. I would put before the Committee that, on Tamiflu, we have shared data with 80 world health authorities, including individual patient data. We have had a multiplicity of independent reviews from the World Health Organisation, CDC Atlanta and a number of specific Government-established Departments or initiatives looking at pandemic planning, which all came left field as a potential utility of the medicine. We have had problems with one independent review group. When I look back on that, there are faults on both sides and miscommunications. It is difficult when you ask for a way to protect patient confidentiality and

there is pushback on the signing of it. That is fine. There is an offer and we should sit and discuss it, but it ends up in e-mail exchanges and there is not a meeting and clarity of mind, and, sadly, we start to see that the emails are being copied in to the media. We know there is another agenda at work here.

There are probably faults on both sides on one independent review, but in the holistic look at the total medicine, and indeed in some of the UK Government's reviews as to whether or not it is appropriate to use a neuraminidase inhibitor in pandemic planning, clearly there is a role for this medicine, and I do not think that is in any way in dispute. I recognise that the Committee wants to think higher on the total transparency, but please do not look at the company on the basis of one independent interaction on one product—but on a broader basis.

As to the other points you raised, on individual patient data, as a company we would agree with a lot of what you say. We should not be so prescriptive on the way in which people want to review that data, but there needs to be enough intellectual rigour and that it is not transparency for its own sake but for a purpose that needs to lead to improvements for patients. It is not just a matter of intellectualising for the sake of it, but everyone should be looking at whether the dataset is going to improve patient outcomes.

The third question you raise is to do with the independence of an advisory panel. Dr Shannon can speak on his own behalf, but, if you are looking for world experts, you will find they are on top of their subject, probably have worked with a multiplicity of companies and have had experience in running trials on a multiplicity of new chemical entities. If anything, it enhances their independence rather than saying that because they did some work for one company they are in the pocket of that company. That is almost insulting to the academics.

Dr Shannon: As far as concerns the independent review panel, I may sound like a broken record but I agree with Dr Goldacre. We also believe that a review panel should be independent. We have our system up and ready to go.

Q82 Chair: If it has to be independent, answer Mr Burns' point. Where you are getting narrower and narrower expertise, he is arguing, as I understand it, that the experts are bound to be the people you would want on your review panel.

Dr Shannon: That is absolutely true.

Q83 Chair: How do you solve it?

Dr Shannon: We are planning step two before we plan or initiate step one. At the moment our system is up and ready to go. We have available a panel of independent experts some of whom have worked with other pharma companies and are ready to act as our initial panel, but we are also in negotiations with a completely independent clinical research organisation to have them nominate a panel that is completely separate from GSK and where we have no involvement whatsoever in the nomination of that panel. It is clear that a panel nominated by GSK will not be acceptable to Roche, Novartis, Pfizer or any other company. We wish and hope that a panel nominated by an independent body will be acceptable to other companies and encourage them to join up to our initiative.

William Burns: Probably the key thing is the transparency with which it is done and that this should be declared.

Dr Goldacre: I certainly would not say that anybody who has received money from a company is inherently biased, but we need to be aware of conflict of interest, and we know it is a risk factor.

William Burns: I can agree with that—absolutely.

Dr Goldacre: I do not think that people on a review panel necessarily need to be people with familiarity with one particular drug or one company's drug, so there will be statisticians and clinical trial methodologists with no ties to any one company, or indeed any company, who may be willing to participate on such a project.

I come back very briefly to Tamiflu, not because I think it is important as a particular drug but because it is the most well documented case where we are aware of discrepancies between trials being reported in different ways in different territories. It is important to be clear that, although it has been reviewed by several different regulators around the world, they have come to very different perspectives and judgments on it. For example, in Japan, Tamiflu has a black box warning on it for use in 12 to 18 year-olds, which it does not have anywhere else. The FDA did not permit the claim that it reduces the risk of complications, which is a medical euphemism meaning pneumonia and death after influenza infection, whereas elsewhere in the world the company is permitted to say that it reduces the rate of complications.

These discrepancies in final conclusions between regulators reflect perhaps two different things: one, that they have seen different data, and there is evidence collected by Cochrane to show that different regulators around the world have been shown different data on Tamiflu; and, secondly, that different regulators come to different conclusions even based on the same information, because this is, as we have already discussed, complex data and different people will hold legitimately conflicting views on it. It is important to be clear that regulators do not necessarily have all of the information and they are not necessarily infallible, and that is just another reason why we need to ensure that as many people as possible have access to the data in order to make their own judgment.

William Burns: In that case it is the second and not the first.

Q84 Roger Williams: Can I take it forward and ask Dr Rawal, in your opinion and that of your organisation, how GSK and Roche compare with the rest of the industry in their approach to these matters?

Dr Rawal: It is an evolving discussion. To set the scene, the ABPI has 68 members who are either full members or research affiliates, so in some way they engage in clinical research work. Of those 31 that I have called smaller companies, their turnover would be less than 75 million. We represent the whole spectrum from smaller to larger companies.

To set the context for this discussion, the disclosure of clinical trial results can be looked at at different levels. First, the disclosure of summary results is already a requirement as per the ABPI code of practice. Indeed, the EU clinical trials database is being upgraded to be able to accept the summary results of all the clinical trials conducted in the EU going back to 2004, so there will be visibility and line of sight to the summary results for those studies going back to 2004. Prospectively, of course, it is a requirement, and ABPI has already announced an intent to put in place measures to monitor the rates of disclosure of clinical trial results. That is at the level of summary results.

It is also important to look at what the EMA is doing. The EMA embarked on a process at the end of last year to increase transparency in the reporting of clinical trials and, in particular, launched five working groups that are looking at the specifics of how to share clinical study reports, for example. The whole clinical study report can extend to thousands of pages, if you include the appendices. That is very different from disclosing summary results, which are generally based on a synopsis of the whole clinical study report.

The five working groups are looking at issues such as protecting patient confidentiality, which is absolutely crucial, because there is sensitive personal information threaded through—particularly in the appendices of the clinical study reports—that would need to be anonymised. They are looking at clinical trial data formats and standardisation of formats; they are looking at the rules of engagement as to how to make those accessible to everybody, or should the requester register and say what they are going to use it for? All those questions are being debated. A fourth group is looking at good analysis practice, and a fifth one at the legal aspects. That shows how complex it is when you get into the discussion about disclosing full clinical study reports.

It is also important to note when that disclosure happens. Up to now, the summary results are required to be disclosed after first marketing authorisation of the product. We need to know in timelines whether we are talking about pre-approval or post-approval of the product. It is important to make that clear.

The third level of transparency is about individual patient datasets—i.e. the raw data that underpin all of what we have just discussed. Those datasets are what I think GSK and Roche are talking about in terms of making access available to independent researchers. Those requests by researchers will be reviewed by an independent panel so that there is rigour and transparency in those analyses and so that medicine and science can be advanced. Those are very complex issues.

ABPI ran a workshop a month ago to talk about clinical study reports. As Nicola Perrin mentioned in the previous session, the Wellcome Trust had a workshop last Friday to talk about disclosure and sharing of datasets. There is general consensus that we need to move forward at an international level here. It is no good the UK just deciding what to do because, by and large, clinical trials are a global enterprise, and, in the UK, clinical trials regulation is governed at EU level. It is really important that this is done in the context of those two facts.

To create data warehouses or repositories, there still needs to be a lot of discussion at international level and across sectors, because clearly this affects academia and other researchers and public and charitable funders, just as much as it affects industry. We all want to advance research and get the maximum benefit, and exploit the data that we are collecting on patients, because that is what serves the patients' interests best—if we can make the most of every single trial patient and their data, and get absolutely what we can out of it to serve for future product development, future trials and future medicines.

Q85 Chair: Very briefly, I want to follow that up. In that perfect world you have tried to describe, will that stop the kind of litigation we have seen just recently, or do you think that is an inevitable consequence of the crazy world we live in?

Dr Rawal: I am not clear which litigation you mean.

Q86 Chair: There was a case in March of this year in which AbbVie sought an injunction to prevent the EMA from releasing raw data in relation to its arthritis drug. It is not a very satisfactory situation to be in, is it?

Dr Rawal: I cannot comment on the specific case. There are provisions under freedom of information to request any part of a marketing authorisation application. It depends on whether we are talking about clinical study reports as opposed to other information in the marketing authorisation application. Issues are there that still need to be addressed around what constitutes commercially confidential information. When is regulatory data protection crucially important in order not to disincentivise the innovative pharmaceutical industry? There will be examples of regulatory data protection that rely on that, as opposed to intellectual property, for the protection of the interests of the developer of those drugs.

Dr Goldacre: The European ombudsman has been clear that there is no commercially confidential information in clinical study reports, and where there is patient-confidential information it is easy to redact that. It is important to be clear that every one of the systems Dr Rawal has set out has holes, and it is great that the ABPI has come very late to aspiring to greater transparency here. For example, the ABPI code of practice, as I understand it, two months ago, does not cover Roche because they are not members of the ABPI.

William Burns: Roche fully subscribes to the ABPI code of practice on a voluntary basis. We have said we will absolutely comply with the code of practice.

Dr Goldacre: That is different from the information I was given by the ABPI, since you are not members of the ABPI.

On the issue of the European Union Clinical Trials Directive sharing results, we are not yet certain what will happen. We are not yet certain what will happen with the EMA's changes for sharing individual patient data and whether that will be retrospective. If it is

only trials completing after 2014, it will do nothing to improve medicine until most of us are dead.

The European Union Clinical Trials Register demonstrates more clearly than anything else how incomplete these systems are by design. The European Clinical Trials Register promised that it would carry results by 2012, and it still shows no signs of doing so. More importantly, it covers only trials conducted after 2004 and only those conducted within the borders of Europe. That is no use at all. We need the results of all of the trials conducted on all of the medicines currently being used in Europe. It does not matter if they are trials submitted as part of the marketing authorisation package or if they are trials done after a drug came to market in Brazil, Russia, India and China. It does not matter if they are for unlicensed uses. If there is a trial on the use of an antidepressant drug to prevent post-traumatic stress disorder or anxiety and we know that currently it is being prescribed for that, even though it does not currently have a marketing authorisation, all of the trials for those indications should be shared as well.

Every single system we have at the moment, by ambition, is incomplete. The very simplest thing that we could do to change all of this would be for the European Medicines Agency to say, as part of their approval process, "Congratulations. Your drug is for sale in Europe. As you know, we hold the trials register that contains all results of all trials for all medicines being used in the European Union. Here are the forms. Give us the results of all of those trials." There is no reason why that could not be done. We have known about this problem for 27 years now at least. I do not think it is industry's fault that we have not moved forward on this; there has just been a failure of ambition on everyone's part.

Q87 David Tredinnick: Following on your theme, Dr Goldacre, as a clinician, how do you think increased access to individual patient data might ultimately impact on individual clinical decision making in public health?

Dr Goldacre: The best currently available information on the extent of missing trial results comes from the NIHR HTA review in 2010, which estimates that about half of all trials do not go on to be published, and trials with positive results are around twice as likely to be published. That may have improved for very recently conducted trials, but that does not reflect the decisions that we make on a day-to-day basis. We do not know what we are missing; we find out only in a piecemeal fashion.

I can give individual stories. For example, doctors who prescribed Reboxetine before we had all of the information in 2010, after IQWiG—the German equivalent of NICE—demanded that all trial results were made publicly available, were not able to have all of the results. I prescribed this drug myself. If I had had all the results, I would not have prescribed it. The company Pfizer was withholding lots of results. Similarly, for all antidepressants, the best available meta-analysis by Cipriani cannot take account of publication bias, so we do not know which antidepressant is best. I do not think we are very commonly prescribing drugs that do more harm than good, but we are probably being misled about which of the many available treatments in one class is the best.

Q88 David Tredinnick: How do you think the right balance should be struck between increasing the transparency of raw trial data and protecting the confidentiality of those involved—we touched on this earlier—many of whom provided their consent many years ago when the modern culture of data sharing could not even have been anticipated?

Dr Goldacre: It is important to be clear that we are breaching the ethical pacts that we forge with patients, and breaking the bond made with them in the consent form, when we fail to publish the summary results of trials. That happens very commonly, so we already trample over the obligations that we have reciprocally between triallists and trial participants. However, it is extremely important that we respect patient confidentiality. None of our requests for summary results have anything to do with patient confidentiality and there is still a problem with getting summary results. As to the details of how we get individual patient data more widely available, there is a huge, long and complex technical discussion to be had on that, but it can only be had among those people who have already committed to the principle that that is something we all want to do. There are many people in industry who reject that proposal.

Q89 David Tredinnick: I have a final question for Mr Burns and Dr Shannon. If your commercial competitors were to make patient level data freely available, would you access it? If so, how would you use it?

Dr Shannon: Would we do it, and how would we do it?

David Tredinnick: If your commercial competitors were to make patient level data freely available, how would you access it and, if so, how would you use it?

Dr Shannon: I can tell you that, by accident, our clinical trial registry—the share system that we talk about here for patient level data—went live last Wednesday for about four hours. In those four hours, even though there was no guidance to that system, three other companies accessed the data, plus Johns Hopkins hospital in the United States.[4] If companies make data available, other companies will access it.

There are many ways in which we can use patient level data on both active drugs and terminated drugs. The history of the pharma industry is that many of us, in pharma, have chased a target for a specific disease, not knowing that another company had failed in their trials for that target. If we understood that other companies had failed in that target and it did not work in the disease, we could either change the trial design to make the trial more appropriate and get better results or drop the target and not move forward. We could also understand better the types of patients in whom the drug works or does not work. We look here

[4] The witness later clarified that, the draft Share website was temporarily available at other times. For information: the Share website https://clinicalstudydata.gsk.com/ was formally launched shortly after the evidence session on Tuesday 7 May.

at the best drug for a patient. What we show in clinical trials is the average result of the effect on a population and what is the best drug for an individual patient, or group of patients, whose specific characteristics may be different. We do not know today from many clinical trials. We could identify which are the right drugs for the right, specific patients, for example.

William Burns: Another way you see this data also playing out is that, since the advent of ClinicalTrials.gov and the publication of the work that is under way, this helps to navigate for doctors who are not in trials. Is there a trial running for a patient with a certain disease? Would they qualify? They can put them in touch with them. It also helps other clinical triallers to say, "I was wondering about comparing it with drug x or looking at sub-population y." Then they see that there may be three other trials running, and they do not start a clinical trial unnecessarily exposing more patients to it until they know what the results are of the trials running. There are elements of this transparency that can enrich and inform.

On the point about legal interventions, I would not be at all surprised if we did not see more tort lawyers in America scouring through the data to see if they can find a basis for some cohort or class action in some way. I would not be at all surprised to see generic companies trying to enrich their dataset in lesser regulated countries out of the public domain. In countries where the files are available for a very modest price, historically some generic companies have had paper copies they have been able to enhance. This is not in the interests of public safety. There is an exposure; we just have to be ready for it. I am not saying it is any reason not to go forward. Absolutely, as an optimist in life, you see two companies here who have said that we are prepared to go down this route and we are prepared for that degree of risk.

Q90 David Tredinnick: Isn't sunlight the great disinfectant? Really what we are talking about is more information, for the right reasons, being out there to stop duplication and improve the condition of the people.

William Burns: Yes, but I think you are speaking to the converted there.

Chair: The unconverted are not with us today. Can I thank all four of you for your contribution this afternoon? We went on somewhat longer than we had anticipated, but thank you very much indeed for coming.

Wednesday 15 May 2013

Members present:

Andrew Miller (Chair)

Jim Dowd
Stephen Metcalfe
Stephen Mosley
Pamela Nash
Sarah Newton
Graham Stringer
David Tredinnick

Examination of Witnesses

Witnesses: **Simon Denegri**, NIHR National Director for Public Participation and Engagement in Research and Chair, INVOLVE, and **Professor Karol Sikora**, Medical Director of Cancer Partners UK and Dean, University of Buckingham Medical School, gave evidence.

Q91 Chair: May I welcome you to the session and thank you for attending? It would be helpful for the record if you would kindly introduce yourselves.

Simon Denegri: Good morning. My name is Simon Denegri. I am the NIHR national director for public participation and engagement in research and also chair of INVOLVE, which is the national advisory group for public involvement in research.

Professor Karol Sikora: I am Professor Karol Sikora, professor of cancer medicine at Hammersmith hospital in west London and dean of the medical school at Buckingham. I am also an oncologist; I have been a consultant in the NHS for 30 years.

Q92 Chair: Thank you. Let me start by simply asking you why patients and, indeed, healthy volunteers choose to participate in clinical trials and what factors might discourage them.

Simon Denegri: The first thing that we ought to say and recognise—it is often understated—is that of course clinical trials would not happen if patients and people did not come forward voluntarily and freely contribute their time. There are a number of reasons why people do that. The first is that there is the opportunity of benefiting from a new treatment or new therapy. There is a very clear sense that comes through in the documented evidence in relation to patients that they feel as though they might get better care. They want to help medical research; they want to help others. They also want to take some control of their disease, and participating in clinical research is one of the ways in which you can do that, or feel that you can do that.

Professor Karol Sikora: Cancer is all I know about, I'm afraid. With cancer, it is rather different. There is a sense of desperation among many patients who have reached the end of the road with conventional medicine. People actively seek out centres where there are clinical trials for cancer. The other thing is that there is an altruistic motive. People will try a new drug, even though it is explained to them that it is unlikely to work for them, but it will give information on, say, the kinetic distribution of the drug in the body, which will be useful to us for further patients. People are very willing to do that.

The problem we have with something like cancer is that you are sometimes raising expectations in these trials in terms of what the patient believes and what you know is the realistic outcome. It is very important from an ethical viewpoint to be completely honest about the likely benefit.

The other problem in clinical trials is that it is about not just length of life, shrinkage of cancer and reduction of blood pressure, but quality of life, and quality of life research is very challenging, mainly because you cannot measure it very easily. In certain types of cancer, there are blood tests that can be done and you can look at the level of growth of the cancer, but what is the quality of someone's life? There are various indices to try to determine that, but they are not very good. The traditional doctor will say, "How are you feeling today?"—that is a quality of life assessment—but we can do better than that now. Getting a holistic view of how the patient is doing with their disease and how they feel about it is much more challenging.

Simon Denegri: I would not disagree on the quality of life aspects, but specifically on your question about barriers to getting people involved in clinical trials, there are a number. One is that we know that knowledge about clinical research and trials is pretty low in the general population. It probably increases as one becomes a patient, particularly if one has a condition such as cancer or if one is going to be treated for a long period of time. They become initiated in how medicine and medical research happens.

Often patients cite very practical reasons why they cannot take part in a clinical trial or clinical research, and those may be that it is happening too far away from home or does not fit in with their life. These things point to the need to involve patients and the public much more in how we design and deliver research.

Q93 Chair: Is there a lack of public trust in medical research when it is sponsored by industry?

Professor Karol Sikora: I think there is. There is no doubt that industry has a very pervasive influence, and I have to be careful because I know that we have some representatives behind us here. In different ways, it has an effect on the public, and of course the internet has driven a new way of directed consumer channelling. Even though you cannot in Europe put an advert direct to consumers for a drug, the internet is free, and you can put up a website for all the high-cost cancer drugs—each has its own website. Patients, provided they trust their direct clinical advisers in

hospital or in general practice, really do not worry too much about that side. In the UK, we have a good ethical structure with the centralisation of research ethics committees, which means that provided the ethics committee is happy, one can only assure the patient that it is likely to be okay, even though the study is funded by industry and it may, if it is positive, result in considerable profit.

Q94 Chair: So even though the patient knows that the driver of the research is a large corporate, because it has the confidence of the doctor whom they trust—
Professor Karol Sikora: Exactly, so the doctor acts as the intermediary. Although it is stated on the consent form that it is sponsored by one of the big companies, they trust the doctor not to do something that would be against their benefit.
Simon Denegri: I agree that the relationship that one has with one's health professional is pivotal in building that trust and seeing perhaps beyond one's immediate assumptions about who the funder is, but there is none the less quite a strong public mistrust of industry. If you look back at the Eurobarometer poll 2010 of people's attitudes to medical research, one of the things that comes through very clearly is people's concern about the influence of the pharmaceutical industry, and that will feature again in the Health Research Authority's own public engagement exercise, published on Monday, so I think we are detecting that. As someone who has, as both a patient and on behalf of patient groups, worked with industry, I think it is a real shame. We have some really good examples from individual companies of them coming together with patients and thinking very innovatively about how to work together. From a patient point of view, working with industry collectively, it can feel a bit like going to a party and meeting the same person, and they are repeatedly looking beyond you at someone who is more interesting and valuable. There is a real opportunity with this debate to see the industry change how it relates and changes its body language towards patients.

Q95 Sarah Newton: I like this analogy of being at a party and looking beyond you, and I really want to stick with the idea of patients and why more people do not get involved in clinical trials. In our written evidence, we had a survey from the research group PatientView called, "Sense about Science". It told us that only 35% of patients had participated in a clinical trial and that 14% had been asked to participate but declined to do so. I am wondering about how people will naturally find out how to join a clinical trial.
Simon Denegri: That is a very good question. I think it is quite difficult at the moment for people to find out about clinical research and how to go about going on a trial. In certain condition areas—cancer being one, as are some of the places where we have excellent clinical research networks, such as in stroke and diabetes—the level of knowledge about opportunities is rising, but it is still quite low. Through the National Institute for Health Research, we are leading the "OK to ask" campaign for international clinical trials day next Monday—20 May—which is part of trying to open the conversation much more wider, giving patients the confidence to ask their doctor whether there are trials they might benefit from, and giving clinicians and health professionals the confidence to broach the question. You are right that even in cancer one in three people has had a discussion, and we need to raise the level and amount of that discussion. At the moment, it is quite difficult for people to find a route in. It is quite hit and miss.
Professor Karol Sikora: One of the difficulties in cancer and other areas is that the entry criteria for the trial must be set. One cannot make it all inclusive, so if you are over a certain age, under a certain age, or don't have an assessable disease, there is absolutely no point in that patient doing a trial. Perhaps we should be a bit more thoughtful about how to offer alternatives if a patient doesn't suit. Often, the patient may be considered for a trial and investigations may be done, but they are then told, "I'm terribly sorry; it's not for you. You don't fit the criteria." That is a let-down for people. If we could have a system in which clinical trials are offered, but there is a back-up if the patient is not suitable, it would be a far better way of keeping the balance of trust.

Q96 Sarah Newton: Could you perhaps expand on that, because it is a really good point? What other ways to help could they be offered? I am sure you are right and that people want to feel that they are not only helping themselves, but contributing to the greater good so that other people do not have to suffer as they are suffering. What other things might they be offered so that they can stay engaged in clinical trials?
Simon Denegri: They may well be able to take part in a questionnaire or survey to improve the service or even the environment they are going into. We must also think about this in a much more long-term fashion by getting people to understand more about research and see it as a potential place where they can participate. They might begin to feel able to ask some very good questions about the evidence underpinning their treatment and have that evidence-based relationship and conversation with health professionals. That is what we want to aim for and aspire to in the long term.

Q97 Sarah Newton: We have received evidence from the UK clinical trials gateway. How do you feel that could be improved as a way of having the sort of dialogue you were talking about and people more prepared to participate in trials?
Simon Denegri: The gateway is a good initiative, and when we tested it with patients and the public at the end of last year, they very much welcomed it. There are two broad issues with it: first, knowledge of it is not great; and, secondly, from a patient perspective, it is a little clunky and does not quite do everything you need. At the moment, you can search generally and nationwide for trials in which you might be able to participate, but you cannot search for trials that are local to you—perhaps 20 or 30 miles down the road—which is a priority for someone with a busy life. We have some near-term things to do to improve it and to make it really fit.
There is a bigger question about what the gateway does with other providers of online technology to

enable patients to build research communities. Patients are increasingly outsmarting us when it comes to the use of technology. We need to embrace that in some way and to work with them much more. There have been some great things in the past with the cystic fibrosis website, CFUnite. That is a really good example of the community, including patients, coming together to help people to register for trials and to find out about the evidence. Those are the sort of things we need to harness much more aggressively.

Q98 Sarah Newton: So working in partnership with trusted bodies such as NGOs or charities representing particular groups of people with particular conditions.
Simon Denegri: Yes, but there are also many good private providers, and we should not discount that. I think it is more about the whole community coming together as quite a large collaborative. It doesn't mean you cannot be competitive, but coming together as a collaborative can produce a sort of learning health system that helps patients to find their way to research much more easily.
Professor Karol Sikora: I think we underestimate the power of the internet and what is going to happen over the next decade. I was giving a talk at my old primary school on Monday, and the amount of IT these seven-year-olds can do is just phenomenal. That generation will be the next generation of patients, and they will be able to access information that our generation certainly could not—and probably still cannot.
The internet will be a very great provider of information to patients. They will look up their specific disease, or have it recorded, and then they will be able to find what trials are available to them. That is probably the brave new world. There will be industrial trials, quality of life trials—all sorts of things—listed that will be personalised to them, because the ones that are not relevant will be taken out. They will be able to see what is available, and the distance as well, because that is obviously important for chronic treatment.

Q99 Chair: You have mentioned the internet a couple of times, Professor Sikora. The problem with some conditions is that the evidence base that is published is pretty thin, and there are some fairly contradictory bits of information. How does one use the internet to get a good picture of what the problem is?
Professor Karol Sikora: You are absolutely right. For cancer, there are 1.4 billion sites now with cancer in them. Some are complete rubbish. Some are completely mad. Some are patent advertising for something.

Q100 Jim Dowd: Did you say 1.4 billion?
Professor Karol Sikora: Exactly. This is on Yahoo! For some reason, Yahoo! has more than Google.
Jim Dowd: Who counted them?
Professor Karol Sikora: It is just amazing. You could not read them all.
The problem we have got for clinical trials is that there are not that many. There are a few good sites now for clinical trials, but they are not personalised: they are not for you—for your illness. The future will be about getting to that point. Who should do that? Whether it should be the Health Research Authority, whether it should be a clinical trials collaborative, or whether it should be organised locally is clearly one of the challenges facing the medical—

Q101 Chair: It just seems to me—this goes way beyond medical research—that peer-reviewed information will have some sort of real, firm kitemark on it.
Professor Karol Sikora: Exactly.
Simon Denegri: We need to think about building up patient knowledge as part of the infrastructure we need to put in place to have a vibrant clinical research community in the UK. One of the ways we do that is to encourage patients—the public—to ask challenging questions. There is a very good campaign run by Sense about Science to ask about evidence. These are the sorts of things that we need to get across to people much more clearly, and equip them and arm them. That can only facilitate them in making a good and informed choice.

Q102 Stephen Metcalfe: Good morning. I fully understand the logic of people looking for trials and trying to find something that will help them. Concern has been expressed, though, that once a participant has taken part in a trial, the results of that are not necessarily communicated back to them, and any potential medical advance that has come from that trial is also not communicated to them, so they do not know what their role was and what benefit there might have been. First, do you accept that and, secondly, how typically is that information communicated back to participants when it is?
Simon Denegri: I absolutely agree with that. When I go round the country doing public meetings, it is one the most common questions and complaints I get from patients—they may have been a trial participant, but no one communicated with them afterwards how that contributed to knowledge about the condition, or how that may or may not have improved treatment, and down to never being thanked for their contribution. I think we do people a real disservice here.
What we do need to do, and have the opportunity to do, is to produce a much stronger overall commitment to patients going into research—a sort of Bill of Rights, if you like, which people like the founders of DIPEx were talking about in the late '80s—which stretches from having good information to a clear consent process, to being able to find out about the results of a trial, and to being thanked as a basic courtesy when it is finished, because that can only encourage their future participation and encourage them to talk to others who will then participate as well.
Professor Karol Sikora: I think it does reflect the growing up of medical communication with patients. When I began as a consultant, we did not tell people they had cancer, so how could you possibly engage in giving them the results of a cancer trial? But now we are in a totally different information transfer and a much more level playing field, so it is very possible to insist that at the end of a trial, when the results are either published or collated—not all trials are

successful, by any means, as you would appreciate—a summary in layman's terms is sent with a letter of thanks to the patient. That would not cost much and it would be very welcome, I think. As you say, Simon, it would encourage an ethos of searching and wanting to be part of it.

Simon Denegri: I think there are some very good places where people get told before it goes into a publication, and I think that's great. I know that might be challenging to some academics and researchers, but I think it's a great example.

Q103 Stephen Metcalfe: I think you are entirely right. That sounds like a potential best practice solution. Are there any occasions when participants don't want to know the outcome of the trials, or is that very rare?

Simon Denegri: That question is a good one, and I think it goes down to what the conversation is with the patient at the very beginning, and to setting clear expectations. Certainly, I would be very concerned if people were getting letters falling on their doormat, unprompted. I think there needs to be very careful thought about how you share these results with them, because some people would be alarmed, perhaps, and would not want it in that way. But I think it goes down to: what is the conversation with the patient at the very beginning of this research?

Professor Karol Sikora: I think that's right, and managing expectations is always vital. If someone has metastatic cancer, it is unlikely that they are going to be cured; it is more likely that they will live longer, even if the trial is successful. But people don't hear that. They hear, "This pill, this injection, is going to cure my cancer," and I think it is up to the clinician running the trial to keep the expectation under control.

Q104 Stephen Metcalfe: Thank you. When you are discussing with potential participants—patients—at an early stage the possibility of taking part in a trial, do you discuss the possibility of sharing their data at some later point, potentially anonymised? In the main, are they happy for those data to be shared?

Professor Karol Sikora: It is very easy to get cancer patients—in fact all patients—into a trial if they trust the treating team; not just the consultant but the whole team, including the nursing staff and other carers. They see that the team wants to do it not just for their own interest, but for the greater good of the whole community and other patients, so most people agree readily. The difficulty comes back, again, to this expectation: are you giving false hope to people by doing it? It is dangerous to do that.

Simon Denegri: I obviously haven't been in a clinical situation like that, but generically I have been part of dialogue exercises with patients about data. There will always be some people who are concerned about it, and some quite rightly because they have a stigmatised disease and have a life experience that is extremely arduous. But, generally speaking, if you enter into a dialogue with a group of patients, they readily get the idea about data and why data need to be shared, or why it is beneficial to do so, and they will readily buy into that, as long as the rules are clear, the risks are clear and they know where they can get further information.

Q105 Stephen Metcalfe: Okay. So would you say that that situation has been improving over the past x number of years, and that there is more engagement backwards and forwards? What about those patients who have been involved in historical trials, who perhaps weren't engaged in that same dialogue? Do you think there is any merit in contacting them to ask if their data can now, retrospectively, be shared, or are there too many risks?

Professor Karol Sikora: That is probably quite a difficult exercise. Most patients with chronic disease, whatever it is, are under some form of follow-up, and if they have participated in a trial in the past, the results should be in their medical records. If it has not been done in the same hospital, at least a copy of the results should be there. So then it is up for the follow-up staff—the consultant, the registrars—to give that information if patients want it.

A lot of people are strangely still uninterested in this. They trust the system too much, but I think that's changing. Younger people want to know more. My generation are on the cusp and the next generation on from me really is not interested—"Whatever you say doctor." But it's changing, and it's changing for a much healthier dialogue.

Q106 Stephen Metcalfe: Do you think there is a benefit in going back over historic data and trying to harvest that? Is there anything to be gained, even if was difficult and costly? Is there something in those historic data that would be of benefit?

Professor Karol Sikora: It may create problems. Someone would have to communicate it and it would depend. If the trial was marvellous and the patient had great benefit from it—fantastic; but if it wasn't it might rekindle unpleasant memories and so on. That is the difficulty, and logistically it may not be that easy. It should be, going forward, because trials are much better documented on a national basis, partly because of the Health Research Authority, but partly because of other structures. You can follow up; you can identify the patient who is in it, so you can get the summary to the patient.

Stephen Metcalfe: One final point, just going back to the idea of recruiting people into trials: the point at which there is the potential to offer someone a trial is the point at which they have probably just been diagnosed with something that is potentially life-changing. Do you think there needs to be a wider public engagement generally about our ability to take part in trials, so that we can improve our knowledge, perhaps in a similar way to the campaign for donor cards that has been run over the years—that actually people just know in the back of their mind that if they were ill they would potentially take part in a trial?

Simon Denegri: I certainly do. I think there is a real, strong case for that. The NIHR "Ok to ask" campaign next week is, I think, the beginnings of a move in that direction. If I would really like to see one thing come out from all the funders and the research community in this, again, going back to my point about seeing public knowledge as part of the infrastructure, I would

actually like them to come together in the same way that they come together to build medical research buildings and recognise that this is something to which they should all contribute voluntarily, and work collaboratively to make happen; because I think too often there is a sort of, not quite pointing a finger—that is unfair—but an expectation that the Government or the NHS will do it. I think that is a completely unreasonable expectation. I think we all have to do it, and we have to be aligned in the way we do it.

Professor Karol Sikora: I think the disease-specific charities—dementia, Alzheimer's, diabetes, cancer—have a very powerful role, but there are other diseases that are perhaps not championed by charities. Hypertension would be one, for example; depression is less championed, and equally valid as a platform for clinical trials. So a solid base, as you suggest, Simon, would be the way forward.

Q107 David Tredinnick: Professor, what information do doctors use when considering treatment options for your patients? For example, to what extent do they use trial results described in the academic literature, NICE guidelines, or systematic reviews?

Professor Karol Sikora: Doctors, really, are stuck with NICE guidelines, and we could not deviate, because the pharmacy will reject if you prescribe a drug outside NICE guidelines. The NICE guidelines are great, and they are very well thought out. The difficulty is they are still too slow for certain drugs, especially in the cancer area. They come too long after the drug has been on the market. So people can pay for the drug. Private patients are getting the drug from their insurer. NHS patients in some places get, and in other places don't get, so it is a problem.

The academic literature is enormous, as you can imagine. The way in which practice changes: some published papers change practice instantly, but they are very rare. It is a sort of drift through a series of presentations at meetings; and then things change. Herceptin and breast cancer was a classic of a sudden change where every patient—and it was accepted by NICE; this was in 2005—was tested for the receptor to Herceptin, and those who were positive would get Herceptin suddenly. So that was a major change, and everywhere, within a week, practice had changed; but that is incredibly rare. It is a drift over two to three years when things go.

Q108 David Tredinnick: How quickly and effectively is emerging evidence incorporated into clinical guidance such as that produced by NICE? I am thinking of what is happening in the United States with the Consortium of Academic Health Centres for Integrative Medicine—53 centres in north America, including some of the most prestigious, which are now using a model called integrative medicine, defined as "the practice of medicine that reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, healthcare professionals and disciplines to achieve optimal health" and well-being. Do you see that as, perhaps, a future model for this country?

Professor Karol Sikora: I think it is. There is no doubt that we are all in little silos. I sit in a clinic tomorrow morning, and I just see cancer patients and think about the cancer. But the patient doesn't just have cancer; they have all sorts of other things. They have social issues, and so on, and a holistic approach, which could involve therapies that are perhaps non-conventional, seems realistic. The difficulty is not the cost, because often the cost is in high-tech medicine rather than in some of these other approaches; the difficulty is changing attitudes and getting out of the hospital and primary care boxes into a seamless flow of patients. As the population gets older, we accumulate chronic diseases because we are successful at keeping people going, so it will be even more important to have a much more holistic approach to integrated care. The current turmoil with accident and emergency is just a reflection of all that coming together. We just do not have systems in place, and we do not have good tools to do clinical trials to measure the effectiveness of the systems.

Simon Denegri: From the point of view of researching patient benefits, I would also start the discussion much earlier and think about the priorities that we set with patients. We have some really good models on that, such as the James Lind Alliance priority setting partnerships model, which is now part of what NIHR does. Patients should be encouraged by the increasing willingness to look holistically at what they need to survive or live with their illness.

Q109 David Tredinnick: Finally, to both of you, the Secretary of State for Health has made it absolutely clear that he wants to put patient choice at the centre of the health service. How important is self-management of health care, particularly for cancer? I am thinking of a presentation I saw by Nicola Gale and Cathy Shneerson at University College hospital London in which they talked about defining self-management of disease. Is that a future paradigm?

Professor Karol Sikora: I think it is. Again, it goes back to the inevitable internet, which we talked about before. All sorts of devices are out there that could be used. Diabetes is a disease that is really up front in this. Diabetes is a biochemical disorder, so it is relatively simple to follow blood sugars and various other biomarkers of response, and so on. Cancer is a bit more complex, but there is no doubt that involving people in understanding not just their illness but how the natural history can flow and how treatments can affect it is going to be very important. Again, people can understand the gadgets now. You cannot do your shopping without understanding at least some basic computer science, so I think it is very much the future, as you suggest.

Simon Denegri: One of the consequences of that, from a research perspective of self-management, is that people increasingly want to self-refer to take part in research, which is one of things that we found from the public survey and the gateway. Actually, people do not want to go through their health professional, because they have not been very helpful to them previously in finding out about trials and research; they actually want to go directly to a clinical trial unit.

We need to think that through in terms of the future patient agenda.

Q110 Stephen Mosley: I have just leant on my iPad, and it has moved on.
Following on from the last question, in modern health care there are two principles for evidence-based research, and there is also the patient choice about which we have just heard. Is there some contradiction between them? If people are self-referring and going for a more holistic approach, does that get in the way of evidence-based research?
Professor Karol Sikora: I don't think so, provided there is time for the professional, whoever it is, to explain the situation. Wanless, in his famous report in 2002, talked about the "fully engaged" patient, and there is no doubt that it is a pleasure to deal with fully engaged patients. The difficulty is that not everyone has the educational level to get to that point, especially with technical details, but provided there is a dialogue between a health professional and the patient, I think all three are possible, including patient choice. On the whole, patients do not choose things that are not recommended by the professional who is looking after them, provided that they seem reasonable and that there is a valid explanation, so I do not think there is a contradiction in that.
Simon Denegri: Neither do I think there is a contradiction between the two. One of the great things about what we have in the UK with the NIHR model is that one of its core principles is that involving and working with patients improves the quality of your research, whatever that research looks like and whatever methodology you use. We have done a very good job of standing by that principle, and I do not see any contradiction whatsoever.

Q111 Stephen Mosley: Whenever I think of medical trials, I cast my mind back a few years to the famous TeGenero case. I was quite surprised when I did my research that it was 2006, a good many years ago; it feels a lot more recent. Do you hear any concerns when you speak to patients that there might be side effects that you are not aware of?
Professor Karol Sikora: In my specialty, because of its nature, people on the whole do not worry too much, because the benefit will far outweigh the downside. If it were a new antidepressant, it could be different. If it were an anti-vomiting agent, for example, would you really want to do that? Again, a full explanation is necessary of why and what possible benefit it could give you, or what benefit it could give to other patients if you enter the trial. That is all about good interaction at the very beginning, when consent is being obtained, to make sure the patient understands the up and the downside of things.
Simon Denegri: I agree. I haven't really got anything to add to that.

Q112 Stephen Mosley: One of the issues that we have heard is that with rarer and more serious conditions, sometimes you do not have enough of an evidence base to progress trials to a certain point, or to the point where a drug can actually be used. A citizens' jury convened by the Genetic Alliance UK suggested that, in such conditions, people might be willing to take greater risks, whereas normally you would not allow anything to be used unless it had gone through phase 3 trials. There might be a case, in some rare conditions, for saying that the risks of going ahead are fewer than the risks of not going ahead. Is there any basis behind that?
Professor Karol Sikora: Again, cancer is probably the disease where the benefit would outweigh the risks. It is just about honesty with the patient: "We have this treatment. It may or may not work. We need to assess it properly, and you fit the bill. Would you like to be in the trial?" If you have a reasonable dialogue with people, most agree.
Another approach is going on in some hospitals, where there are several competing trials. I say "competing": there are several trials for exactly the same group of patients. The patient is given a wad of patient-related protocols written in lay language and asked to choose one. That is not so helpful. The patient cannot expect to understand whether a vaccine, a drug or an antibody is better, and they get very confused. I think the information overload can be mitigated by proper counselling with professional staff who understand it fully and explain the choices to the patient, who then makes the ultimate decision.
It is a bit like going to a financial man about pension plans and things like that. It is very complicated. There are risks and upsides, but you have no idea how it will all pan out. It is the same with a patient going into a trial.

Q113 Stephen Mosley: But legally, it cannot be given to a patient until the phase 3 trials have been completed.
Professor Karol Sikora: Exactly.

Q114 Stephen Mosley: Is there an argument for relaxing that case in a few rare situations?
Professor Karol Sikora: Certainly, in cancer, it has been relaxed a bit. If phase 2 is very positive—in other words, if there is a very strong hint of a response—then extended access is usually granted by the company making the drug, and usually used in certain defined ways. The information is still collected, so although it is not a formal clinical trial, the information is of trial quality. The data set filled in and returned for future use, including side effects and response, is centrally collected.
Simon Denegri: I have two thoughts around it. One is that it is symptomatic, and perhaps inevitable, of a more citizen-driven approach to research. You are going to see this desire, and I support it. I think there are two aspects of it. One is a very beneficial one if we can reach a model where patients are regulatory partners. If you talk to patients, they are as frustrated as anybody else about the lengthy consent process. They have very good reality checks, and they should be regarded as partners by the MHRA, the HRA and others.
The second one, about which I have a little bit more worry, is that as long as there is a very solid partnership by those arguing for such change, such as patients, and the makers of the medicine, I feel more comfortable. Where I have a problem is that it is not

always clear to me that the patient interest is paramount here. It could be used by some people to argue for a speeding up of the process, because it makes commercial sense. I have worries about that, but as long as the partnership with the patient is solid, I am more comfortable with it.

Chair: Thank you very much indeed. That was extremely helpful. We will now go straight on to our second panel.

Examination of Witnesses

Witnesses: **Tracey Brown**, Managing Director, Sense About Science, and **Dr Helen Jamison**, Deputy Director, Science Media Centre, gave evidence.

Q115 Chair: I welcome both of you to the hearing. I would be grateful if you introduced yourselves for the record.

Tracey Brown: I am Tracey Brown from Sense about Science.

Dr Helen Jamison: I am Helen Jamison from the Science Media Centre.

Q116 Chair: Okay. I think you have been listening in to the previous session. Why do you think it is important that information about clinical trials is made open to the public?

Tracey Brown: To start where the previous discussion was, in relation to patients and to those who participate in clinical trials, there is an expectation that what they are doing is contributing to the future treatment of their disease, or at least to its future understanding. It comes as a shock to many patients who are involved in clinical trials to find that some of the information from those has not been shared at all, and therefore, cannot possibly benefit future treatments. It may even result in the same trial being run again in a future group of patients.

Beyond that, there is the issue of that information going on to help researchers to do a number of different things. One is to determine the course of future research, which is to say which trials are beneficial to run. It is highly unethical to run trials, particularly those that put patients at risk, a second time. It is also a very important question, not just for researchers, but for those who are determining which courses of treatment are effective—whether that is individual clinicians or regulators, and we talked about NICE—to determine which things work best and in which kind of patients. That is impossible to do unless you have the full results at your fingertips.

Dr Helen Jamison: I would probably echo a lot of what Tracey said. Although the Science Media Centre is not directly involved in the AllTrials campaign, we are generally very supportive of openness, and that is one of the reasons why we exist. We feel that it is very important that both the public and policy makers, whenever they are making decisions, can do so on the basis of full, accurate evidence that they have available to them. I think there is also a responsibility on the part of those carrying out scientific research and clinical trials to let the public know either how they are spending the money, or the results of what they are doing. We are also finding that a lack of openness can often lead to mistrust and confusion. There are a lot of very good reasons why openness and transparency are important.

Tracey Brown: Chair, can I add a further point? I think there is a misconception about how science advances that lies behind some of the discussion about the issue. We have a pretty robust approach to testing protocols and to the way that clinical trials are designed precisely because people share not just in order to understand the efficacy or the safety of a particular course of treatment, but to understand the best way to research these things and the pitfalls that you might fall into in the course of designing that kind of research. We do not have the modern scientific approach that we have today because everybody has secretly gone off and done things in the cupboard; we have it because people have tested each other's ideas, pulled them apart and asked if something could have been done better. That is a very important part of scientific medical advance.

Q117 Chair: Interestingly, in the Royal Society report, "Science as an open enterprise" from June of last year, there is a section that argues about transparency engendering public trust, but it goes on to say, "Opening up scientific data is not an unqualified good", citing "the legitimate boundaries of openness which must be maintained in order to protect commercial value, privacy, safety and security." Leaving aside the commercial bits at this stage, and thinking particularly about the patients, don't you agree that while opening up is a good idea, the prerequisite is better information going to the patient about the meaning of the scientific data?

Tracey Brown: I certainly agree that all forms of communication about these issues carry with them some responsibilities. I feel very twitchy when I hear things like, "Opening up is not an unqualified good." I know what is meant by that in the context of the Royal Society report, but what I am hearing in the context of the AllTrials agenda, which is aimed at solving this horrible problem in medicine of hiding results, is that people hide all kinds of other things behind that. Everybody nods along to the idea that opening up is not an unqualified good, and they mean a number of different things by that: sometimes, they mean that it is a pain in the neck to have to publish trials that did not show that their drug was very effective, and we should watch for that.

Clearly, we do not want a situation where, as a result of the publication of data, people put things into the public domain in binary code, or where there is data dumping, and that somehow ticks a box. We are not looking for a box-ticking exercise; we are looking for outcomes that benefit patients and research. Therefore,

yes, we need an intelligent approach. Sometimes, we perhaps need a bit more work to explain it, but that is nothing compared to the job of explaining what is going on when you have only half the information at your fingertips. Think about the challenge that represents when you have something like a scare about a vaccine. It is a huge challenge for independent researchers to come out and explain to the public what is going on, when they themselves might feel nervous about that, because they do not know that they have got their hands on the full information. So, through hiding a lot of this stuff, we are really undermining our ability to have a sensible public discussion.

Q118 Stephen Metcalfe: Sorry, you may already have answered this, and if you did, I apologise because I did not quite hear. Why would someone conduct a clinical trial and then not publish the results? Is it purely and simply because the drug they were trialling was not effective and they do not want to be embarrassed, or are there are other reasons behind this?

Tracey Brown: If you have conducted three trials and two of them make your drug look very good and the other makes it look like it does not do much at all, you are clearly inclined towards the first two. The thing is there are a number of different things going on. We should also not underestimate the lack of compulsion, the laziness and the sloth in these things; there is a bit of that. If you look at the academic publication of trials, it is a better record than the industry-funded trials, but it is not that much better historically—not so that we would want to crow about it. There are issues to do with making the system easy to comply with and making the compulsion stronger overall. But, yes, there are good reasons why people do not want to publish trials that do not make their drugs look good; that is inevitable, particularly if they are in a competitive market. The marginal improvements that one new drug in a "me too" market might offer might be tiny and might, therefore, disappear in a further trial.

Q119 Chair: So you are arguing in favour of full release of information. What impact do you think that would have on the pharmaceutical industry?

Tracey Brown: When you say full release of information, I should just clarify that. It is helpful to think of this at four levels. One is the registration of trials; that is level 1. That has been a problem, certainly historically, although there have been some improvements since the 2007 FDA regulations and other interventions. We do not even have the contents list, if you like, of what has been done, never mind being able to track down some of the results. That is something that reviewers who are looking across a whole range of studies really struggle with; they spend a lot of time just trying to find out what has actually been done but been left in a cupboard somewhere. Registration is about knowing what the trial is for and registering the protocols.

The second level of information, which is what AllTrials is calling for, is the basic summary of the clinical study report. That says what was actually found, what the primary outcomes were and what the protocols were. We would like to see as much information there as possible, but that certainly gives you some indication of what research has been done and how it has been undertaken.

The area for quite a lot of discussion at the moment is what I would call level 3, which is the full clinical study report. That contains in many cases quite a lot. It is a very large report—quite often, it even runs to thousands of pages—and it may contain quite a lot of individual patient data, things that might be tracked to individual patients or other things that constitute reasons why people might be concerned. There is a discussion about the release of those. I just note that we are seeing their release by the European Medicines Agency already for those drugs that they have them for.

Then there is the fourth level, which is individual patient data. A lot of very productive discussion is going on about how to establish good protocols for sharing that among the research community—for example, setting out the same requirements for secondary research as you would for primary research, looking at the same data.

Dr Helen Jamison: There is probably not a great deal that we at the Science Media Centre can comment on from that perspective, because we do not have so much expertise in this area, but I think that one of the things that the pharmaceutical industry might need to consider in a move towards greater openness is the impact in terms of how they communicate the results of those clinical trials and that data. One thing that we have struggled with in the past when responding to controversial and difficult stories in the headlines about clinical trials and other areas more generally is that there is sometimes a reluctance on the part of industry to engage when an issue is on the front pages. Often, that can be the case with scientists and academics who are slightly related to Government as well. The impact of that is that, generally, it leaves a bit of a vacuum at a time when actually more information is needed. At the Science Media Centre, we often become very reliant then on independent academics based in universities. So I think a move towards greater openness on the part of industry would be a very good thing, but it would have to get down to grass-roots level in terms of how they engage with the national news as well as the public and the rest of the scientific community.

Q120 Pamela Nash: Ms Brown, just to be clear, is the aim of the AllTrials campaign to have all four levels published?

Tracey Brown: No, the aim of the AllTrials campaign is to ensure that levels 1 and 2 are published. Levels 1 and 2 do not have a huge amount of practical implication. It's just a shocker that they are not published already. Levels 3 and 4—level 4 particularly has a certain practical implication, depending on the organisation. The requirements of level 3—what would be an equivalent to a clinical study report; there are such things, but for an academic, for example—just need to be ironed out and worked on. It is not a huge barrier to publishing that information. There is quite important information at level 3 about serious adverse events, for example, that

may need to be shared, but that just takes a little more work and thinking about.
We are really pleased that, in signing up to AllTrials, GlaxoSmithKline, for example, committed to publishing a lot of their level 3 data. Obviously, we are going to look at what they encounter in doing that. That is an ongoing discussion with them. A lot of the people who have signed up to AllTrials are committed to that, too, but what we want to do is just to get past the idea that secrecy is okay. That is really the ultimate aim of AllTrials. It is just to find out what people have done and what they have found, at a very basic level, and then we can go on to look at some of the implications of sharing that.

Q121 Chair: Can I just halt things there for a moment? In your written evidence, you say: "For all trials (phase 2 and above) conducted since 1990…Full clinical study reports, or equivalent, should be made publicly available." That is what you are saying, is it?
Tracey Brown: Yes. The thing is that what has come about from that discussion is that because people have not been particularly thinking about publication, within clinical study reports are bits of information that people want to redact. I have set it out as four clear lines of information. The reality is, of course, that it is much messier than that. Clinical study reports contain individual patient data, and there is some discussion about that, but it is the full findings that we would want to see. Having said that, I am now looking at some of the discussion that is going on between some parties about publishing information on serious adverse events—

Q122 Chair: So in the context of level 3 and the word "full", you don't quite mean that; you mean "qualified full".
Tracey Brown: What we are finding out is that "full" means something different for different people, depending on what they have included in that. I think we need to keep this idea of levels of information to try to have sensible discussions about it, but we need to look at what different parties—the differences between academics and those who are providing regulator information and so on—have got in that "full". We are saying, "Open your box." We do not know however if different people are putting different things in each of the boxes.

Q123 Chair: It would be helpful for clarity if you could reflect on your written evidence and what you have just said, and perhaps drop us a note on that.
Tracey Brown: I will do that, because there have been three very important discussions since the submission of written evidence that I would like to share with you. I will update you on those.
Chair: Yes, indeed. Back to you, Pamela.

Q124 Pamela Nash: That will be helpful. I was going to go on to the criticism from the Medical Research Council, which, as I am sure you are aware, has said that it is not standard practice for full clinical study reports always to be published. Cancer Research UK has said that that might not be a particularly useful document. Is that criticism you recognise? Is that part of the discussions since the written evidence was submitted?
Tracey Brown: The thing that should have been added on the end of everything is, "or equivalent". Once we had that discussion with the Medical Research Council, I think it was happy. As I understand it, its concern was, "We do not want to start asking academics to prepare a regulatory marketing authorisation document that they have no need for," and quite clearly that is not the case. They should not have any problem, because under requirements already in operation, they are supposed to publish their protocols and the primary and secondary outcomes of their trials, so it should not present a problem for them to do that. It might not look like a similar format.

Q125 Pamela Nash: Okay. My understanding is that you are asking for the publication of trials as far back as 1990. Is that correct?
Tracey Brown: A paper is due, so I cannot share figures on this at the moment. Most of the things that doctors are prescribing relate to marketing authorisations that were granted some time ago, and therefore it is reasonable. Where we put a cut-off will probably end up being rather arbitrary, but the rump of currently prescribed medicines were authorised in the time since 1990; obviously, predating all the current discussion that is going on in Europe. It would make sense therefore to have that. We want to be careful about constantly shooting this ball up the pitch, because everything that is being talked about in European regulation at the moment, for example, is about the future. It is not only that in, say, 2014 we are going to have the results of those studies, but it is going to be a long time before the vast majority of what patients are prescribed relates to the post-2014 period of studies. We will continue to prescribe some very successful drugs—apparently successful drugs—from previous times, so that is why it is important.

Q126 Pamela Nash: As a lay person, I would say that it would be easier to bring in rules now for the future, when it would be anticipated that this type of publication would be required. There has been criticism, even looking forward. Cancer Research UK has said that it might take three months' additional work to produce the information. Is that not something you would recognise? You are saying that you would not anticipate that that burden would be put on researchers.
Tracey Brown: I am not quite sure how it came about that people were thinking that non-commercial researchers would be producing clinical study reports. Clearly, it would be strange to produce a regulatory document, if you were not seeking regulatory approval. If it were the case, I would imagine that it would take that time, but I cannot ever see a situation in which anyone would realistically be calling for the production of those. However, it is absolutely not unrealistic at all to expect anyone involved in clinical research to be able to publish the primary and secondary outcomes and the protocols of their research—effectively, publish their results. They are required to do so. It is not as though this is a

requirement that does not already exist in the running of clinical trials. I know that you have the HRA speaking to you later this morning, and they, I am sure, have something to say about the ethical component of running clinical trials, requiring that people undertake those responsibilities. It is just a question of the fact that no one has actually enforced it.

Q127 Pamela Nash: On that point, do you see Government as having a role here in enforcing this or would this be a voluntary register and publication?
Tracey Brown: Ideally, you would want much to happen, because people know it is the right thing to do, before you start introducing huge sticks and carrots to the whole situation. Also because then you have solutions. If you just, again, look at GSK being involved in this: by being involved, they are innovating things that work for them and we can start looking at how those data can be held, what level of redaction is reasonable, and so forth. However, there are a number of places where this needs then to be reflected in, perhaps not heavy-handed regulation entirely, but also in professional standards, for example. So we need to look at things like what constitutes a breach of professional standards. We need to look at things like what undertakings publishers and journals can make to ensure that trials that are not registered and not giving their top-line reporting do not then get published—or at least that that information is asked for, so there is a trace through.
But I think at some point we need to look at what kind of regulatory mechanisms should be in place for a number of things. One is that we should look at—if there are organisations or individuals who consistently fail to meet those standards—what kind of sanctions might exist for that. I think we need to look at what the regulators are doing to ensure compliance. So the FDA site, ClinicalTrials.gov, for example, could be developed. I think we should have a similar sort of interface, with a site in Europe. I do not understand why we do not yet have that. It is a straightforward interface; it is like a recipe card of the clinical trial, and then you add the bit at the end that says how it turned out. You can upload other information and links there, and so forth.
The thing that it misses is something that our UK Charity Commission succeeds in doing rather well, which is being able to highlight when people start to be late with filing their results. That would be really simple—you speak to anyone who is reasonably okay with programming a computer and that is not a particularly difficult thing to do. So some sort of automated policing mechanism of the performance would be a really sensible move. It just takes a bit of political will to do it, I think.

Q128 Pamela Nash: You mentioned Europe, but the implications of planning for a trial does not have any borders. Are you speaking to your equivalent in other countries? Is there any vision for international co-operation on publishing trial results?
Tracey Brown: Well, over 300 organisations have signed up to AllTrials in just a few months, and of those I think over 70 are international bodies, many of which are regulators or organisations with a significant influence on the development of this discussion. Just two weeks ago, all the medical schools, led by Dartmouth medical school in North America, have taken on this role themselves, running an AllTrials campaign.
People are pretty serious, in most countries, about sorting this problem out. It is a global issue. I know that some discussion has been had and I know that the pharmaceutical industry has raised concerns about making the UK an uncompetitive place to do clinical trials. The issue here is not about where you do it. So long as people want to sell their drugs in the UK or in Europe, then wherever they have done the trial, we need to have the results.

Q129 David Tredinnick: I have a couple of questions for Tracey Brown, initially. Do you think that publishing clinical study reports would meet the criteria set by the Royal Society of intelligent openness?
Tracey Brown: As I mentioned, not if they were in binary code, or without the associated bits of software that had been used to process bits of the data. I mean, it depends. We are discovering that—

Q130 David Tredinnick: So it is an interface issue, is it? A presentation issue.
Tracey Brown: It can be, yes. In other cases, it is straightforward. But this really just needs to be worked out. I suppose we are talking about the level 3 of information, also to work out what is a reasonable basis to redact that information.

Q131 David Tredinnick: Are there any conversations with the Royal Society?
Tracey Brown: Well, we are actually having conversations with people who have that information and are working out on what basis they should redact it. In some cases, people are over-applying, as often happens when they are nervous about a regulatory implication. It may well be that some of the redactions that we are seeing in what is being published in that level 3 are because people are unduly anxious about data protection regulations—as you know, it is a highly punitive system—or because that discussion about what is a reasonable level of disclosure has not happened. But, yes, the principle there is making sure that what you present is something that other people can make sensible use of and make head or tail of.

Q132 David Tredinnick: You have kind of touched on a bit of this before, but is the lack of historical patient consent a problem when it comes to the retrospective sharing of individual patient-level data, and if so, how can that be resolved?
Tracey Brown: That was something that your last panel spent some time talking about. As I have said, there are two separate issues, and I understand that Research Councils UK have been talking about this. You are talking about individual patient data where issues of identification could come up. Nobody is talking about publishing names and addresses. Obviously, what we are talking about is anonymised

data, but there may be occasions where the anonymisation is not enough to prevent you from working out where somebody was or the nature of the thing. There is one particular thing that I want to flag up. We need to work out what the protocol is for talking about serious adverse events, because quite often they involve one particular patient. We need to understand. We do not want that information withdrawn from discussion; it is a very important thing. We just need to work out a system whereby people can share that and at what level they can share it.

Q133 David Tredinnick: You said earlier on that information from trials is not being shared. Do you think it is the case that some evidence that is available is ignored? For example, of 156 randomised controlled trials, more have been positive than negative—64 positive and only 11 negative in respect of homeopathic medicine.
Tracey Brown: Do I think—

Q134 David Tredinnick: Do you think that some evidence like that has been ignored, perhaps wilfully, by some organisations? There were 64 that were positive and only 11 negative out of 156 randomised controlled trials conducted on homeopathic medicines.
Tracey Brown: I think you would have to show me the systematic review where you felt that that had been ignored.

Q135 David Tredinnick: Shall I do that? Shall I make sure you get the information?
Tracey Brown: Yes, please do.

Q136 David Tredinnick: One last question: do you think there is too much emphasis on randomised controlled trials and not enough in respect of meta-analysis and patient reported outcomes—actually what patients feel?
Tracey Brown: In this instance, we are talking about what to do with clinical trials and how other kinds of evidence are taken into account. Systematic reviews generally do look at other kinds of evidence, too. I do not think that the remit here could extend to every other kind of research, otherwise we are going to get ourselves in quite a muddle.

Q137 Jim Dowd: I think this is for Dr Jamison, but obviously if you wish to contribute Ms Brown, feel free. I want to look at something you made reference to earlier about the reporting of clinical trials. The vast majority of people, as we all understand, will get their impression not from learned journals and the detailed work and scientific analysis, but from the way it is reported. We have seen episodes in recent years, ranging from BSE and MMR and other issues, which have caused great consternation. In your experience, what sources do journalists use when reporting clinical trials?
Dr Helen Jamison: Most of the national news journalists whom we work with on a regular basis who are producing the reports that have a great influence over the public use quite a number of different sources. They have individual contacts, receive press releases and attend press briefings. Those come from or are with a number of different organisations—so the academic journals themselves publishing the trials, charities that might be involved in the trials, funders and organisations that might have provided financial support, industry, and universities. They also looked at case studies, I think, in quite a number of cases, to get a human interest story from any issues they might be covering.
I think there is a really wide range of sources that national news journalists use when they are reporting on clinical trials, but it is also worth saying that a big proportion of their stories come from the diary stories that they do. Daily news journalists especially often receive press releases from some of the bigger, higher-impact journals such as *Nature*, *Science*, the *BMJ* and *The Lancet*. Those form a large proportion of the sources from which they get information about clinical trials, but it can be a whole host of different places.

Q138 Jim Dowd: Have you detected a specific difference of approach between specialist scientific journalists and general news journalists?
Dr Helen Jamison: In the UK especially, we are really lucky to have a great group of specialist science and health reporters. I think they are much more keyed in to the scientific process, so they are much more likely to have great relationships and an understanding of the science that is going on within universities and partly within industry. They are definitely following academic journals and clinical trials much more closely than perhaps general news correspondents. General news correspondents may tend to get more of their stories about these issues from the news wires or from stories that very quickly hit the headlines.
The other thing that is worth saying is that, although there is definitely a narrative at the moment where the UK and other countries are concerned about losing specialist reporters in national news outlets, science is pretty healthy in newsrooms across the UK. In the vast majority of cases, if a story was about a clinical trial, even if it became quite a political issue, it would tend to stay with the science and health specialist rather than be taken off them, even if it was to find itself on the front pages. Generally, we are lucky to have a good group of journalists who follow these issues and understand the nuances in quite a lot of detail.

Q139 Jim Dowd: Would greater transparency help or hinder the quality of media reporting?
Dr Helen Jamison: That is a very good question, and it is a difficult one to answer. There is obviously a risk that, if there is more information out there, there is an opportunity for groups and individuals to either misuse that information or for groups who have an agenda to seize on it. But I am not necessarily sure that that would lead to increasingly poor reporting, for some of the reasons that I have just given. Because we have a very good science media environment at the moment, I think that many of the national news journalists who are specialists in this area would be aware of that being a possibility. There are a small

number of them who follow issues now so closely, and I think that they would find more information much more useful and would have the time and the inclination to use that information.

It is worth pointing out as well as a caveat to that that there is definitely an increase in terms of the opportunities that new media and the internet bring, and there is definitely a shift towards data journalism and writers mining data to produce stories originally themselves, but at the moment that is still very much largely with science bloggers or science writers. It is also worth saying that I am not sure that a lot of busy national news journalists, who are writing five stories a day, have the time and resources to be able to really delve into the detail of data, unless they have been following an issue for four or five years, or they are writing a special long-form feature piece.

Q140 Jim Dowd: One of the fears that has been alluded to, with greater transparency and greater release of data, is what has been called inappropriate secondary analysis. Do you regard that as a realistic problem?

Dr Helen Jamison: It is a possibility, but I go back to what I just said, which is that I don't see the natural result of that being poorer reporting. I do not think that we are in the situation that we were in when we had the MMR scandal in the 1990s. Science reporting is much better than it used to be. I think the media have learned a lot of lessons. We cannot guarantee that, if you put more data out there, it will not be seized upon for secondary analysis, or even analysed incorrectly, leading to confusion. That may happen, but I think science journalists are much better prepared for those kinds of issues. I also think it is fair to say that, if you do not put that data out there, it may equally lead to scare stories, mistrust and confusion.

Thirdly, we at the Science Media Centre spend a lot of time working with scientists who are already learning about increasing openness and what that means for them. They are already dealing with similar issues. Many of them have had data and information requested through freedom of information requests; some of them have even had data illegally hacked. Even in the most controversial and difficult situations, when data gets released to the public, we always actively encourage scientists to deal with that and face it head on, rather than hiding it. We are always about greater openness.

In the 10 years that we have existed, we have probably run 700 or 800 press briefings and worked on thousands of stories involving some of the most sensitive and controversial issues you could think of. The vast majority of those instances have always gone very well, and have been positive experiences because of greater openness. We are always actively encouraging experts. Even when there is an issue of data misuse and misunderstanding, the best way to tackle that is to be open rather than secretive about it.

Q141 Jim Dowd: Yes, we had a problem in this place not so long ago relating to the illegal release of data on Members' expenses.

Tracey Brown: May I add a point? The dangers of not being able to do any kind of secondary analysis far outweigh the prospect of inappropriate secondary analysis. Busy journalists or anyone else looking for guidance on what the evidence is on an issue benefit enormously from having independent voices and analysis. Carl Heneghan, who runs the Centre for Evidence-Based Medicine at Oxford, has spent years trying to discover not just what the results are on Tamiflu but how many pieces of research have been conducted on it. How would you ever expect him to comment on a scare story about the Tamiflu vaccine? We do not even know if it is a scare story or not, because although he has worked so hard to find out what has actually taken place, he is still in a position where he does not fully know. That is the point. We are cutting the legs off our research community as a voice that could come in on a discussion about whether things work or not.

Q142 Jim Dowd: Finally, post-Leveson—it is very recent—you have brought in your 10 principles for best practice. I know it is early days. Has that produced any significant or measurable improvement in the quality of reporting?

Dr Helen Jamison: I think it is very hard to say. I think one thing that has happened is that our guidelines have been welcomed by a lot of people in the field. Whether that translates to them being used on a daily basis only time will tell. It has certainly raised a lot of awareness of some of the issues around good science and health reporting. We are working closely with the BBC College of Journalism on its science training for its journalists. Whether or not we eventually see our guidelines enshrined in any kind of legislation—whatever happens post-Leveson remains to be seen—it has done a lot to raise some of the issues. Most of the time, we actively encourage scientists to deal with the media, with all the things that that means, but it has been a really good chance to raise the issues of how the media report on important science and health issues. I think the guidelines have done that and will keep doing it.

Q143 Chair: But you must remain somewhat frustrated by the headline writers. There was one last year about a particular medical report that struck me. The headline was that, with a particular medication, you were less likely to die, which seemed to me a wonderful offer.

Dr Helen Jamison: That is very true. In the last 10 or 15 years, there have been great drives in the improvement of science and health coverage in the UK. Headlines are one of the big bugbears that still exist. In the guidelines that we produced, headlines were the thing that everybody rowed about the most. There is a lot of strong feeling about headlines. On one hand, we can see that that is the bit that draws the eye to the article and, being realistic, that is the bit that catches people's attention. We always make a plea to the media that, when they call something a cure or a miracle, they must remember patients. To go back to your earlier points about how patients become involved in clinical trials, many patients speak to the medical research charities or their GP wanting to join

a clinical trial for the latest miracle cure, and we haven't quite won the battle with the headlines, but we will keep trying.

Q144 Graham Stringer: Moving on from Jim's question about openness, when there is misreporting of clinical trials, how much of it is to do with shoddy journalism, and even if the scientists and clinicians are being open, how much is it to do with them not quite knowing how to frame their results?

Dr Helen Jamison: That is a good question. There are many different reasons that influence how bad or good journalism is. There are three main groups that have a role. The first is journalists, and occasionally it may be shoddy journalism, although in our experience that is rare. Much of the time they are working hard and are under pressure from their news rooms, with competition from their colleagues. That may put them under pressure and lead them to get things wrong and to cut corners, but most of the journalists we know strive to get things right and take their responsibility seriously.

With scientists, some still feel wary of engaging with the new media, so they are likely to run in the opposite direction, or not be well prepared. Again, a lot is changing in that field, and many of them now see that they have a responsibility to engage and are having media training to enable them to engage much better than they used to.

The third important group that plays a significant role but is often more behind the scenes is press officers and communications experts either in universities or industry or at the research funders. As with all professions and so on in life, there are good press officers and bad press officers. Sometimes, misreporting may result from bad press releases. A bad press release may be hype on the part of the organisation, or the scientists might have encouraged it to go beyond because they are excited about what they have found. There is a real issue, and often when there is a spectacularly bad story, which thankfully happens rarely, it has been a perfect storm of many different factors all playing together to give a bad story at the end, but the different reasons behind that may be complex.

Q145 Graham Stringer: You have made a point about putting out relative as well as absolute figures, and 50% improvement of very little is still very little. Are there any other examples of where you have been able to guide scientists and clinicians to improve the way they communicate, so that you do not get misleading stories?

Dr Helen Jamison: There are lots of ways, either formally or informally, that we guide press officers and scientists on a daily basis, such as making sure they put their work or study into context in terms of whether they have just observed something happening or actually tested it, whether what they found contradicts what is already out there and is unusual or in line with the consensus, making sure they are always up front and open about the caveats and limitations on what they have found, and when they engage with journalists being very clear not only about what they have shown but what they have not shown, so trying to foresee the headlines that might appear the next day saying, "What we have not shown is this."

One thing we are considering and will lead on from our work around Leveson is to adapt the guidelines for journalists as a guide for press and communications officers, and also for scientists, because they apply equally to all three groups when communicating science.

Chair: Thank you very much for a very informative session. We will go straight on to our third panel.

Examination of Witnesses

Witnesses: **Bill Davidson**, Acting Deputy Director and Head of Research Standards and Support, Department of Health, **Peter Knight**, Deputy Director, Head of Research Information and Intelligence, Department of Health, **Dr Janet Wisely**, Chief Executive, Health Research Authority, and **Sir Kent Woods**, Chief Executive, Medicines and Healthcare Products Regulatory Agency, gave evidence.

Q146 Chair: May I welcome the panel? With four of you, it is going to be quite a tight session to get all the information, so if you feel at the end that there were things that you would like to add, we would welcome a note from you as a follow-up. Would you kindly introduce yourselves, please?

Dr Janet Wisely: Good morning. I am Janet Wisely, the Chief Executive of the Health Research Authority.

Sir Kent Woods: I am Sir Kent Woods, the Chief Executive of the Medicines and Healthcare Products Regulatory Agency, and I am currently also the chairman of the management board of the European Medicines Agency.

Bill Davidson: Good morning. My name is Bill Davidson. I am the acting deputy director and head of research standards and support at the Department of Health.

Peter Knight: Good morning. My name is Peter Knight. I am the deputy director at the Department of Health and head of research information and intelligence.

Q147 Chair: Sir Kent, this is almost one of your last outings in your role, isn't it?

Sir Kent Woods: It may be.

Q148 Chair: May I start by getting some clarity for us about where responsibilities lie. How do the roles of the HRA, the MHRA and the NIHR differ? Where does the responsibility for the increasing number of clinical trials in the UK ultimately lie?

Dr Janet Wisely: The Health Research Authority has very specific roles within regulation which relate to the approval through the research ethics committees and also access to advice through section 251 of the NHS Act—that is confidential data without consent. Within those regulatory roles, we have a memorandum of understanding to ensure that we do not duplicate the role of the MHRA through the approvals. We also have a much wider role, which is largely about making it easier to do good quality research within the NHS that links to our role to promote and protect the interests of patients and the public in health research. I think we will come to talk about some of the initiatives we have got around advice, guidance and training, and the whole approval processes.

Sir Kent Woods: The MHRA is responsible for the authorisation of clinical trials of pharmaceuticals to be conducted in the UK under the provisions of the clinical trials directive transposed into UK regulations. We also have a responsibility for oversight of good clinical practice in trials and can inspect trials and their conduct. We also have the policy lead in negotiations within Europe on the revision of the clinical trials directive, which is currently under way.

Bill Davidson: The National Institute for Health Research is not separate from the Department of Health. It is the name we give to the funding that we give to research. We give that funding in four main ways: research programmes that involve research projects themselves; infrastructure that supports the delivery of research; through faculty, which is developing people to do the research; and through systems. I am responsible for the elements of the National Institute for Health Research that support research management.

Peter Knight: Building on what Bill has just said, I am responsible for the information part or infrastructure within the NIHR. As Bill has rightly illustrated, there are four component parts, and we represent two of those.

Q149 Chair: The boundaries between the various organisations are pretty complicated. Do you think researchers understand the differing roles? Is it straightforward for them to set up a clinical trial? Can they do it without any knowledge of these respective roles?

Dr Janet Wisely: There are good sources of advice out there. There is the clinical trials toolkit, which is very good at signposting a lot of the advice and guidance. The Health Research Authority recognises that we have a role to provide further support and guidance to researchers. Many do have a good understanding, and others find it difficult to navigate what is a complex system.

I think the regulation is well laid out, and we have submitted to a previous inquiry the boundaries between the roles of the HRA through the National Research Ethics Service, the MHRA, the HFEA and the HTA, which is very clear. Where people have more difficulty is in understanding the boundaries of governance. The Academy of Medical Sciences very helpfully distinguished between the regulation of research and the governance of research, and I think people find it harder to understand some of the boundaries around governance.

The other thing I would add is that, even where people do understand the system, they do not always understand why the system operates as it does, which can lead to a lack of buy-in, so we have recognised through the HRA that, when we deliver the efficiencies, particularly around governance, what is left needs to be much better explained, so that researchers buy into the process. To evidence that, of the 6,000 applications to ethics last year, 1,000 did not meet an initial checklist validation. That is partly about quality control of the applications, and I think it is also about a lack of buy-in to why some of the information is being ask for.

Sir Kent Woods: The point you have raised is very important, Chairman, and we have done a lot over the years since the clinical trials directive was introduced to try to ease the path of researchers, particularly in respect of the regulatory requirements. Janet has referred to the clinical trials toolkit, to which the MHRA contributed. We have a great deal of information on our website. We also work quite closely with the research community through workshops and seminars. We also have a helpline—the clinical trials unit takes about 3,000 phone calls and 3,000 e-mail inquiries a year specifically on the regulatory requirements—and we provide regulatory and scientific advice at various levels, depending on the level of expertise of the applicants and the complexity of the trial.

Bill Davidson: The regulatory framework for research has become increasingly complex, which is one of the main reasons why we established the HRA in 2011. In the Care Bill that was introduced in Parliament last week, the HRA is given a duty to co-ordinate and standardise regulatory practice. There is also a set of duties of mutual co-operation between the HRA and various others with responsibilities in this area, such as the MHRA, in order to bring about some of the simplification that will help the environment for research in this country to flourish.

Q150 Chair: The clinical trials toolkit has a route map, which I have just been looking at, and it is reminiscent of the map of the London underground. It is very elegant and rather beautiful, but it is rather confusing for someone who is not familiar with it. Is it not surprising that there is some confusion out there and that it generates 3,000 phone calls and thousands of e-mails?

Dr Janet Wisely: We think it is complex, and we think that people need to understand it, but it is also a professional activity, so I think we do have a duty to support people through the process. We would also recognise that it is a complex activity to undertake a clinical trial, and however much we improve the efficiencies around approvals, it is still going to be quite a complex task. I was involved in the development of the clinical trials toolkit, too, and we were slightly cautious that mapping it out makes it look like a big picture. But the regulation is well organised, and I think that, in general, people come to

us or the MHRA and find ways through that regulatory landscape.

Sir Kent Woods: I would also mention that researchers approaching the regulatory set-up for clinical trials come with very different levels of prior understanding. The most difficult and challenging research groups would perhaps be ones from academia that are relatively new to the clinical trials field and without the resources of a regulatory affairs department behind them, for instance. We try very hard to reach this particular group. We find that that situation applies particularly in cutting-edge areas of research—for instance, stem cell therapy and regenerative medicine—where we are dealing with small groups which are not particularly well resourced, other than for their research capability, and which do not have behind them the infrastructure that would normally help them through. From industry's point of view, all companies doing trials will have well-established regulatory affairs groups who are very familiar with the landscape. It is the academic community and particularly the smaller biotech companies where we really need to work hard.

Q151 Stephen Mosley: Dr Wisely, the HRA issued a paper on Monday looking at its role in transparency. What types of research will fall within the scope of that transparency document?

Dr Janet Wisely: It is different for different parts. For trial registration, we have said it would be all clinical trials—that is broadly the medicines—but the general principles of transparency would be applied to all the types of studies we review. Those would range from clinical trials, health services research and education-based research.

That does give us challenges, because one of the things we need to do is make sure that the plans for publication are realistic and appropriate for the type of study. We have just done a small audit looking at final reports submitted to ethics committees to see whether, at that point, you could judge whether people had published according to the plans they had set out to ethics committee when they got their ethics committee approval—that is already part of the ethics committee review process. Of 115 studies, 33 had done what they said they would do, in publishing, and two—phase 1 studies—had done likewise, in not publishing; the rest were still talking about intentions. But the person who did that audit was concerned that some of the educational based projects—I think there were 40—had really been very over-ambitious about the plans they had set out to the ethics committee in the first place. So we need to get better at judging at the outset, as well as at the end, and to put in place mechanisms for checking.

I agreed with the set-out of the different layers of transparency. There is no excuse for not registering a clinical trial. We need to be clear what we mean by publication, but again, it must happen. If you are going to draw conclusions, you need some quality check, but just putting the results up there without conclusions is probably okay for quite small studies.

Q152 Chair: Just so we all understand the language, what do you define as a clinical trial?

Dr Janet Wisely: It would be something with a clinical intervention. We have said we will introduce these measures from September, because we need to be absolutely clear what we mean. We will do it based on the integrated research application system through which you generate all your applications in the UK at the moment. You are asked a set of questions at the beginning that determines what data sets you then get asked about. Some are easy: clinical trials of medicinal products is an easy categorisation. Clinical trials—perhaps a surgical intervention or a device study—are also easy. We will then need to define other clinical interventions and get the ethics committee to check that they are happy with that categorisation when they require the study to be registered.

Q153 Stephen Mosley: How would that process work? Would the people doing the trials have to report to yourselves—I know they have to go through the ethics committees—or would you have to go and look at a random subsection?

Dr Janet Wisely: Again, there would be a mix. It would be a condition of the ethics approval. At the time you apply to an ethics committee, it probably would be too early to register, because most applications that get to an ethics committee get a provisional opinion. We do not want to add an extra burden, so that some time after you have got your ethics committee approval you have to come back and tell us that you have registered. It would be a condition of the approval that you register within a time frame that we will have determined by September.

We have simple mechanisms to check at the end of the study whether people have registered and published as they should. We have already found through our audit that it was a quite task to look through the final reports. We need a better framework for those reports, but we might not need to do it on an individual application basis. For some, we will be able to rely on the sponsor.

For instance, when the NIHR funds research, we know that, as a funder, it ensures that studies are registered and published, so we don't need to double-check. The MRC has got very good rates for publication registering, so it may be that for some we do a random audit within an overall assurance at a sponsor level and for others we do the audit on an application level.

Q154 Stephen Mosley: What will happen if the HRA detects non-compliance?

Dr Janet Wisely: One of the things that we set out in the paper that we published on Monday is that we need to work with those that have the professional accountability to set out what the sanctions would be. For instance, we need to have those conversations with the GMC. From the Health Research Authority's perspective, for studies that have happened, it is quite difficult for us to have a role beyond identifying it and working with others that have those responsibilities, but we do need to look at what information we may provide to ethics committees in the case of applications from the same sponsor or same

individuals—they could be new applications to the ethics committee—and then we may have a role to ask why it has not been published, and we may not be minded to approve another study until the previous one had.

Q155 Stephen Mosley: On a slightly different issue, I know the Academy of Medical Sciences has described the difficulty in researchers gaining R and D permissions from individual NHS trusts as the single greatest barrier to health research. I know that the HRA are going to be running a feasibility study later this year, and there is the streamlining of clinical trial approvals. How is that progressing?

Dr Janet Wisely: We are in the testing phase of an early feasibility study that will be reported to our board on 24 June. Then we will determine whether we move forward to implement any of the proposals or put solutions on other platforms. We are testing, through our Manchester REC—research ethics committee—office, a single validation point. We are testing whether we can get the researcher to put in one application to us for the ethics and the Trust R and D approval, so that we can do the validation through the ethics service and that that is accepted by the Trust. The basic platform for an HRA assessment must be the single application.

Separately to that, we have recognised that the different components of the R and D Trust approval have different issues to look at. They range from things that really should not be done at a local level at all, so we have to find ways of switching off local behaviour—for instance, the duplication of the review of the patient information sheet. The ethics committee is looking at that. There is no justifiable reason for the local R and D approval to do a second review of it, beyond checking the local contact details, so that is a switch-off behaviour. Then there are other areas where we are looking to see where there is a need for a local decision and whether that local decision could be taken based on a central assessment.

So those are areas where we are looking at what the range of the HRA's role may be. There are various things such as data, radiation, pharmacy issues and suitability of the investigator. We have planning and testing groups that are looking at those different components to see what buy-in there would be for us to be able to do that assessment, so that the local decision becomes one of capacity and capability based on an assessment done by the HRA.

Q156 David Tredinnick: What has been your involvement in the European Medicines Agency's recent efforts to develop a new policy on access to clinical trial data?

Sir Kent Woods: This is part of a continuing programme on behalf of the EMA to make greater transparent availability of the data they hold. It began with an expanded release of documents programme in November 2010. In the following two years, the agency released 1.6 million pages of documents, so this is a very considerable administrative challenge, and a costly one. The phase that is now under way is that that is being broadened, hopefully to achieve the routine release of the clinical trials data that the EMA holds in relation to specific regulatory decisions and market authorisations, once that decision has been taken. It is not without controversy, and in particular there are competing views about the way in which patient confidentiality can be protected; issues and debate about commercial confidentiality—what is and what is not commercially confidential; legal aspects; and questions about the ways in which the research community will carry out secondary analyses and whether they need some rules and protocols.

The EMA launched that piece of work at a large public meeting at the end of last year. Following that, five working groups were set up to examine the specific subsidiary aspects, as I have described. The working group reports were published at the end of April and there will now be a process of reflection inside the agency to produce a draft policy as to how we go forward. That policy is due be released in June for consultation. We hope that that consultation will close in September and that the agency will be able to set out clearly the way that it intends to go forward from 1 January next year.

Q157 David Tredinnick: The report of the recent European Union research collaboration CAMbrella project about looking at the use of complementary and alternative medicine across Europe, which was funded by several million euros, highlights the need for more comparative effectiveness research into what is called integrative medicine. I mentioned to another panel that integrative medicine is defined by 53 centres of academic excellence in America as—I will abbreviate—a practice that "makes use of all appropriate therapeutic approaches, healthcare professionals and disciplines to achieve optimal health and healing." Bearing in mind the Secretary of State for Health's decision that patients should be at the centre and have choice in health care, do you think it is appropriate that there should be more research into this area? Under the Health and Social Care Act, patients are going to be asking for a wider range of treatments, and I am not sure that any of the agencies in the United Kingdom have got to grips with that yet. I am really just asking for a broad comment—I know that my question is slightly off the centre.

Sir Kent Woods: The issue of research commissioning, funding and prioritisation does not fall within my remit. I really cannot give you a useful response.

Dr Janet Wisely: I think that from the perspective of, say, an ethics committee, they would want to ensure that any study was ethical. Therefore, if you were setting something up, you would want to look at whether there was a genuine research question to ask and whether it was relevant to the patient and to the public. I think a consideration at that level would really be the only role for the Health Research Authority.

Bill Davidson: I agree with that. It is quite proper that research gets funded on its merits. If there is a rationale for the research, it seems sensible to look into it.

Peter Knight: The same issue. If there is a rationale for the research and it is good quality research, it should be funded.

Q158 David Tredinnick: Thank you.
Going back to my first question, the EMA advisory groups failed to reach agreement on several matters. You touched on the issue particularly with respect to the commercial confidentiality of clinical trial data. Does the Department of Health consider clinical study reports of individual patient-led trial data to be commercially confidential?
Sir Kent Woods: Perhaps I can respond to that first. We in the MHRA would not regard such reports as blanket commercially confidential. There may be elements within the report that could be argued to be commercially in confidence; we would need to be persuaded. In fact, for clinical trial results, our view has generally been that there is very little scope for commercial confidentiality. It tends to be more in the pre-clinical, the laboratory and perhaps the synthesis area—the manufacturing side—where commercially confidential information is contained; but our stance over the years, as we have gone further into this, has been to push back further and further, to ask why, specifically, should specific elements of clinical trial data be considered commercially in confidence. We are far more concerned about personal confidential data than commercial confidential data.

Q159 David Tredinnick: Are you aligning yourselves with Sense About Science, then? Do you take their view? Sense About Science, who presented to us earlier on, take a view that as much medical data as possible should be available. It would seem to be in the public interest—although I am certainly not a spokesman for them.
Sir Kent Woods: I would agree with that architecture of the problem. The first basic piece of information is public knowledge: a particular trial, with a particular protocol, has been embarked on—that ought to be absolutely transparent. Also, the results of the trial, in summary form: we would agree, in order to ensure that people who need to make decisions on the basis of trials, as clinicians, as patients, whatever, have access to the conclusions—the final results of their studies. I think the difficult bit comes when you go firstly to look at the clinical study report in its full detail and, beyond that, the raw data—the individual patient data. I think there are some operational difficulties, and there are also some policy difficulties as to how those are handled.
The clinical study reports, in order to ensure that one is not releasing personal, identifiable data, do need to be quite carefully scrutinised before release, and they may need to be redacted in places; and that is a very labour-intensive process. I mentioned that the EMA had released 1.6 million pages of data over two years. We think that cost somewhere between €2 million and €3 million to do, so it is not simply the principle that we have concerns about: it is the operational practicalities of it, and the justification for the resources that go into it. This is a very laborious process. If there is a simpler way of ensuring that all non-confidential information is in the public domain, it would be a huge help for everybody.

Q160 Chair: Does the Department concur with that?
Peter Knight: It does, and the Department is very clear about the position on patient confidentiality, and that is quite a concern. Listening to the previous panel, I was encouraged to hear about the controlled release and looking at redaction, and that is exactly where the Department would be coming from.

Q161 Graham Stringer: Do you have any outstanding concerns about the draft EU clinical trials regulations? Are you at all concerned about Glenis Willmott's proposed amendments to those regulations?
Sir Kent Woods: I think that the regulations as proposed by the Commission, which are now going through Council negotiations, are very much in the right direction. They incorporate a number of improvements to the original clinical trials directive, which we, as a member state, have been unhappy with right back to 2004. I think the areas I particularly welcome are around the recognition that there should be some risk proportionality about how clinical trials are authorised, and that there is not a one-size-fits-all approach. Some trials intrinsically present a greater risk to participants and others much less so.
The second area we very much welcome is the move towards the simplification of the process of carrying out a trial in multiple member states. A lot of research is carried out in more than one country, and one of the drawbacks of the original clinical trials directive, essentially giving individual member states responsibility one by one for the trials done in their territory, was to make it very difficult and very cumbersome to apply to do a study in several countries; so we in the UK have been working with other member states very hard in recent years, to try to devise a sort of mutual recognition system—a way of collectively coming to an assessment of a clinical trial application over several countries. Those are now being incorporated into the proposals for the clinical trials regulation. All that is very welcome.
The areas of concern are still under negotiation. Glenis Willmott's recommendation around the release of the full clinical study report does leave the operational and practical difficulty of how that should be done and by whom. It does not completely get away from the problem I have mentioned of the need to make sure that one is not releasing personal confidential data, and therefore how one is going to do that redaction process. As has been mentioned by previous witnesses, it also gives some difficulties for the non-commercial researcher who would not routinely be preparing a clinical study report of the pattern that is laid down in the ICH guidance. One would have to be very clear as to what the equivalence of a CSR would be for research that is not being submitted for a market authorisation. It might in effect be something like the sort of published report of a study that currently goes into an academic journal. I would be concerned about the burden implied in that recommendation, bearing in mind that one of the main drivers for the revision of the clinical trials directive was to make it simpler and easier to do research in Europe. In the past four or five years the number of clinical trials brought forward on pharmaceuticals in Europe has fallen by 25%, and there is a strong feeling

that a significant contributor to that has been the complexity of the legislation. So taking as a starting point the revision of the directive, how can we make this simpler? Adding another layer of complexity is swimming in the wrong direction.

Q162 Graham Stringer: So you are actually saying that you are against mandatory publication of all CSRs?

Sir Kent Woods: I would need to give very serious consideration to how that can be done in a way that is useful to the people who will be drawing on that information and that is operationally feasible, and it will need to protect the patient confidentiality that is potentially embedded in the CSR. These are very detailed reports. They have become more and more detailed as the years have gone by. They are prepared for a specific purpose, which is to help regulatory authorities reach decisions about whether or not that product should have a marketing authorisation. That is the genesis of the CSR. It may not be the best vehicle to use if we are looking for widening transparency.

Q163 Graham Stringer: I do not want to put words in your mouth, and I am sure that you would not like me to, but you are worried about swamping of information?

Sir Kent Woods: Yes, that would be one aspect; it could swamp the end user with a level of detail that is not needed or helpful, and it could make the process of completing clinical research a little bit more burdensome, particularly for organisations that are not set up to put products forward for market authorisation.

Q164 Graham Stringer: You mentioned that you welcomed the fact that the new regulations were more risk based than they had been previously. Do you think they deal as well as they could do, particularly with phase 3 of the trials, with orphan diseases—diseases that not many people suffer from? It is very difficult to get as many people to participate in the trials. Do you think they deal with that situation, or are they going to make it more difficult for those rare diseases?

Sir Kent Woods: I do not see anything in the proposals that would make it more difficult, but, in the case of rare diseases, it is a serious challenge to identify adequate numbers of potential participants and to marshal them into a protocol subject to informed consent. There are already provisions within the existing legislation for circumstances where there are so few patients with the condition that the market authorisation for a product has to be authorised on a lesser level of data than would be the case if this was a common condition. Orphan diseases and treatments of orphan diseases also attract some support in the regulatory system in scientific advice and waivers and fees and so forth. Efforts are already being made to deal with this issue. It is not completely solved but I do not think that the revision as it is currently going is likely to influence this greatly one way or the other.

Q165 Graham Stringer: A final question: are clinical trials likely to change in their structure in the future and are the proposed European regulations likely to be flexible enough to deal with those changes in design?

Sir Kent Woods: That is a very important point. We have seen over the last 10 years that the clinical trials directive has in it some inflexibilities, which we wish to see changed. Therefore, the ability to adapt the regulatory framework more quickly than every 10 or 15 years is important. You are absolutely right that research designs will change. They should change. Indeed, as an agency, we strongly encourage researchers to look at, for instance, adaptive trial designs, which are more efficient in their use of time and in the number of patients they need. We certainly do not wish to inhibit developments in methodology by creating a rigid, inflexible regulatory structure with revision. I think the Commission's intention is to put some of the key areas of the revision under the provision of delegated legislation, so if it is necessary in the future to further refine various aspects, that can be done without revising the entire legal code.

Q166 Jim Dowd: A couple of you have mentioned the importance of protecting personal data as a priority. The Caldicott 2 review, of which I am sure you are all aware, identified what it felt was a grey area for individual patient level trial data, where patients could be identified despite being technically anonymised. Do you agree with the area that they pointed out?

Peter Knight: Yes, I do agree. I have done a major piece of research around this area over the last few years. It is an area where anonymisation is supposed to be a starting point—you can't get back to an individual. However, with other data sets that are around and freely available and the risks of re-identifying by meshing those data sets together, it is quite an important aspect to reflect on. Data protection law is one thing we have for protecting that whole area, but we also have both contract law and HR law. Researchers undertaking activity have a duty to ensure confidentiality regardless. That is important in terms of the aspects of the legal framework we operate in. So yes, that area is understood. I think it is more broad than just saying, "What are the data protection aspects of this?" It is about how a researcher receives data, how the disclosure of that data is then within their remit to operate, and what action would be taken if somebody breached that agreement.

Q167 Jim Dowd: Do you feel that the suggestion of an accredited safe haven is a reasonable mechanism for dealing with this?

Peter Knight: Yes, and within the Health and Social Care Act, the health and social care information centre has effectively got that duty. There is also the clinical practice research data link. We have got a process of accrediting the safe haven through what was the National Information Governance Board—its responsibilities have now been transferred to the HRA. Section 251 of the HSC Act 20123 sets out responsibilities under the duty of confidentiality,

making sure that data is processed in an appropriate, safe and secure way.

Q168 Jim Dowd: We are running short of time, so I will restrict this to one final question. You will be aware of what was identified as the consent for consent difficulty. What action has been taken to address that?

Peter Knight: So the department, working with the Information Commissioner over a number of years, having sought legal advice on this, has set in the NHS Constitution a clear position around consent for consent. Consent for consent is broadly about saying, "Can I contact you without having your permission to contact?" That is the anathema of what the problem is. The Information Commissioner was quite clear: set the expectation of the population about what you are going to do. We have done that as a pledge in the NHS constitution, which sets out that the NHS will contact you about research that is relevant to you and you are eligible to participate in, and then get on and do it, effectively. That is the guidance we received and the position we validated through our legal branch. The constitution is the starting point and that requires then to be cascaded elsewhere, so that GP surgeries are very clearly positioned around what we do with data and the ability to contact you for research through your clinical line of accountability—i.e. the patient and clinician relationship. So that is where the Department has got to.

Q169 Chair: Do you send out guidance to trusts about how they should collect data? As an example, I have come across a situation where the first question on a document was how to opt out, rather than the benefits of being part of a trial.

Peter Knight: Can I just be quite clear? If that is consenting into a trial, absolutely, that is a clear position. If it is about use of data, in legal terms, there is no definition of opt-out. The Data Protection Act is very clear about this: you have the right to object to your data being used in an identifiable form.

Q170 Chair: But that should not be the first question.

Peter Knight: No, no. Absolutely, but it is very important to recognise that the opt-out process is not a legal construct.

Q171 Chair: Sir Kent, you were nodding vigorously.

Peter Knight: And the HRA in guidance terms?

Dr Janet Wisely: For the HRA, the challenge—the frustration for researchers is well understood in the NHS, but Caldicott 2 has laid out a clear framework that really had not changed much from the initial review—is that researchers need a legal basis to access data. So that is consent for consent if you are not part of the clinical team, unless the data are anonymised. We may be able to do further work to identify where researchers—where they are clinicians and are part of the NHS—could be considered as part of a clinical team. I think we could take a more proportionate view on approval there.

I also add that in terms of some work we have done through some patient and public involvement, we are hearing the same as Caldicott did—that people, patients and the public are very comfortable about research having access to anonymised data. They are very content with people in the NHS having access to their data, particularly patients for researchers, but there was caution about a wider access potentially from outside the NHS to their notes. I think Caldicott 2 sets out quite a sensible framework.

Q172 Stephen Metcalfe: Once a trial has been completed and the evidence emerges that this can improve outcomes for patients, how quickly and effectively is that information disseminated out to clinicians and incorporated into what could be considered standard medical practice? How is that achieved, and how quickly is it done?

Bill Davidson: One of the things that we did in last year's Health and Social Care Act was introduce a duty across all parts of the system, not only to promote the conduct of research, but to promote the use in the health service of evidence from research. That duty applies to clinical commissioning groups and to NHS England, so they have a key role in making sure that the activity at the front line is translated into clinical practice. There is also NICE and the guidance that it issues. We heard from a previous witness about some of the time lines there. I do not lead on that and cannot comment on what their normal time lines are, I am afraid.

Sir Kent Woods: Can I perhaps add to that? You focused in your question on the efficacy side. As an agency, we are very much concerned to see that any new evidence on the benefit-risk relationship is communicated to prescribers and patients as quickly as possible. We have well-established communication channels to do that. If there is a new piece of research, or a new regulatory decision on a safety issue, we will put that out through a press release, through the professional bodies, and we will put it on our website. That is, as it were, the immediate output instantaneously.

The second phase is to include it in our regular drug safety update bulletin, which goes out once a month. And then the third is to get it into the standard reference works, like the British National Formulary, which is revised every six months, so that that new knowledge is accessible to clinicians at the earliest possible moment. But it is a real challenge, because the evidence base on any product on the market is constantly being expanded and developed. It is not a once-only judgment about the risk-benefit relationship.

This will evolve over time, as we get more experience in a wider range of patients with more complex conditions, with more co-medication. So our role as the regulatory agency is not just in relation to the company, but it is in relation to the wider public and the health professions to make sure that what we know—our current understanding of the risk-benefit relationship—is actually as widely known as we could possibly achieve.

Q173 Stephen Metcalfe: Anyone want to add to that?

Back to you, Mr Davidson. You said there is sort of an obligation on the commissioning groups, but how

are they finding out? What is the actual practical process? Is it something you have to go and search for, or is it being forced down the chain, as this evidence becomes available, that there is an improvement in the way something is treated? How is that getting to the front line, so that we all benefit?

Bill Davidson: That is a good question. One of the key mechanisms is the guidance that is issued by NICE. Kent has described the things that the MHRA does on top of that, through the Formulary.

Q174 Stephen Metcalfe: Sorry, just to interrupt you. How much guidance is issued in any given month or year from NICE, and is it a practical proposition to say, "That's the way it's done."? You see the point I am trying to make. Without knowing the scale, it might be impossible for someone to deal with.

Bill Davidson: I can't say. I am sorry, I cannot comment on NICE.

Q175 Stephen Metcalfe: But that would be the path, right?

Sir Kent Woods: If I can comment. For many years I was in clinical practice and I did make use of the outputs of NICE and I have kept, obviously, in touch with their work. Although the volume of guidance and guidelines that comes out of NICE is large, the accessibility, certainly through their website, I have always found to be very good. If I were commissioning a service or if I, as a clinician, was providing a service in a certain area for a certain condition, I would not have any trouble getting into that information, because it is structured in a way which would take me straight to the condition and the particular treatments that were of interest to me.

Chair: Thank you very much for a helpful session. We have one more session in this inquiry. If there is any further information you feel it appropriate to submit, I should be grateful for it. Thank you for your attendance.

Monday 3 June 2013

Members present:

Andrew Miller (Chair)

Stephen Metcalfe
Stephen Mosley
Pamela Nash
Graham Stringer
Roger Williams

Examination of Witnesses

Witnesses: **Rt Hon David Willetts MP**, Minister of State for Universities and Science, Department for Business, Innovation and Skills, and **Rt Hon Earl Howe**, Parliamentary Under-Secretary of State for Quality, Department of Health, gave evidence.

Q176 Chair: Gentlemen, can I welcome you to the session? We are coming to the end of our evidence sessions in our inquiry into clinical trials. It has been a fascinating exercise, and we hope that this afternoon can shed light on some of the issues that have cropped up during our inquiry. Earl Howe, if I could start off on a broad issue, as a rough proportion how much of your time do you spend on health research issues? You have an incredibly wide brief that goes well beyond the limitations of this inquiry. How much time do you spend on it?

Earl Howe: I regard research as a very important part of my portfolio. In terms of my time, it includes a number of tasks: PQs, correspondence, meetings and briefing visits. For example, last week I was at Addenbrooke's looking at their neurological research. It is a little difficult to answer what proportion of my time it takes up. I am available when required to ensure that I give sufficient attention to it. The time given to any part of my portfolio inevitably varies. In the round, innovation, life sciences and medicines collectively take up a good deal of my time, and research bears upon all those things very closely. If you were to pin me down to how many hours a week or days a month, I would probably have to come back to you on that, but it would be several hours a week.

Q177 Chair: Thank you for that, and I appreciate that measuring something like this is not an exact science.

Mr Willetts, you have a specific responsibility for life sciences, in that you obviously spill over into the work of the Department of Health. If you were sitting in the Cabinet just now, tell us a secret. What more would you be asking the Department of Health to do in terms of its research effort?

Mr Willetts: That is a very ingenious question. I would say let us do more of what has emerged since the life sciences strategy, which is that clearly we need to work together. I have appreciated an excellent working relationship with Earl Howe as well as with Jeremy Hunt and his predecessor. For example, I have noticed that, when talking to the life sciences industry wearing my BIS and science hat, and Earl Howe with his responsibilities for the health service, and we meet them jointly, as we are now doing, they very much appreciate the fact that there are two Ministers with rather different responsibilities working together. A few weeks ago we had a very successful visit to Switzerland, calling on Roche, Novartis and other companies. They said there were very few other Governments where they would see at the same time in the same meeting the Minister responsible for health care and the Minister responsible for science with a shared agenda. We could do even more of that.

Q178 Chair: How much more?

Mr Willetts: Earl Howe must talk from the Department of Health's perspective, but from our perspective in BIS, we are keen to strengthen our science base and as a result to see more companies choosing Britain as the place to do their R and D and invest. We have some major life science companies with a very significant presence here already, such as GSK or AstraZeneca. There are other major life sciences companies that, to be honest, I would like to see doing rather more in the UK. Our active strategy has meant that already, even as the industry goes through this big restructuring, the levels of overall investment in life sciences in the UK have been maintained. I would like to see us do even better and persuade some of the other life sciences companies, which currently may not be quite so active here, that we have such a joined-up approach embodied in our life sciences strategy and that Britain is a place where they would like to do more of their clinical trials and R and D.

Q179 Stephen Mosley: More specifically, what are you doing to try to achieve that?

Mr Willetts: The life sciences strategy was published in December 2011. We did a one-year-on update with further new ambitions, such as the sequencing of 100,000 genomes. We now feel that we have a sufficiently clear overall strategy that we do take it abroad. As I said, the visit to Switzerland was a good example. With my responsibilities for strategic relationship management, I am regularly meeting the major life sciences companies that are active in the UK, and I make it a priority on overseas trade missions to call on them in the US and elsewhere.

Earl Howe: In having those conversations, we are able to say that we have done quite a bit already to make the climate in this country much more benign and attractive to them. For example, we have followed through very diligently the recommendations of the report by the Academy of Medical Sciences in 2010, including setting up the Health Research Authority, which was one of its major recommendations. I think that by common consent the HRA has got off to a

very good start indeed. There are things like the Patent Box, which David Willetts' Department has championed, and measures taken by the National Institute for Health Research, such as the 70-day benchmark for commencing a clinical trial once approved. There are various things that send the right signals, I believe, to companies in the sense that you have just mentioned.

Q180 Stephen Mosley: Earl Howe, I am interested in the 70-day benchmark that you mention. Do you have the statistics for how many NHS trusts are meeting that benchmark?
Earl Howe: I did anticipate that you might ask me this. Unfortunately, the advice I have received is that we do not yet have robust data. I am told that the data collection is "maturing", it having been piloted last year. We will be in a position to give a precise answer to your question later this year. I am sorry I do not have robust figures.

Q181 Stephen Mosley: I assume that you remember "The Plan for Growth" in 2011, which committed the Government to publishing these figures by 2012.
Earl Howe: The NIHR included the clinical trial initiation benchmark in new contracts with NHS trusts from 1 April 2012. Currently, 41 new contracts have been established, and in the period between April last year and April this year it introduced a data submission process, which is now being tested. From July this year, NHS providers are requested to publish their performance regarding the benchmark on their websites, and the NIHR will be monitoring the extent to which they do that.

Q182 Stephen Mosley: Do you think the 70-day target will be achievable?
Earl Howe: Yes, I do, but, if I were candid, it may take a little time before we see majority compliance with it, and that is partly because some trusts are working on older-type contracts and have not signed up to this yet. When contracts are renewed over the coming years they will include the new benchmark as a stipulation, but inevitably it will be a gradual process of implementation.

Q183 Stephen Mosley: We have heard that one of the main barriers to starting a clinical trial in the UK is the process by which researchers sometimes have to get multiple permissions from each individual NHS trust. I am aware that options for resolving this issue are being examined by the HRA in a feasibility study run in collaboration with the Department of Health. Do you have any indications of how that work is continuing and when it is likely to report?
Earl Howe: The Health Research Authority is looking at ways to speed up the whole research journey and it is running a feasibility study, including a number of pilots, to test the effect of rationalising and combining NHS study-wide review with elements of the Research Ethics Committee review into a single HRA assessment. It is very much on the case in that regard. The HRA, however, has brought together the functions relating to Research Ethics Committees and is developing a unified approval process for research, which has been very warmly welcomed as an idea. That builds on the current IRAS system—integrated research application system—and will bring together the bodies involved in approving and advising on research behind the scene: in other words, Research Ethics Committees, trusts, the MHRA, the National Information Governance Board and so on. While we cannot expect overnight results, there is cause to hope that in the HRA we have a body that sees it as its job to streamline the processes.

Q184 Stephen Mosley: Do you have any time scales for when you hope that will be implemented?
Earl Howe: I may have to take advice and come back to you on exactly what the milestones are in that regard, and I am happy to do that.

Q185 Pamela Nash: Following on Mr Mosley's last question, is there evidence of any setback to this progress with the new organisation of the NHS when so much power has been devolved?
Earl Howe: No, there is not. There are a number of statistics that I believe give us cause for optimism, in that the trends are heading in the right direction. For example, over 99% of NHS trusts actively recruited patients on to clinical research network studies last year. That is a big improvement. There was a 7% increase on the previous year in terms of the number of participants recruited: over 630,000. The number of new trials—phases one to four—in the NIHR clinical research network has more than doubled over the past five years. The work of the NIHR in particular has already shown dividends in that sense.

Q186 Pamela Nash: Mr Willetts, the strategy for life sciences two years ago contained a pledge to relaunch the Clinical Trials Gateway. Can you update us on the progress of that? Can you share with the Committee what the Department has invested in this project in terms of staffing and finances?
Mr Willetts: The Clinical Trials Gateway might be more for Earl Howe.
Earl Howe: It is. The Clinical Trials Gateway, which has recently been updated and renewed and is in the process of being improved still further, is an initiative of the NIHR. It is designed to enable members of the public and NHS patients to access information on clinical trials that may be relevant to them. We are aware that knowledge of the gateway is less than we would like. I understand that the NIHR is taking various steps to promote the existence of the gateway, as indeed the NHS itself must do. In the NHS constitution there is now a pledge to promote the existence of clinical trials, so there is an onus on the system itself to do this. One of the refinements that the gateway is looking to achieve is a more geographic focus to it so that, if you are living in a certain part of the country, you can find out what trials are going on nearby, but there is no doubt that it is another initiative that has the potential to involve more patients in trials.

Q187 Pamela Nash: Can you tell us a bit more about how the gateway is being promoted? I am particularly

interested in how it is promoted to healthy people and not someone who might have a specific illness.

Earl Howe: The NIHR has ensured that all parts of the NHS are made aware of the gateway's existence so that, at relevant opportunities, clinicians and others are encouraged to draw attention to it when they have a patient sitting in front of them. I cannot be more specific than that. I know there has been an information campaign by the NIHR through the NHS. I can supply you with precise details, if you would like me to.

Q188 Pamela Nash: That would be helpful to the Committee. It is a concern to me that, if the Minister doesn't know, how the public is supposed to know what is going on and how the gateway has been promoted.

Earl Howe: I do know that the NIHR has made it its job to promulgate the existence of the gateway but with limited success so far, and it is continuing to promote it. If you are asking me about the precise mechanisms with which it has done that, I will need to come back to you.

Q189 Chair: Before you move on, can I push you a little harder on this? I raised this point with a previous witness having come across, in one hospital, an issue surrounding a clinical trial that was brought to the attention of patients. The first the patient was told about it was in a document that started off by saying, "This is the procedure you follow if you want to opt out." That is not a terribly good way of encouraging people to participate and have confidence in clinical trials, is it? Would you agree with me and the previous witness that we should proactively encourage trusts not to adopt that kind of procedure?

Earl Howe: I most certainly do. I think it was with that very thought in mind that the NIHR, through Dame Sally Davies, last month launched the campaign "It's OK to Ask". The whole point of that campaign, which incidentally was launched on 20 May, International Clinical Trials Day, was to raise awareness among patients and patient groups about the role of research in the NHS; the role of patients in research; that it is okay to ask your doctor about clinical research and, at the same time, to encourage clinicians and those working in the clinical environment—for example, people working in care homes—to think positively about research in the context of those they look after, and how they might channel interest that patients express positively. There were badges and space on various websites devoted to this. Being proactive is very much part of this, and it links to your question about the Clinical Trials Gateway, which was part of the publicity campaign.

Q190 Pamela Nash: I have a final question on the gateway, and you may want to write to us about this later. I was interested to know whether in the promotions you are looking at examples of best practice elsewhere. From the evidence we have received, Cancer Research UK, for instance, has its own trials database that receives eight times as much traffic as the Clinical Trials Gateway. Is this something you are aware of? Are they speaking to other people in the sector?

Earl Howe: In terms of improving the profile of the Clinical Trials Gateway.

Pamela Nash: Yes.

Earl Howe: I will have to come back to you on that.

Q191 Roger Williams: To move on to the NICE guidelines, we have been told in evidence that, while people have high regard for them, when drugs are developed, for instance, for cancer care, the period between referral and the time the guideline appears can be up to two years. Are you satisfied with that timeline, and is there anything that could be done to speed up the process?

Earl Howe: How long it takes depends on the type of work that NICE is doing. With some of its single technology appraisals, the timelines are much shorter. One has to acknowledge that over the last few years NICE has significantly accelerated the rate at which it is able to produce results. If it were the case that it took two years for NICE to do everything, I would not be satisfied. I do not believe that is so. It takes that kind of time scale for certain sorts of work. Don't forget that NICE is now engaged in a range of work. It is engaged in producing a library of about 180 quality standards to inform commissioning; it is engaged, as it has been for many years, in clinical guidelines, and the methods guide that it publishes explains in detail how it approaches the evidence base and so on. It is quite a complex process, and it does take 18 to 24 months to produce a clinical guideline. Technology appraisal guidance, on the other hand, can take the form of either a single technology appraisal or multiple technology appraisals. Single technology appraisal takes around a year; the development of multiple technology appraisals takes around two years, but the reasons for the difference are hopefully obvious.

Q192 Roger Williams: You will be able to understand that, as Members of Parliament, we have constituents who have heard that drugs are available but they cannot be prescribed through the national health service and the huge concern that causes.

Earl Howe: There is a common misconception among the public about this. Merely because NICE has not pronounced on a drug does not mean to say it is not available on the NHS. If a drug is licensed, it is available on the NHS providing that commissioners are prepared to pay for it, but, even if a drug is not licensed, an individual clinician on their own responsibility can prescribe it for an individual patient. There is no barrier in this sense if there is a medicine from which a clinician thinks a patient would benefit.

Q193 Roger Williams: Once NICE has produced a guideline, sometimes that needs to be looked at again. What is the process that triggers that?

Earl Howe: NICE routinely reviews clinical guidelines every three or four years to consider whether they should be updated and can take into account any new evidence. It also has processes in place to bring forward updates if significant new

evidence emerges before the scheduled review point. The general answer is that it is flexible and responsive in this regard, and it is as consultative as it possibly can be.

Q194 Roger Williams: It is sometimes said that the evidence NICE looks at is slanted in such a way that it looks at evidence that is very positive because some of the negative work that has been done might never have been published. Do you understand that, and do you think that is a problem?

Earl Howe: I do not think that is a problem. If you talk to the pharmaceutical industry, it would say that NICE is altogether too negative. If you look at the percentage of drugs that NICE approves in one shape or form, it is around 80%. The answer is that NICE guidance and technology appraisals are based on a thorough assessment of the best and latest available evidence. It looks very carefully at clinical trials data in the case of drugs; it consults widely in the development of guidance; and it consults stakeholders on the methods and processes that it uses to develop its guidance. If you talk to NICE, I am sure it would hotly repudiate the suggestion that it is biased on one side or another to look at negative as opposed to positive data. I think it wants to be as even-handed as it can.

Q195 Roger Williams: I was not suggesting it is biased but that the information at its disposal and its use may be biased.

Earl Howe: I beg your pardon. No is the answer; I do not get that impression. There was one particular case recently, which you will be aware of, where the suggestion was made that NICE was not made aware of negative data when it should have been. That was on Tamiflu. I think you will be getting a memorandum from the NAO on that issue. Am I aware of any cases where important data on clinical trials were not released either to NICE or the MHRA? I am not aware of any cases where that has happened. That particular issue is in my brief, so officials have looked into that.

Q196 Chair: Mr Willetts, what do the pharmaceutical companies say to you about the NICE processes?

Mr Willetts: They are looking at it from their perspective of course. Sometimes they argue that the hurdles to get NICE acceptance in the UK are rather too high. This very much supports what Earl Howe was saying. In many ways, they see NICE as a particularly stringent process.

Q197 Chair: Who is right?

Mr Willetts: These are deep waters. NICE is a great advance, and it is right to have this type of appraisal. I can remember, as doubtless you can, the days before NICE. It is right to have that national framework. In terms of the life sciences strategy and our responsibilities in BIS, sometimes the NHS is slow to take up and prescribe drugs even after they have passed the NICE guidelines, and in some ways the industry would be a bit more relaxed or a bit more accepting of NICE if they felt, even after NICE approval, it was then going to be reliably prescribed. Earl Howe is the expert on this, but sometimes the speed of getting something into a formulary and it being used in an individual hospital seems quite slow, even after NICE approval.

Q198 Pamela Nash: The current Prime Minister famously said that this Government would be the most transparent ever. How do clinical trials fit into this, and what does the Department feel is the correct level of transparency for clinical trials?

Earl Howe: The Government support the principle of disclosure in relation to clinical trials data. In our judgment, very little of the information that is submitted to the MHRA could be regarded as commercially or personally confidential at the clinical trial stage. The MHRA, from where I sit, has done quite a lot of work to ensure that information about clinical trials that it receives is put in the public domain. It publishes public assessment reports following the approval of new medicines. It began publishing summaries of product characteristics of all UK-approved medicines on its website last year, and those summaries are a distillation of the safety and efficacy data. It is considering what more it could do. In terms of the principle, I can couple David's Department with my own on this. We are squarely signed up to the principle of transparency, but there are important considerations around it, the chief of which has to be the need to ensure that individual patient confidentiality is respected. I do not think anyone seriously contests that, but there are ways in which we and the pharmaceutical industry see a way through this, namely, the safe havens idea for parking information with a trusted intermediary.

In talking through the issues around transparency and clinical trials, one has to separate out distinct elements of what we are talking about. The first stage is the registration of the clinical trial where clearly there is no problem about transparency. There are clinical trials registries and so on to make that information accessible. The Clinical Trials Gateway is a good case in point. It has to be said that none of the current registries is very user-friendly. We are looking at how to improve that aspect.

Then there is publication of the outcomes of clinical trials. The NIHR and MRC both require all clinical trials outcomes to be published. That is going to be monitored through Researchfish, which is a software program. Then there is publication of protocols and analyses, and, there, we think that the aims of transparency can be achieved through defining what measures should be made available, but not necessarily mandating, for reasons which I can go into if you like, that the entire clinical study report—the CSR—should be made publicly available. There are good reasons why that would not be a proportionate thing to do, but to make available the central metrics is important. We then get on to access to individual participant data where the idea of the safe haven comes in. I hope that has given you a sense that we are working on a number of fronts to achieve that. I can perhaps go into that further, if you would like me to.

Q199 Pamela Nash: Before you go into that further, are you referring only to future trials, or is the publication of data and information of previous trials being considered by the Department?
Earl Howe: Certainly we are talking about future clinical trials, but we are also encouraging the industry to make available past data—and to some extent they are doing that, although I am afraid I do not have the stats here. We know that GSK in particular is addressing this issue quite energetically, but, if you ask me about the precise extent to which past data have already been published, I apologise that I do not have that data in front of me.

Q200 Pamela Nash: You mentioned GSK voluntarily tackling this at the moment. Do you think it is appropriate or realistic that the Government would force companies to produce previous data from trials?
Earl Howe: We have to define what data we expect and want them to publish. All this is the subject of discussion at EU level at the moment in the context of the revision of the Clinical Trials Directive—in other words, the creation of a clinical trials regulation. Instead of having a directive, the proposal is that there will be a regulation. Discussions are going on almost as we speak about the level of granularity that will be required in this regulation for publication. It is not yet clear. It is a fast-moving scene. I am told that at the end of last week the European Parliament's Environment, Public Health and Food Safety Committee voted in favour of laying down the content of the clinical trials summary in legislation and making it compulsory for the summaries to be accompanied by a summary understandable to a lay person. The committee added to the draft regulation that a clinical study report submitted in support of a marketing authorisation should be made available through the EU portal within 30 days. We are now getting down to an interesting point in the discussion and level of detail. We are supportive of the way things are going. As you know, the process at European level takes its time to work through, but things are looking quite promising.

Q201 Chair: To follow up that point, what role have you been taking in these discussions at European level?
Earl Howe: None, because they are being led by the Medicines and Healthcare Products Regulatory Agency, but I have been receiving briefs on what they are proposing to do.

Q202 Chair: Have they taken a lead role, or are they responding to other European initiatives?
Earl Howe: Sparing their blushes, the MHRA has been very much at the forefront in all of these discussions and has influenced the EU Commission very heavily on the direction of travel it has taken throughout these negotiations. I think it deserves a lot of credit.

Q203 Chair: When some parliamentary colleagues come back and seek to blame Europe for changes, the correct answer is that the MHRA has been taking a lead role in these discussions.
Earl Howe: In these discussions. Looking back to when the current Clinical Trials Directive was in gestation and implemented, there was a general lack of perception across Europe about the extent to which we were shooting ourselves in the foot by making Europe a less attractive place in which to conduct clinical trials. We have learned those lessons over the last few years, so the present activity at European level is designed to get us back to where all member states want to be, which is to make Europe a more attractive platform for research. The various elements of the Commission's proposal are ones I can supply you with, if you wish.

Q204 Pamela Nash: Mr Willetts, in the discussions about the transparency of clinical trials, in your role have you heard any concerns from the life sciences sector? Does this give you any concern about how it could affect growth in that area in the UK?
Mr Willetts: No. I think they understand that the Government overall are committed to transparency. There are some tricky policy issues. Patient confidentiality is a very important principle. Delivering it in practice and what the arrangements are so as to maintain patient trust is not at all straightforward. The safe haven option that has emerged in several contexts is very productive, and they see it as a useful step forward.

Q205 Stephen Metcalfe: Earlier you mentioned Tamiflu, of which I understand we have a significant stockpile. Could you run us through what evidence is used or how the Government assess the evidence before they make a commitment to stockpile such a drug?
Earl Howe: The answer is twofold. Tamiflu is a licensed medicine and is assessed for safety, quality and efficacy by the MHRA in order to achieve marketing authorisation, so there is information there. NICE was also tasked to assess Tamiflu, and the balance of cost-benefit came out favourably. It is very much, as it often is for clinicians, to look to NICE's assessment for a steer in this regard, if you like.

Q206 Stephen Metcalfe: I can understand how the drug itself is assessed and its efficacy is evaluated, but how did the Government come to build up a stockpile covering 80% of the population, and how was that process driven? That is a slightly different thing from working out the effectiveness of the drug.
Earl Howe: Of course. This decision was taken before the current Government took office. I have to say that I am not aware of the basis on which the previous Government made that assessment.

Q207 Stephen Metcalfe: That is fair enough. Presumably, you have not had a similar circumstance since, where you have been through the process to evaluate how decisions are made.
Earl Howe: I stand to be corrected, but I think that process is ongoing because the stocks of Tamiflu that were built up need replacement. It will be Dame Sally

Davies's office, the CMO's office and Public Health England that will be involved in that decision.

Q208 Stephen Metcalfe: The decision about whether it is still effective or the decision about the level at which to maintain the stockpile.
Earl Howe: The decision on what level of stockpile there should be.

Q209 Stephen Metcalfe: Will that come across your desk?
Earl Howe: It is unlikely to be a decision for me. I believe this will fall more in the domain of my colleague Anna Soubry, the Minister for Public Health.

Q210 Stephen Metcalfe: At the time the original decisions were being taken there was some conflict, as I understand it, between the Cabinet Office and the Scientific Pandemic Influenza Advisory Committee, and they came to different conclusions about how effective Tamiflu was. Why was that? Why did that happen?
Earl Howe: I have nothing in my brief about this because I came prepared for clinical trials rather than stockpiles of Tamiflu. My understanding is that NICE's initial appraisal of the cost-benefit of Tamiflu was somewhat equivocal in terms of its clinical and cost-effectiveness. It then revised its opinion in a more positive way. That may have been the origin of any differences of view that you refer to.

Q211 Stephen Metcalfe: Let's get back to clinical trials. The Government are a major customer of drug companies. Do they use their buying power or influence with those companies to try to improve the transparency of commercially funded drugs trials?
Earl Howe: You are right to say that the Government are an important customer. The NHS is an important customer for drug companies, although in terms of their global sales we are a very small player indeed. It is arguable that anything we might do in terms of negotiating prices would have much effect in getting companies to invest in clinical trials. The considerations that companies look at mainly when taking those decisions are around the science base in the country concerned, taxation and perhaps a whole range of other factors that are unrelated to the extent to which the products are bought in that country. If you speak to the pharmaceutical companies, you may hear them say that the pricing arrangements do have an influence on their decision making. I cannot speak for them, but, if one looks at it analytically, the two issues are distinct.

Q212 Stephen Metcalfe: I think we touched on the involvement in the European Medicines Agency's clinical trials advisory groups. We were told or led to believe that no one from the Department of Health, MHRA, the Health Research Authority or NICE took part in those advisory groups, but I think you said earlier that was not the case.
Earl Howe: My understanding is that, as regards the discussions at EU Commission level, the MHRA has played a prominent role. I have no notes to tell you who served on the advisory groups and whether we had adequate representation, but I can certainly find out that information for you.

Q213 Stephen Metcalfe: That would be very useful, because I was going to ask you why, if that is accurate, we did not take part in those advisory groups. Perhaps you could expand on that, if there was some reason behind that.
Earl Howe: We should not forget that, in Sir Kent Woods, we have somebody who is British as chair of the EMA, and he does a very fine job, but at a lower level on the advisory groups or at a more operational level I will need to come back to you.
Stephen Metcalfe: That is fine.

Q214 Chair: Our understanding is that 15 Governments were represented in the advisory groups but nobody from the UK. It would be helpful to know what the facts are.
Earl Howe: I will find out and let you know.

Q215 Stephen Metcalfe: One of those advisory groups was looking at what the EMA's new clinical trials transparency policy should be. Do you have a view on what that policy should be?
Earl Howe: Yes. As I mentioned in answer to an earlier question, there are various distinct elements in the various stages of a clinical trial that we can isolate in answering that question, starting with registration and moving right through to availability of individual patient data. Aside from the qualification David referred to about patient confidentiality and privacy—which is an important issue because, unless one preserves that, one does not retain the confidence of patients—we are pleased by the tenor and direction of travel of the Commission in putting together its proposals on transparency in the context of the Clinical Trials Directive.
It is not just up to the MHRA or indeed Government here. The onus is also on those who own the data to lead the way, and in this respect we welcome what has already happened among a number of companies. I mentioned earlier GSK, which has done good work in this area, as has the ABPI on behalf of the industry with its transparency toolkit that it is now developing. We must not forget that, regardless of what we as a Government believe in terms of promoting transparency, which we do, nevertheless we operate in a European-wide system where an increasing number of medicines are being licensed at EU level by the EMA. We welcome the approach that the EMA is taking to releasing data. In our judgment, it seems to be a proportionate approach, and it is important that any solution is agreed at an international level. We have supported the work of the EMA in developing the EudraCT database to provide a public registry of all trials of medicines in the EU. That has been the case since 2004, when the Clinical Trials Directive was introduced. It is being further developed to allow the publication of results summaries later this year. We are aware of current legal challenges to the EMA position on the disclosure of clinical trial information, but, in line with the Prime Minister's commitment, there needs to be more transparency in clinical trials

data. We are wholeheartedly in favour of that, and we are committed to ensuring that this process moves forward.

Q216 Stephen Metcalfe: I am sure you are aware that the European Parliament's Environment, Public Health and Food Safety Committee last week approved the draft EU Clinical Trials Regulations.
Earl Howe: Yes.

Q217 Stephen Metcalfe: On that basis, were you happy that they passed that?
Earl Howe: They have reached what seems to us to be a sensible and proportionate decision on this.

Q218 Stephen Metcalfe: Is there anything else you would have liked to see, or any changes or differences?
Earl Howe: No. We were concerned at one point that they were going to insist on the publication of CSRs for every single clinical trial. There are some clinical trials that are not related to interventional medicines. Some are related to the surgical procedures for inserting hip replacements, where it would be unduly burdensome to require publication of a fully fledged CSR. We think that publication of summaries is the right level.

Q219 Chair: On a slightly broader, philosophical point, what role do you think the Government have to play in ensuring that people have access to research that they fund both as taxpayers and as donors to charity?
Mr Willetts: The basic principle is pretty clear. We would usually expect that publicly funded research should be made publicly available. That is a policy we are implementing with research findings and, increasingly, though there are some rather tricky technical issues, with the data underpinning those findings. As you know, open data is one of the Government's key commitments.
Earl Howe: It is a requirement that the results of any clinical trial or research, as far as I am aware, funded by either the MRC or the NIHR should be put in the public domain.

Q220 Chair: When you say "any", does that include non-commercial players?
Earl Howe: When it comes to academic trials—

Q221 Chair: Academic or charitable sector trials that might be funded through public funds.
Earl Howe: If there is an element of public funding, my understanding is that the contract requires publication of the result.

Q222 Chair: Is this what is meant by the Government's recommendation to register non-commercial clinical trials?
Earl Howe: No. The registration of a trial is putting in the public domain the fact that the trial is happening, whereas your question was much more about the results of the trial, was it not?

Q223 Chair: The second would not come without the first, would it?
Earl Howe: Of course.

Q224 Chair: I have registered that I am going to conduct a trial. I am now conducting the trial in a non-commercial environment. Does the register cover that work?
Earl Howe: Yes. All trials need to be registered, whatever their nature. Research Ethics Committees consider the proposals the applicant puts forward for the registration and publication of the research involved; the dissemination of the findings including, incidentally, to those people who took part in the study; and, if tissue is involved, making available any data or tissue collected for the research. Since April this year, the Health Research Authority has been undertaking checks of applicants to Research Ethics Committees and the reports that they publish to see whether they have registered and published as they declared they would to the Research Ethics Committees.

Q225 Chair: You would expect compliance to be 100%.
Earl Howe: We would expect compliance to be 100%, given that these people have undertaken to do this. We would certainly expect that they fulfil their undertaking.
Chair: Gentlemen, thank you very much for your time this afternoon.

Written evidence

Written evidence submitted by the Department of Health

INTRODUCTION

1. The Government ensures the safety of patients in clinical trials via the regulator—the Medicines and Healthcare products Regulatory Agency (MHRA)—and Health Research Authority (HRA) while providing national infrastructure through the NHS to encourage clinical trials to be conducted in the UK.

2. Clinical trials required to test new medicines are regulated by MHRA. Regulation is governed by the EU Clinical Trial Directive which has been transposed into UK law.

3. The following evidence addresses the matters set out in the inquiry's terms of reference.

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

4. In recent years we have seen a decline in clinical trial activity in the EU. The number of clinical trials conducted in the EU fell by 25% between 2007 and 2011. In the UK, the number of trials fell by 22% over the same period. This decline cannot solely be attributed to the Clinical Trials Directive:[1] an independent review by the Academy of Medical Sciences of the regulation and governance of health research found that "the governance arrangements within NHS Trusts are the single greatest barrier to health research",[2] which the Government is addressing through initiatives of its National Institute for Health Research (NIHR).[3] However, the current legislation has had an effect on the cost and feasibility of conducting clinical trials and the complexity of the regulatory framework has been cited as a barrier.

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

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

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

- the introduction of risk-adapted regulation of clinical trials, including the introduction of the concept of low-intervention studies, the streamlining and simplifying of the safety reporting requirements and the adoption of a proportionate monitoring approach;
- the introduction of one application for multi-state clinical trials replacing individual applications in different Member States which we believe has the potential to decrease the burden on researchers and promote the conduct of clinical trials in the EU (although we will be looking to improve the efficiency of the process); and
- the concept of one single submission and one single decision replacing the current separate regulatory approval and approval by Ethics Committees. This concept is introduced for both single and multi state trials.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21. The system of regulation of medicine is predicated on the provision of all relevant information to regulators in order to conduct their assessment of the safety, quality and efficacy of the application. The marketing authorisation holder is responsible in legislation for submission of all information relevant to the evaluation of the medicinal product included in the dossier submitted in support of their application. Each application is accompanied by a signed declaration confirming inclusion of all relevant information. The MHRA

does not have evidence that there is systematic or large scale withholding of data, but has investigated cases in the past where clinical trials and safety data were not properly reported.

22. For example, the MHRA carried out an investigation into GSK's compliance with legal obligations to report key safety information and on promotion of unlicensed uses of Paroxetine (Seroxat). The investigation concluded that GSK could and should have communicated safety information sooner than they did but that the law was not sufficiently clear to support legal action. In response, the UK legislation on reporting requirements was strengthened in 2008. European law has now also been strengthened, the latest changes coming into force in August 2012.

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

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

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

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

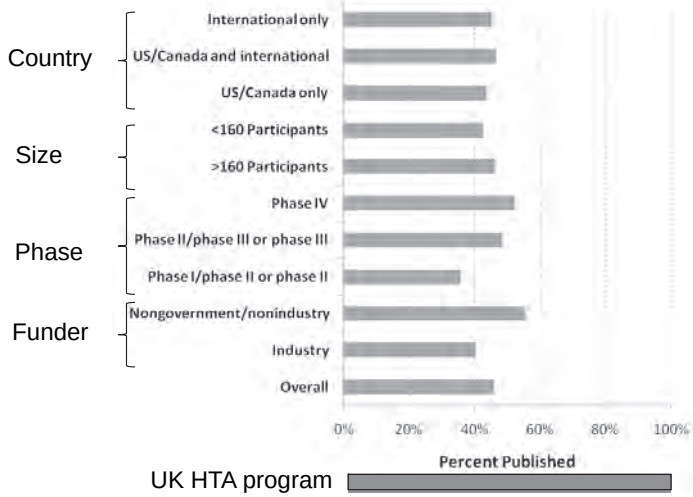
27. In evidence on 31 January 2013[4] to the Joint Committee scrutinising the draft Care and Support Bill that would establish HRA as an executive non-Departmental public body, the HRA chief executive, Dr Janet Wisely, said HRA would, with a view to building confidence in research, support having a role for the HRA in promoting transparency in research mentioned on the face of the Bill. The Government awaits the Joint Committee's report and recommendations with interest and will give them careful consideration.

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

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

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

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



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

New trials of aprotinin ignored previous trials

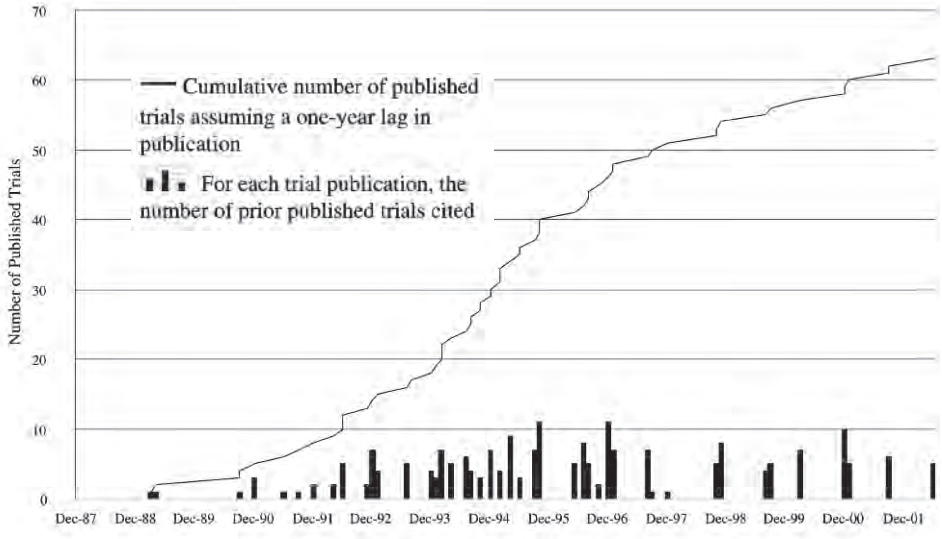


Figure 6 Citations of prior publications

29. On 8 February, the HRA board agreed to sign the AllTrials.net petition,[5] which calls for all trials past and present to be registered, and the full methods and the results reported.

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

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

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

31. Since July 2012, the MHRA has begun publication of all UK approved SPCs (Summaries of Product Characteristics) and PILs (Patient Information Leaflets) on its website.[6] The MHRA is publishing this information in stages. This first wave is for products that have been checked and are up to date with the licensing history. Information on further products will be added over the coming months.

Since October 2005, MHRA has published public assessment reports following approval of new medicines, providing details of the information on which its decision to approve a marketing authorisation was based.[7] The EMA publishes similar public assessment reports for all new medicines approved by the European Commission.[8] Public assessment reports have been published in the EU since the adoption of the European Community Code for medicinal products[9]).

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

33. This Register gives public access to information[10] on interventional clinical trials of medicines authorised in the 27 EU Member States and Iceland, Liechtenstein and Norway since May 2004. The database also allows the public to search for information on all clinical trials of investigational medicinal products authorised to be carried out outside the EU if these trials are part of a paediatric investigation plan. The Register does not, however, currently include the results from these clinical trials.

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

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

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

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

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

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

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

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

February 2013

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

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

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

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

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

Supplementary written evidence submitted by the Department of Health

When I gave evidence on 3 June for the Committee's inquiry on Clinical Trials, I undertook to provide further information on a number of points.

HRA Feasibility Study—Timetable (Q184)

The Health Research Authority (HRA) has a programme of work to unify the approval process for research and promote consistent and proportionate standards for compliance and inspection. As part of this programme, the Authority began a study in January 2013, to assess the feasibility of rationalising and combining elements of legal and management review with elements of research ethics committee review into a single assessment by the HRA. This would allow NHS organisations to rely on the single review and to decide whether to host a research project swiftly, based solely on local capacity and capability. The findings are expected to identify, and show how to realise: potential to reduce study set-up times, improve the quality and consistency of ethical review, and simplify the approvals process thus reducing the effort and costs involved for researchers. The HRA Board is due to consider the findings of the feasibility study on 24 June. A timetable for implementation is expected to be agreed later in the summer 2013.

Alongside the single assessment review work, a new technical platform for the Integrated Research Application System (IRAS) is being procured for release in early 2015. The new technical platform for IRAS, along with new information systems supporting the research ethics service, will provide an integrated application and approval system enabling communication between review bodies about research applications to be held in one place. This will improve transparency of the review process and make it easier for researchers to navigate the approvals system.

UK Clinical Trials Gateway (Q186–7)

The Department has invested from 2008 to date a total of £611,000 in the UK Clinical Trials Gateway. These costs include: the development work of the database and website, limited advertising and promotional materials, and administrative costs for Editorial Group.

The staffing of the UK Clinical Trials Gateway is provided via contract under arrangement with the University of Leeds, as part of the National Institute for Health Research. The support and development of the UK Clinical Trials Gateway is part of the duties of a team of staff at the University, which equates to two whole time equivalents. In addition, two Department officials support the Editorial Group as part of their overall duties.

The volume of access to the website for May 2013 is: 41,115 pages viewed by 11,570 unique visitors, who visited the site 13,069 times in total. Additionally, accessing the mobile phone and tablet version of UK Clinical Trials Gateway there have been approximately 8,500 downloads of the application since the launch in 2011.

The launch was promoted via leaflets and other printed materials including postcards and posters. In line with Government policy there has not been high level advertising of the system, but it has been promoted at numerous relevant events and recommended in speeches by the Prime Minister, DH Ministers and senior officials. Both the website and the specifically-developed downloadable application for the iPhone, iPad and Android devices have been promoted by INVOLVE (the NIHR-funded Patient and Public Involvement body) at a number of events including the recent "It's OK to Ask" launch on international clinical trials day (20 May 2013), which aims to prompt to patients and clinicians the importance of life sciences research.

Clinical Trials Databases—Engagement with Cancer Research UK (Q190)

The Department of Health established an Editorial Group for the UK Clinical Trials Gateway with a membership that represents: patients and the public; Industry, the charitable sector and officials from the Department. Cancer Research UK has been a long standing member of the Editorial Group and has advised, with a range of stakeholders, on the original development of the UK Clinical Trials Gateway database, website design and promotional materials.

European Medicines Agency Advisory Groups (Q212)

Kent Woods, chief executive of the Medicines and Healthcare products Regulatory Agency (MHRA), attended the workshop organised by the European Medicines Agency (EMA) on 22 November 2012, on clinical trial data and transparency in his capacity as chair of the EMA Management Board. This was held in order to gather the views, interests and concerns of a range of institutions, groups and individuals with an interest in the topic. Officials from the Department and the MHRA were not present at subsequent advisory groups. The MHRA are looking forward to seeing the draft transparency policy from the EMA, and officials intend to respond to the consultation that is due to start this month. The MHRA will contribute to the further development and agreement of the policy through the relevant committees, including Commission for Human Medicinal Product (CHMP). MHRA officials have also been heavily involved in the working groups established to determine the modalities for publication of the summaries of result from clinical trials held on EudraCT.

The UK environment for clinical trials and transparency in clinical trial data are issues of great importance to the Government, and I look forward to seeing the Committee's conclusions and recommendations.

June 2013

Written evidence submitted by Sense About Science

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

1. Background

1.1 Sense About Science established the AllTrials campaign with Bad Science, *BMJ*, James Lind Initiative and Centre for Evidence Based Medicine. AllTrials is calling for all clinical trials to be registered and results to be reported, from both industry and academia. The best available evidence shows that about half of all clinical trials have never been published, and trials with negative results about a treatment are much more likely not to be published.[11] There have been years of discussions about addressing this problem but they have been slow and have failed to produce a decisive public commitment.

1.2 The campaign was launched on 9 January 2013. The AllTrials.net petition has been signed by over 30,000 individuals and 178 organisations including 97 patient groups. Appendix 1 contains the petition text and the names of the supporting organisations.

1.3 Sense About Science is a charity that equips people to make sense of science and evidence. We are a source of information, we challenge misinformation and we champion research and high quality evidence. We work with thousands of scientists, scientific bodies, research publishers, policy makers, the public, community groups and media, to promote sound science and evidence in public discussions.

2. Clinical Trial Participants

2.1 On 18 January 2013, fifty three clinical trial participants wrote to the European Medicines Agency (EMA) saying that the lack of regulations requiring clinical trials to be published is a betrayal of their trust. They said: "we all agreed to participate in the trials in the belief that we were helping to improve knowledge and treatments. We now understand that many participants in trials have been misled... This means that the findings generated from our participation and that of thousands of others in the trials may not be available to the doctors, researchers and regulators who work on particular diseases or make decisions about their treatments. It also means that some of the trials could be repeated in the future, when they do not need to be." (Appendix 2)

2.2 The signatories to the letter asked the EMA to put in place measures to ensure that the protocols for all clinical trials from now on—and all clinical trials since the 1980s—are posted on a public register; and that the primary and secondary outcomes measured in all these trials and the clinical study reports are published.

2.3 Richard Stephens, Chair of the NIHR Cancer Consumer Liaison Group, who signed the letter as a cancer patient and clinical trial participant said, "The Department of Health report, *Innovation Health and Wealth*, sets out a goal for the NHS that every willing patient should be able to take part in research. In our publication, *Action On Access*, we call for research to be embedded in clinical practice. Already 20% of cancer patients in the UK take part in clinical trials as part of their treatment options. We expect that the results of trials will be made freely available to researchers, clinicians and administrators, in order to deliver better treatments, better services, and better outcomes for patients. So all clinical trials should be on a central accessible register, and all trials should be reporting their results, even if they do not change clinical practice. Patients who choose to take part in clinical trials believe that by doing so, we are helping other patients in the future. I believe it is immoral to recruit patients to clinical trials and then not report or share the results. We participate in order to increase knowledge and to help others. We do not expect the knowledge to be kept secret or the help for others to be denied." (Appendix 3)

2.4 GSK signed up to the AllTrials petition on 5 February 2013. Their statement set out their plans to publish the full results of all the trials they have conducted going back to their formation as a company. It also recognises the concerns of patients: "Our commitment also acknowledges the very great contribution made by the individuals who participate in clinical research. All those involved in the conduct and publication of clinical research, whether healthcare companies like GSK, academia or research organisations, have a role to play in ensuring that the data they generate are made publicly available to help bring patient benefit."[12]

2.5 Between 16 and 18 of January 2013, Sense About Science conducted a survey through PatientView (which has access to an international network of 120,000 patient groups). The results of this survey indicated

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

[12] GSK announces support for AllTrials campaign for clinical data transparency http://www.gsk.com/media/press-releases/2013/GSK-announces-support-forAll-Trials-campaign-for-clinical-data-transparency.html

that 75% of people who have a medical condition (and 72% of all respondents) say that they would be more likely to take part in a clinical trial if they knew the results would be published. (Appendix 4)

3. Recommendations

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

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

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

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

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

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

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

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

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

February 2013

APPENDIX 1

ALLTRIALS PETITION AND SUPPORTING ORGANISATIONS

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

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

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

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

Signed by:

Adelaide Health Technology Assessment
American Institute for Technology and Science Education
American Medical Students Association
Association of Clinical Biochemistry
Association of Medical Research Charities
Association of Research Ethics Committee
Belgian Centre for Evidence Based Medicine
Berne Declaration
BioMed Central
British Library
British Nutrition Foundation
British Society for the Study of Vulval Diseases
Canadian HIV Trials Network
Centre for Reviews and Dissemination
Centre for Statistics in Medicine
Centre of Evidence Based Dermatology
Chemist and Druggist Magazine
Clinical Pharmacist
Cochrane Collaboration
Committee On Publication Ethics
Critical Appraisal Skills Programme
Critical Appraisal Skills Programme International Network
Critical Appraisal Skills Programme Mexico
Critical Appraisal Skills Programme Spain
Dianthus Medical Ltd
Doctors Reform Society
Drugs and Therapeutics Bulletin
eCancer
Equator Network
European Continuing Medical Education Forum
European Federation of Clinical Chemistry and Laboratory Medicine
Faculty of Intensive Care Medicine
German Network for Evidence Based Medicine
GIMBE Foundation
GSK
HealthWatch
Health Action International Europe
Health Action International Global
Healthy Skepticism UK
Hospital Pediátrico de Sinaloa
IBase
Idea Pharma
Ideal
Institute for Quality and Efficiency in Healthcare
Intensive Care Foundation
Intensive Care Society
International Coalition for treatment preparedness in Eastern Europe and Central Asia
International Institute for Advanced Studies of Psychotherapy and Applied Mental Health
International Society for Evidence Based Health Care
Journal of Cognitive and Behavioural Psychotherapies
Journal of Kathmandu Medical College
London School of Hygiene and Tropical Medicine
Medical Research Council
Medicos Sin Marca
Medsin
Minervation
National Physicians Alliance
Netherlands Epidemiological Society
NICE
No Grazie Pago Io
North London Humanist Group
Norwegian Knowledge Centre for Health Services
Nottingham Clinical Trials Unit
Open
Open Knowledge Foundation
Open Science Federation
Oxford Vaccine Group
Pharmaceutical Journal
Pharmaware
PLOS
Royal Statistical Society
Russian Society for Evidence Based Medicine
Sabre Research UK
Tatarstan Medical Student Association
Thinkwell
Trip
UK Clinical Pharmacy Association
UK Dermatology Clinical Trials Unit
UK Research Integrity Office
Wellcome Trust
World Association of Medical Editors

PATIENT GROUPS

AIDS Coalition to Unleash Power Paris
AIDS Treatment Activists Coalition
Action for M.E
Age UK
Action for Sick Children
Afiya Trust
Alkaptonuria Society
Alpha 1 Awareness UK
Alzheimer's Society
Anticoagulation Europe
Arrhythmia Alliance
Arthritis Care
Asthma UK
Beat
Bliss
Blood Pressure Association
Bowel Cancer UK
Brain and Spine Foundation UK
Breakthrough Breast Cancer
Brains Trust
Brain Tumour Charity
Bristol and Avon Chinese Women's Group
British Dupuytren's Society
British Heart Foundation
British Obesity Surgery Patients
British Lung Foundation
Cancer Research UK
Cardiomyopathy Association
Changing Faces
Crohn's and Colitis UK
Counsel and Care
CSV
Cystic Fibrosis Unite
Diabetes UK
Different Strokes
Disabilities Trust
Ear Foundation
Encaphalitis Society
Epilepsy Action
Epilepsy Society
Genetic Alliance UK
ITP Support Association
INPUT
James Whale Fund for Kidney Cancer
June Hancock Mesothelioma Research Fund
Kidney Alliance
La Leche League GB
Leukaemia CARE
Lyme Disease Action
Lymphoedema Support Network
Lymphoma Association
Macmillan Cancer Care
Macular Society
MDS UK Patient Support Group
Migraine Trust
Motor Neurone Disease Association
Mouth Cancer Foundation
Muscular Dystrophy Campaign
Myeloma UK
MS Society
National Ankylosing Spondylitis Trust
National Association of Deafened People
National Childbirth Trust
National Osteoporosis Society
National Rheumatoid Arthritis Society
National Voices
NI Chest & Stroke
Norwegian Cancer Society
No Panic
Pain UK
Parkinsons UK
Patients Association
Patients Involved in NICE
Pelvic Pain Support Network
The Pernicious Anaemia Society
The Pituitary Foundation
Prostate Cancer UK
Positive People Armenian Network
PXE (PiXiE) Europe
Rare Disease UK
Rethink
Royal National Institute of Blind People
Royal Society for Public Health NGO forum
Sarcoma UK
Sarcoma Patients Euronet
Scleroderma Society
STARS
Stichting Tekenbeetziekten
Stonewall
Target Ovarian Cancer
Terrence Higgins Trust
Treatment Action Campaign
Treatment Action Group
Together for short lives
Urostomy Association
Well UK
Young Minds

APPENDIX 2

LETTER TO THE EMA FROM CLINICAL TRIAL PARTICIPANTS

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

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

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

This means that the findings generated from our participation and that of thousands of others in the trials may not be available to the doctors, researchers and regulators who work on particular diseases or make

decisions about their treatments. It also means that some of the trials could be repeated in the future, when they do not need to be.

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

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

Name	*Description of trial*	*Date of trial*
Iain Chalmers	Oxford Vaccine Group's test of a new pneumococcal vaccine	c 2008–2009
Richard Stephens	Trial of drug combinations in Lymphoma	1998
	Trial of PET scans as prognostic indicators in Lymphoma	1999
	Trial of blood anti-clotting agents in heart patients	2007
Lauren Gore	Test of potential new eczema treatment on healthy volunteers.	August 2012
Richard Smith	The trial was a double blind randomised controlled crossover trial to see if the polypill would reduce blood pressure and blood lipids. It lasted about six months. The polypill did reduce blood pressure and blood lipids.	2011
Sarah Stevens	Undertaken at St Barts Hospital for GW Pharma to assess affectiveness of Sativex for muscle spasms (trial was double blind). Condition: multiple sclerosis.	c 2006
Dominic Haigh	TREK Study Description: Participants from several different European countries were given either a patch immunising against traveller's diarrhoea or an inert placebo and dispatched to countries where they might become infected with the disease. I went to stay in Guatemala City for a week.	January 2010
Nancy Kane	Beta SNP trial; study examining whether differences in genes affect how vitamin A is used by the body.	October 2012
Ralph Cantellow	The PACE trial was a randomised controlled trial of treatments for chronic fatigue syndrome also known as myalgic encephalomyelitis or myalgic encephalopathy. The trial, which involved 640 patients, was conducted in six hospitals in England and Scotland and compared the safety and effectiveness of four treatments: Specialist medical care (SMC) alone, and SMC plus one of the following therapies: adaptive pacing therapy cognitive behaviour therapy, and graded exercise therapy.	March 2003–January 2010
Mei Lee	Phase 3 trials of Novartis's vaccine against neisseria meningitides B	2009–2010
Sam L	It was an antidepressant study looking at drugs affecting glutamate (ketamine and a new drug AZD6765)	February–March 2010
Charis Croft	The trial is between subcutaneous injections and sublingual tablets as a mechanism for administering immunotherapy to relieve hay fever arising from grass pollen.	September 2012–ongoing
Joanne Evans	Trialling BMN110 enzyme replacement therapy for Morquio's Syndrome (Mucopolysaccharide IVA)	August 2011–January 2012
Phil Booth	Trials of anti-epilepsy and pre-diabetes treatments	1988–1989
Rachel Pearce	My trial is called SOFT (Suppression of Ovarian Function Trial) and is a 3-arm trial testing the benefits and disadvantages of: Tamoxifen, Tamoxifen + ovarian function suppression, Exemestane + ovarian function suppression in premenopausal women with hormone receptor positive breast cancer.	2003–2011
Thomas Edward Hills	Single dose of a generic formulation of bicalutamide (anti-androgen for prostate Ca)—pharmacokinetic study.	c June 2005
Helen Ap-Rhisiart, on behalf of my daughter, now aged twelve	Oxford Vaccine Group (Univ Oxford) meningitis C/ pneumonia combination vaccine study.	2000–2003
Brian Sewell	Trial for a drug to control high blood pressure	1992

Name	*Description of trial*	*Date of trial*
Caroline Richmond	Vitamin C and the common cold	c 1984
	MRSA in denture wearers	c 2005
	COPD	2013
Ryan Geleit	First into human trial to assess a new compound for the treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome	February 2012
Richard Desmond	Concorde trial into the efficacy of treating infection with HIV	1989–1991
A'Llyn Ettien	Yearlong trial of drug combination to prevent bone thinning	2005–2006
	3-month trial of birth control patch comparing usability to ring	Summer 2007
James Warwick	Final phase RCT for a new meningitis vaccine developed by Novartis	October 2010–2011
Kevin Nickells	Clinical trial into the affects of alcohol on nicotine dependency	August 2010
Michael Wing	The trial was based at St Georges Hospital, Tooting, London. I underwent 12 hours of an intravenous infusion of deuterium enriched water preceded and followed by a blood test. I also had a repeat blood test 2 weeks later. The study was to identify the maturation rate of lymphocytes.	2001–2002
Khairil Hodgson	FluCamp a phase 2a, randomized, double blind, placebo controlled study to Investigate the effects of VX 787 administered to adult volunteers experimentally inoculated with live influenza virus	August 2012
Dr Aaron Dale	Addenbrookes Hospital for GSK for a painkiller	2007
	FluCamp to test an influenza vaccine	December 2012
Kathryn M Burke	The trial was Fingolimod (Gilenya) phase III. The trial was to test safety and efficacy.	2007
Harry Purser	Trial for a peripheral system analgesic.	April 2010
Gillian Lang	During pregnancy my blood pressure was monitored and samples of placenta taken following the birth	March–November 2002
Hester Tidcombe on behalf of my son	Post-authorisation safety study of GSK's pandemic flu vaccine in the UK	November 2009
Chris Murphy	For diabetes	Autumn 2004
Hilary Foote	The effects of natural bran food supplement on irritable bowel syndrome	c 1994
Michael James Fox	The trial was for the norovirus	Summer 2009
Darran Shepherd	Malaria vaccination trial	January 2010
Christopher John Parlett	I participated in three medical trials at the Department of Respiratory Medicine and Allergy, King's College, London All trials were said to be for the testing of alternatives to current corticosteroid treatments for asthma.	2001–2003
Denise Syndercombe Court	Tamoxifen +/- (Zoladex) randomised- given for 2 years duration. Given for stage I/II breast cancer in premenopausal women (including those with positive nodes)	1994–1995
Linton Lahoud	Effects of light on sleep	c 2011
Dr Gemma Bashevoy	A trial for a malaria vaccine	January 2011–September 2012
Dr Maxim Bashevoy	A clinical trial for hay fever using a drug called rPhleum (immunotherapy)	c 2009
Nicola Branch	Trialling a gel to help reduce the spread of HIV amongst heterosexuals in Africa	2004–2005
Leslie Rose	Phase I study of effects of a beta-blocker on muscle blood flow. Injection of a radio-label into anterior tibialis muscle, followed by treadmill exercise testing.	1980
	Acupuncture in neck pain. The purpose of the study was to evaluate electro-acupuncture in comparison with normal acupuncture and placebo electro-acupuncture.	2004
Adam Barnett		
Katherine Hunter		
Kieran Crean		

Name	*Description of trial*	*Date of trial*
Matthew Valentine, MD	Roche trial of Oseltamivir (Tamiflu). Recruited with active flu-like illness as a medical student at Oregon Health and Sciences University in Portland, Oregon, USA for randomized controlled trial of Oseltamivir	Autumn 1998
Amanda Burls	The intervention was probiotic yoghurt versus non-probiotic yoghurt for IBS	2005
Martin Law	Get Moving run by the MRC epidemiology Unit	October 2012–February 2013
Carmen Major		
Cynthia Dumas	Phase III randomized study of treatment based on response to induction chemotherapy in patients with higher risk childhood acute lymphocytic leukaemia	April 2001- July 2003
Amanda Kerr on behalf of my son	Infant vaccine trial	2008–2009
Sean Murphy	Interaction of an antihistamine and an anti-fungal drug	1993
	Interaction of a 5HT1A receptor agonist and alcohol.	1993
Veronica Klein		
Michelle Fraser		

APPENDIX 3

NOTE ON PUBLICATION OF THE OPEN LETTER FROM CLINICAL TRIAL PARTICIPANTS TO THE EMA

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

> **Tracey Brown, Director, Sense About Science:** "There is no good reason to delay full reporting of clinical trial results. It will have huge benefits for patients, health workers, doctors, pharmacists, regulators and researchers. It will benefit treatment decisions now and research into future options and it will encourage more people to be involved in clinical trials. The first tranche of results from our international patient survey[1] is showing that 78% of people who have a medical condition (and 72% of all respondents) say they would be more likely to take part in a clinical trial if they were assured the results would be published."
>
> **Ben Goldacre, doctor and author of Bad Pharma:** "We need the results of clinical trials to make informed decisions about which treatment is best, but half of all such trials have never been published, which exaggerates and distorts the evidence we have. This is medicine's dirty secret, so it's great to see patients speaking out, and so many eminent organisations joining up, to finally fix this problem. Withholding trial results is indefensible, and should never have been allowed to happen."
>
> **Carl Heneghan, Director, Centre for Evidence-Based Medicine, University of Oxford**: "When trial results aren't published substantial harms occur, patients die and ineffective treatments waste precious health care resources. Is this what patients expect when they sign up to consent in a trial? Certainly not."

Comments from signatories to the letter:

> **Richard Stephens who signed the letter as a cancer patient and clinical trial participant**: "The Department of Health report, *Innovation Health and Wealth*, sets out a goal for the NHS that every willing patient should be able to take part in research. In our publication, *Action On Access*, we call for research to be embedded in clinical practice. Already 20% of cancer patients take part in clinical trials as part of their treatment options. The *National Cancer Patient Experience Survey* (2012) showed that two thirds of cancer patients are open to being asked about participating in research, and of those who are approached, 95% are glad to have been asked, even if they choose not to participate themselves."
>
> > "Patients who choose to take part in clinical trials believe that by doing so, we are helping other patients in the future. We expect that the results of trials will be made freely available to researchers, clinicians and administrators, in order to deliver better treatments, better services, and better outcomes for patients. So all clinical trials should be on a central accessible register, and all trials should be reporting their results, even if they do not change clinical practice. I believe it is immoral to recruit patients to clinical trials and then not report or share the results. We participate in order to increase knowledge and to help others. We do not expect the knowledge to be kept secret or the help for others to be denied."

Iain Chalmers took part in the Oxford Vaccine Group's test of a new pneumococcal vaccine, c2008–2009: "I agreed to a request from the Oxford Vaccine Group to participate in a trial of a new formulation of pneumococcal vaccine. I asked to be sent the results of the study, and was assured that I would be; but I wasn't. When I received a request to volunteer for another vaccine trial being done by the same group I rang to ask to see a copy of the protocol, but I was informed it was confidential. I declined that invitation, and will do so for any future invitations I receive from this research group until this problem is solved."

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

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

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

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

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

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

Nicola Branch took part in a trial on a gel to help reduce the spread of HIV amongst heterosexuals in Africa, 2004–2005: "I think trials are very important to enable scientists to develop drugs and other medical products to improve treatments for people around the world. Trials are not risk averse and people who participate in them should be given full access to information about what's involved hence the need for a register. And one where we as 'guinea pigs' can leave uncensored comments about our experiences."

APPENDIX 4

SURVEY OF PATIENT GROUPS AND MEMBERS ON CLINICAL TRIAL PARTICIPATION CIRCULATED BY PATIENTVIEW TO THEIR INTERNATIONAL NETWORK OF PATIENT GROUPS. RESPONSES COLLECTED BETWEEN 16/1/13–18/1/13

TOTAL NUMBER OF RESPONDENTS: 195

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

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

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

Yes	55	**28.35%**
No	139	**71.65%**

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

Yes	29	**14.87%**
No	166	**85.13%**

Number of Respondents who are Patients: 111

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

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

Have you ever participated in a clinical trial?

Yes	39	**35.14%**
No	72	**64.86%**

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

Yes	15	**13.51%**
No	96	**86.49%**

Further written evidence submitted by Sense About Science

THE RATIONALE FOR FULL AND RETROSPECTIVE CLINICAL TRIAL REGISTRATION AND REPORTING, FOR RESEARCH, INNOVATION AND EFFECTIVE HEALTHCARE

1. Improving Treatments for Patients

— With full information about effects and side effects, a better risk/benefit calculation can be made by doctors, and individual patients. Healthcare commissioners and regulators can make a more accurate cost/benefit assessment which ensures that the treatments available are those that are truly the most effective.

— With full information we would expect greater confidence all round that full information about risks and benefit is known. It will also reduce the potential for flipping between "wonder drug" and "killer drug" stories and their associated effects among patients of overoptimistic demand (people failing to report side effects, taking others' medication etc) and suddenly stopping medication.

2. Improving Research and Innovation

— The effect of publishing the full reports of clinical trials will be to provide a richer research base for both industry and academia. This means greater potential for collaboration and interdisciplinary work, more productive research, and potential value from unused Intellectual Property.

— Scientific research is self correcting. Research advances through critical analysis and review, which are essential for identifying flaws in study design, statistical errors, missed observations of both benefits and risks and the best ways to conduct further research. This process has been necessarily partial because of partial publication. Full publication will restore this vital part of the research checking process, which is the basis of greater confidence in research findings whatever their provenance.

— Efficient reviews. A large proportion of the time currently spent on systematic reviews by organisations such as the Cochrane Collaboration, publicly funded clinical researchers as well as by companies seeking information about proposed applications, goes on attempting to discover what has been done already rather than on assessing it.

3. Avoiding the Waste of Pointless Repetition of Studies

— Clinical trials cost; UK cost per patient of a clinical trial: 9, 758 euros.[13]

— Contractors report that they are asked to conduct research for one entity and do so even though they have already conducted similar work under a confidential contract for another entity and know that the intervention does or doesn't work.[14]

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

[14] Chalmers, I (2006). TGN1412 and the Lancet's solicitation of reports of phase 1 trials. Lancet; 368, 2206–2207

— Conducting clinical trials on patients to discover something that has already been discovered, however unintentionally on the part of those conducting the research, is misleading participants, wasting resources on expensive and unnecessary research and putting patients at unnecessary risk.[15] For years, patients who had suffered a heart attack were prescribed drugs to prevent heart rhythm abnormalities. By 1990, it was estimated they were killing between 40,000 and 70,000 per year. Had a trial conducted in 1980 suggesting the drugs were lethal been published, this catastrophe might have been prevented.[16]

THE "BURDEN"

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

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

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

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

March 2013

Appendix 1

STATEMENTS BY THE PHARMACEUTICAL INDUSTRY ON CLINICAL TRIAL TRANSPARENCY

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

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

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

4. ABPI statement on new clinical trial transparency measures.

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

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

18 January 2013

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

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

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

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

In addition, the release of commercially confidential information could undermine investment in the research and development of future medicines. This is ultimately not in the interests of patients, who would not be well served by dis-incentivising research based biopharmaceutical companies and commercial organisations from

[15] McGauran *et al* (2010). Trials; doi:10.1186/1745–6215–11–37 Table S2: Examples of reporting bias in the medical literature
[16] Moore, T (1995). Deadly medicine. New York; Simon and Schuster

other life sciences sectors from making the substantial investments and shouldering the risks that are necessary to develop new innovative medicines.

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

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

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

Response from AllTrials to ABPI statement

23 January 2013

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

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

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

Reply from ABPI to AllTrials statement

24 January 2013

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

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

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

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

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

AllTrials asks ABPI some direct questions

29 January 2013

Thank you for your reply. Your comments are still on the subject of individual patient data. As our last response to you emphasised, AllTrials is calling for publication of clinical study reports for all treatments in use internationally. Your position on this is as unclear as it was before you issued two replies. There is no need

to wait until 2014 for an EMA consultation on individual patient data to end before answering our questions on clinical study reports. Attempts to address transparency have suffered from these kinds of irrelevant delays since first being raised in the 1980s, which suggests that industry does have objections to the publication of clinical study reports for treatments in current use. If so, these should be set out clearly and specifically. Perhaps a better way to clarify it would be for ABPI to answer directly the following questions:

> Do you agree that clinical study reports etc should be provided for all treatments in current use (and that where these are not available an account given of this by the Principal Investigator)?
>
> Do you agree that this information should be publicly available?
>
> Will you amend your 2012 guidelines to this effect?
>
> Will you support an amendment to the EU Clinical Trials Regulation to this effect?
>
> What, if any, are your commercial objections to publication of clinical study reports?
>
> What kind of situations do you think would justify withholding clinical study reports?

ABPI answers

1 February 2013

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

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

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

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

Do you agree that this information should be publicly available?

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

Will you amend your 2012 guidelines to this effect?

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

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

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

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

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

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

In general patient identifiable data and commercially sensitive information can be redacted rather than the study report withheld. However, when a company does not have a patent for a product it relies on "regulatory data protection" to get the necessary market exclusivity to recoup the investment made. This period is 10 years in the EU. If the entire file with all studies is released other companies can get approvals around the world.

Anyone can get an approval as long as they submit the necessary data—regulators do not require that they generate the data themselves. This would not support the development of innovative medicines.

Appendix 2

GSK STATEMENT ANNOUNCING SUPPORT FOR THE ALLTRIALS CAMPAIGN AND OUR RESPONSE

GSK announces support for AllTrials campaign for clinical data transparency

5 February 2013

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

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

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

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

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

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

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

6 February 2013

> "GSK signing up to the campaign is very important, of course, because they are a large global player in clinical research so they have a lot of potentially useful information to share, but also because they are finding a way to put in place the infrastructure needed to do this. Which makes it realistic for others and sets a new standard. Their position will also make it possible to have a sensible discussion with regulators about the way that they make information available. And it will hopefully put a stop to the ridiculous obfuscation and foot-dragging that have characterised reactions to AllTrials from some other parts of industry.
>
> I think that since AllTrials went live it is becoming clearer by the day that this is moving in only one direction, as thousands of doctors, researchers and members of the public signed up and organisations have joined them. It's clear from their statement about the practical details that GSK has been thinking about this issue for some time; AllTrials' influence has really been in getting the decisive public commitment.
>
> GSK say in their statement that they owe it to patients who have taken part in their trials. I think that is very, very true. Companies who have yet to take this seriously should ask themselves where they want to be on that duty a few years from now."

Appendix 3

ROCHE STATEMENT ON NEW PROCESS FOR ACCESSING CLINICAL TRIAL DATA AND OUR RESPONSE

26th February 2013

Roche launches new process for accessing clinical trial data

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

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

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

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

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

Amendments to the Roche data transparency policy include:

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

Access to CSRs: Roche supports the release of full CSRs, summaries and safety updates for its approved medicines by the EMA. In line with relevant country or regional laws, this information will be edited in consultation with Roche to ensure patient confidentiality and to protect legitimate commercial interests, including intellectual property rights. Roche will provide any CSR on request that cannot be obtained from the EMA for third party researchers with this specific process coming into effect by April 2013. This will enable access to all Roche CSRs for researchers.

Tamiflu (oseltamivir) data

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

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

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

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

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

26 February 2013

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

Appendix 4

ABPI STATEMENT ON NEW CLINICAL TRIAL TRANSPARENCY MEASURES

27 February 2013

ABPI announces new clinical trial transparency measures

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

These measures support the current requirement in the ABPI Code of Practice which stipulates that current and future trials must be registered within 21 days of enrolling the first patient, and results must be published within one year of marketing authorisation or one year from completion for marketed products.[17]

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

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

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

> "The ABPI is a strong advocate for transparency in clinical trial data and so I am pleased to announce the introduction of new measures which will encourage greater compliance. Hiring a third party provider to ensure that companies fulfil their obligations in the ABPI Code of Practice to register clinical trials and publish summary results, is a significant step and illustrates how seriously we take this issue."
>
> "On the issue of historical data we also want to ensure that we work collaboratively with all health stakeholders and international colleagues to agree a pragmatic approach which is in the interests of patients while protecting the commercial research model. The pharmaceutical industry has always accepted that making data more transparent is important, but all parties must now decide together how exactly this is achieved."

Supplementary written evidence submitted by Sense About Science

This note is in response to a request from the Chair to Tracey Brown during the oral evidence session on 15th May to clarify differences between oral and written evidence.

Since we submitted written evidence in February 2013 detailed discussions on what is needed for clinical trial transparency have been going on among organisations who have signed up to the AllTrials campaign. These include a Wellcome Trust hosted workshop; a discussion of clinical trial transparency in non-commercial trials hosted by Glenis Willmott MEP; and a series of stakeholder meetings run by the Health Research Authority as it drafted the Transparent research report as well as informal discussions among members of the campaign.

There are four levels of information sharing:

1. Study registration.
2. Summary results.

[17] Specifically, these measures support the current ABPI Code of Practice which requires in Clause 21.3 disclosure of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature. The joint positions include requirements that current and future trials must be registered within 21 days of enrolling the first patient, and results must be published within one year of marketing authorisation or one year from completion for marketed products.

3. Clinical study reports and their equivalents.
4. Full individual patient data from clinical trials.

The information may be contained in a range of formats depending on who is generating it and for what purpose. The reality is that there is overlap between levels 2–4. Clinical study reports may contain appendices and sections with some individual patient data for example.

Level 1 is a register of all trials that have taken place. Registration of a trial includes setting out what the trial is for and the protocol. Trial registration is often ignored.

Level 2, summary results, sets out what was found and what was done in summary form. This could be in a journal paper or the results section of a register, for example www.clinicaltrials.gov. These are still not universally shared. Summary results should include trial information such as participant details and recruitment; protocol; primary and secondary endpoints measured; details of statistical analysis; and so on.

The AllTrials campaign is calling for all clinical trials to be registered and the results reported therefore we are calling for levels 1 and 2. It is already a requirement under the Helsinki convention for anyone who conducts a trial to register it and publish a summary of what was found. This obligation is routinely not met.

Level 3 clinical study reports (CSRs) are generally produced for licensing and regulatory purposes. We recommend that anyone who produces or has produced an ICH-GCP standard CSR should have to share this, redacted to the same extent as the European Medicines Agency redacts the CRS it releases. If the trial sponsor is not planning to go down the regulatory route then they should not have to produce a full ICH-GCP standard CSR.

May 2013

Tracey Brown asked me to email you about things she didn't get a chance to mention at her oral evidence session on 15 June and I thought that these are be points it would be useful to put to the Ministers on Monday.

Will the UK Government make a clear statement in support of transparency along the lines of what was voted for in Brussels yesterday? A committee of MEPs voted yesterday to add amendments to the clinical trials regulation in support of transparency and data sharing including a requirement that all clinical trials conducted in the EU must be registered and summary results reported within a year of their end with financial penalties for those who don't comply, and a statement that information in a clinical study report should not be considered commercially confidential. Will the UK Government support that?

Will the UK Government intervene to support the European Medicines Agency's policy of openness? The EMA has had injunctions issued against it in two court cases brought by pharmaceutical companies AbbVie and InterMune who challenged the Agency's policy to give access to CSRs it holds. It has been left to the Agency's lawyers to decide that the EMA should not release anymore CSRs it holds from any trials. The EMA has told us that organisations including the European consumer group BEUC and the European ombudsman and several member states have applied to intervene in the court cases in support of the EMA. Will the UK government?

30 May 2013

Written evidence submitted from the Editor and Deputy Editor of the British Medical Journal

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

Here is our response to the Committee's questions:

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

1(i) Not entirely, although the revisions will greatly improve the regulation of clinical trials (Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. European Commission. 2012).[18] We agree with Dr Peter Gøtzsche of the Nordic Cochrane Centre, whose recent peer reviewed article in the BMJ said "The new European Union Regulation on Clinical Trials ... aims to simplify the process for application and approval of trials and make it more uniform throughout the EU. It also includes a lighter regime for low risk trials—for example, those using licensed medicines. It contains much good sense, but there are still deficiencies in providing access to information and protection to patients."[19]

[18] http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal

[19] Gøtzsche P C. Deficiencies in proposed new EU regulation of clinical trials. BMJ 2013;345:e8522 doi: http://dx.doi.org/10.1136/bmj.e8522

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

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

1(iii) The BMJ endorses Gøtzsche's evidence based recommendations for further amendments to the proposed EU Regulation on Clinical Trials, as summarised here:[20]

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

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

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

2(i) The HRA is relatively new and is finding its feet. However, we are encouraged by the statements made by Janet Wisely of the HRA's National Research Ethics Service about how she plans to monitor compliance on registration and reporting of the results of trials.[21]

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

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

3(i) What evidence is there? As the BMJ states hidden clinical trial data are systematically undermining doctors' ability to prescribe treatment with confidence.[22] Many widely used drugs across all fields of medicine have been represented as safer and more effective than they are, endangering people's lives and wasting public money. It is well documented that researchers and companies often withhold clinical trial results from doctors and patients. Half of all trials are never published (Song F, Parekh S, Hooper L, Loke Y K, Ryder J, Sutton A J, Hing C, Kwok , Pang C, Harvey I. Dissemination and publication of research findings: an updated review of related biases. Health Technology Assessment 2010; Vol. 14: No. 8). In many cases—such as those of oseltamivir (Tamiflu) and rimonabant—direct requests for information about trials have been refused. The US government's requirements for timely reporting of clinical trial results at its register have been ignored by the authors and sponsors of four out of five eligible trials.[23] Numerous studies have shown strong evidence of publication bias, where unfavourable or negative results are not published.

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

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

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

This is not simply an academic matter. Missing data about the risks of medical interventions in trials can skew the evidence base (body of knowledge) that drives medical practice and policy, can harm patients by exposing them to drugs and devices that may be less effective and safe than we currently think, and can lead to futile priority setting and expense by health systems. Moreover, researchers or others who deliberately conceal trial results have breached their ethical duty to trial participants. A BMJ editorial last year said: "Concealment of data should be regarded as the serious ethical breach that it is, and clinical researchers who fail to disclose data should be subject to disciplinary action by professional organisations. This may achieve quicker results than legislation in individual countries, although this is also desirable."[24]

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

3(iv) One key example is that of the neuraminidase inhibitors oseltamivir (Tamiflu). In 2009, during the swine flu (H1N1 influenza) pandemic, the BMJ published an updated Cochrane review on neuraminidase inhibitors in adults with influenza (Jefferson T, Jones M, Doshi P, Del Mar C. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. BMJ 2009;339:b5106).The review and a linked investigation undertaken jointly by the BMJ and Channel 4 News cast doubt not only on the effectiveness and safety of oseltamivir (Tamiflu), but also on the system by which drugs are evaluated, regulated, and promoted, which is giving doctors, patients, and the public a false sense of security (Cohen D. Complications: tracking down the data on oseltamivir. BMJ2009;339:b5387). Jefferson *et*

[21] http://www.bmj.com/content/345/bmj.e7304/rr/613776
[22] http://www.bmj.com/open-data
[23] http://www.clinicaltrials.gov/
[24] Lehman R, Loder E. Missing clinical trial data. BMJ 2013;343:d8158 doi: http://dx.doi.org/10.1136/bmj.d8158

al, concluded that they had no confidence in claims that oseltamivir reduces the risk of complications and hospital admission in people with influenza. In doing so they reached a similar conclusion to the Food and Drug Administration in the United States and a health technology assessment performed for the UK's National Institute for Health and Clinical Excellence (NICE), which both found insufficient evidence on complications. Yet claims that oseltamivir reduces complications have been a key justification for promoting the drug's widespread use. Governments around the world have spent billions of pounds on a drug that the scientific community has found itself unable to judge. The BMJ has made public key correspondence with the drug's manufacturer, Roche, and with international organisations that recommend or regulate drugs.[25] Currently:

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

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

4(i) Governments: Voluntary agreements have been shown to be ineffective in achieving transparency on the results of clinical trials. Calls for greater transparency have been made for the past 20 years with little visible effect. Where individuals have made important strides, as for example 20 years ago at GSK, a change of leadership at an organisation can reverse any temporary gains. Legislation is the only certain way of mandating publication of trial results. This should be enacted at the European level. Experience at the FDA shows that legislation is not in itself enough. Rigorous audit and sanctions for trialists and sponsors who fail to comply will also be needed.

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

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

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

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

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

4(vii) Campaigners: The BMJ is a joint founder of the current AllTrials campaign.[26] The campaign calls on governments, regulators, and research bodies to ensure that the aims and methodological details of all clinical trials, past and present, are publicly registered and their full methods and results reported. By 19

[25] http://www.bmj.com/tamiflu
[26] http://www.alltrials.net/

February 2013, just over a month after launch, the AllTrials online petition had more than 30,800 signatories including many international organisations concerned with medical research and treatments and more than 80 patients' organisations.[27]

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

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

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

Submitted by:

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

Dr Fiona Godlee has been Editor in Chief of the BMJ since 2005. She qualified as a doctor in 1985, trained as a general physician in Cambridge and London, and is a Fellow of the Royal College of Physicians. Since joining the BMJ (British Medical Journal) in 1990 she has written on a broad range of issues, including the impact of environmental degradation on health, the future of the World Health Organisation, the ethics of academic publication, the problems of editorial peer review, and the need for greater openness in medicine and research. In 1994 she spent a year at Harvard University as a Harkness Fellow evaluating efforts to bridge the gap between medical research and practice. On returning to the UK, she led the development of BMJ Clinical Evidence, which evaluates the best available evidence on the benefits and harms of treatments and is now provided worldwide to over a million clinicians in nine languages. In 2000 she moved to Current Science Group to establish the open access online publisher BioMed Central as Editorial Director for Medicine. In 2003 she returned to the BMJ Group to head up its new Knowledge division. She has served as President of the World Association of Medical Editors (WAME) and Chair of the Committee on Publication Ethics (COPE) and is co-editor of Peer Review in Health Sciences.

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

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

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

February 2013

[27] http://www.alltrials.net/supporters/

Written evidence submitted by the Academy of Medical Sciences

SUMMARY

— Clinical and health research is vital to the health and wealth of the UK. The Academy of Medical Sciences has been at the forefront of calls to strengthen the support, regulation and governance of this area.

— The Clinical Trials Regulation is an improvement to the Clinical Trials Directive, although outstanding concerns remain. A major barrier to clinical research in the UK is the delay and duplication in obtaining research permissions from each NHS Trust involved in a trial.

— The Academy welcomes the establishment of the Health Research Authority. Although too early to judge success, we are supportive of the HRA's initial plans.

— We welcome the debate on, and efforts to improve, clinical trials transparency. Inevitably the results of clinical and health research are influenced by chance and other sources of variation. If only research with extreme, or favourable, results reach the public domain, a biased conclusion regarding interventions will be drawn. Transparency about the methods and results of all research is the best guard against such biased conclusions.

— The existence, methods and results of clinical and health research involving patients whether positive or negative should be made swiftly available for patient, social and scientific benefit. Many mechanisms to promote transparency, including registries, are best tackled in a coordinated and consistent manner at an international level involving the wide range of stakeholders.

— The Academy believes that the results of clinical and health research should be placed in the public domain through peer-reviewed media such as scientific journals. Validated research summary reports and clinical study reports without patient level data should be posted on a public web-based database, after regulatory approval and where relevant. Further consideration should be given to mechanisms to allow access to more detailed data given the need to protect patient confidentiality and to ensure that data is intelligible, assessable, reliable and usable.

— The Academy would be happy to give oral evidence to the Committee.

INTRODUCTION

1. The independent Academy of Medical Sciences promotes advances in medical sciences and campaigns to ensure that these are converted into health benefits for society. Our elected Fellowship includes some of the UK's foremost experts in medical science some of whom provided advice on this response (see Appendix 1).

2. Clinical and health research improves the health and wealth of the UK.[28] Recently the UK's strength in health research has been threatened. Our global market share of patients in pharmaceutical trials has fallen from 6% to 1.4% and there has been a similar experience in academic trials.[29] Central to this decline has been inappropriate regulation that prevents many clinical trials starting quickly and causes unnecessary costs. A proportionate and appropriate system of regulation and governance is essential to improving patient and public health by supporting UK clinical trials and attracting clinical trials from abroad. The Academy has played a leading role in streamlining research regulation through our reports and consultation responses.[30]

THE CLINICAL TRIALS REGULATION (CTR) AND THE MAIN BARRIERS TO CONDUCTING CLINICAL TRIALS IN THE UK AND EU

Strengths of the proposals for the CTR

3. The Academy believes that the proposals for the new CTR are an improvement on the current Clinical Trials Directive (CTD). Particularly welcome are:

— Greater proportionality and greater scope for risk adaptation.

— Formal introduction of co-sponsorship to help partnerships between universities and hospitals, between EU countries, and within the UK.

— Ambitious timelines to speed up the approval process that should be retained and encompass UK-specific assessments.

— The use of a Regulation rather than a Directive that will reduce differing national interpretations.

— Single submission via an EU portal that will facilitate multi-national trials.

4. We welcome the Medicine and Healthcare products Regulatory Agency's (MHRA's) engagement with stakeholders and the establishment of a reference group on which the Academy is represented.

[28] Academy of Medical Sciences (2010). *Biomedical research—platform for increasing health and wealth in the UK* http://www.acmedsci.ac.uk/p48prid84.html

[29] NESTA (2011) *All together now: improving cross sector collaboration in the UK biomedical industry.* http://www.nesta.org.uk/library/documents/Report_67_Biomed_web.pdf

[30] Further information is available from: http://www.acmedsci.ac.uk/index.php?pid=47&prid=88 http://www.acmedsci.ac.uk/index.php?pid=47&prid=118 http://www.acmedsci.ac.uk/p100puid220.html http://www.acmedsci.ac.uk/p100puid176.html and http://www.acmedsci.ac.uk/p100puid256.html

5. Despite the above improvements a number of concerns remain:

Clarity and clarification

6. Five areas that require further clarification are:

- How European institutions will create and implement the IT systems required to establish a single application portal and single application dossier. The publication of plans to deliver these systems would provide reassurance.
- How personal data will be protected in the new public database and EU portal; and further information on the timing of the disclosure of such data.
- Whether the US National Institute of Health (NIH) register clinicaltrials.gov will be included among the World Health Organization (WHO) accredited primary registries on which clinical trials are required to be registered. Clinicaltrials.gov is the main registry used worldwide by sponsors but is not listed as a WHO primary register. We are keen to avoid unnecessary proliferation of registries, see paragraphs 36 and 44.
- An assessment of whether allowing sponsors to choose the National Competent Authority (NCA) to which they apply means that stronger NCAs, such as the MHRA, receive many more applications. This could lead to excessive burdens on some NCAs that might impede their ability to regulate research nationally.
- That insurance arrangements for multi-state trials (while welcome) will not be too cumbersome.

7. Although legally and internally consistent, some of the definitions in the CTR are different from those used by scientists. For example, the term "low intervention trials" is not widely recognised scientifically. Confusion around terminology may lead to conservative interpretations of the CTR that could inhibit research. We therefore strongly encourage clearer guidance and communication with stakeholders and an accepted glossary of terms.

Proportionality and established treatments

8. While measures to increase the proportionality of the CTR are welcome, we are keen that this will be reflected in practice. For example, measures to introduce proportionality should ensure that trials testing established treatments with good safety profiles for novel uses should be considered low risk if the case for this is made. Where the safety profile of an intervention is very well known, adding burdens of monitoring does not benefit public health.

Increased focus on trial conduct and oversight

9. The CTR should focus more on the facilitation of overall trial conduct and oversight, including:

- More efficient approaches to trial conduct and monitoring in non-commercial settings that focus less on approaches derived from the International Conference on Harmonisation guidelines for Good Clinical Practice ("ICH-GCP"). The interpretation and implementation of ICH-GCP in practice has focused on specific aspects of its wording rather than its overarching intended objectives. This has resulted in rigid procedures that have been unduly prescriptive and obstructive. We welcome the HRA's recent statement that GCP training for researchers should be appropriate and proportionate to the type of research undertaken.[31]
- The requirement for prior interview for consent that would pose a challenge to some studies where the only contact with participants is by post or electronically. A solution might be to change the text from "prior interview" to "prior dialogue" as this would allow greater choice in the method of communication.

Streamlined research generates results and data for further analysis

10. As discussed in a later section, we welcome the debate on, and efforts to improve, transparency around the existence, methods and results of clinical trials. It is important that the resource requirements of any new systems in the CTR to improve transparency are proportionate.

Additional barriers to clinical trials

11. The Academy's 2011 report on the regulation and governance of health research identified delay and duplication inherent in obtaining research permissions from each NHS Trust involved in a trial as the greatest barrier to health research in England (see also paragraph 16).[32] Largely this barrier remains, however, we welcome recent steps by the National Institute for Health Research (NIHR) to incentivise reductions in the

[31] HRA (2012). Training requirements for researchers. http://www.hra.nhs.uk/hra-news-and-announcements/training-requirements-for-researchers/

[32] Academy of Medical Sciences (2011). *A new pathway for the regulation and governance of health research.* http://www.acmedsci.ac.uk/p47prid88.html

timeline. This includes the introduction of benchmarks for the approval and delivery of clinical trials linked to NIHR's funding of NHS organisations.

12. Other barriers include a lack of understanding about the complex regulatory and governance framework and lack of a "one stop shop" or single portal for application and guidance.

The Role of the Health Research Authority (HRA) in Relation to Clinical Trials

13. We support the initial plans of the HRA, although it is too early to judge whether it will be successful. The HRA is currently being established in primary legislation in the draft Care and Support Bill that has provided an opportunity to see how the HRA compares to our vision of a single regulator.[33,34]

14. We welcome the HRA's focus on promoting the co-ordination and standardisation of the regulation and governance pathway of health and social care research in the UK and, as with the CTR, in seeking to ensure that such regulation is proportionate. This should help to reduce bureaucracy.

15. The HRA and MHRA have recently announced that they will not continue development and launch of e-submissions at this time, which formed a core component of the HRA's vision of a single unified process for applications.[35] This vision was also articulated in our report. Further clarity is needed on how the HRA will coordinate the activities of review bodies, with sufficient authority and levers to provide a single route for all approvals and permissions.

16. Our vision for the HRA included the creation of a National Research Governance Service within the HRA that would support NHS Trusts and researchers by undertaking all **study-wide NHS research governance checks** just once. This was to ensure common standards and a consistent interpretation of the requirements. This recommendation was not taken forward and the Care and Support Bill does not explicitly mention the HRA's role in facilitating NHS research governance.[36]

17. We welcomed the HRA's recent announcement of a feasibility project that will explore whether it can support NHS Trusts by providing them with a simplified, streamlined and quality assured assessment for all research in the NHS.[37] If successfully implemented, this would address the major barrier to research identified in our report.

18. The HRA should have a role in **developing metrics and indicators** for the regulation and governance pathway as a whole, and monitoring these to ensure that improvements are being made. It will be important to ensure that the timeline is not being manipulated (eg by "stopping the clock" more often) and that the introduction of new benchmarks for Trust's research performance does not discourage them from undertaking certain types of research (eg more complex trials or those on rare diseases). Reliable metrics are extremely important both in terms of providing feedback on the success of initiatives but also in communicating success internationally to companies and researchers seeking locations for clinical trials.

19. In fulfilling its roles and functions, the HRA needs to **engage with a wide range of stakeholders**. The HRA has been in dialogue with patients and their representatives since its establishment and we welcome the establishment of the HRA's Collaboration and Development group, on which the Academy is represented.

20. The recent transfer of responsibility for the research use of **confidential patient information** to the HRA provides a good opportunity to reduce complexity in this area of regulation and governance that has led to conflicting interpretations of it by researchers, Trusts, patients and other stakeholders.

21. We welcome the HRA's announcement of plans to follow up the commitments that researchers make to research ethics committees relating to the registration and **publication of trials** (see below).

Clinical Trials Transparency and Disclosure of Data

The importance of openness

22. The Academy strongly supports efforts to increase transparency around the existence, methods and results of clinical and health research. There is an excellent case for making the findings of research that involves patients available, because:

- Individuals often contribute to research for altruistic reasons and expect the results to be accessible by all.
- Failure to do so may mean that patients are unnecessarily put at risk in studies when results are already known.

[33] Academy of Medical Sciences (2013). *Response to the joint scrutiny committee inquiry on the draft care and support bill.* http://www.acmedsci.ac.uk/p100puid264.html

[34] Academy of Medical Sciences (2012). *Response to the Department of Health consultation on the draft Care and Support Bill.* http://www.acmedsci.ac.uk/p100puid256.html

[35] Further information on this topic can be found at: http://www.hra.nhs.uk/hra-news-and-announcements/future-of-iras/

[36] Academy of Medical Sciences (2013). *Response to the joint scrutiny committee inquiry into the draft Care and Support Bill.* http://www.acmedsci.ac.uk/p100puid264.html

[37] HRA (2012). *HRA given go-ahead for feasibility study: HRA assessment for approval of research in the NHS.* http://www.hra.nhs.uk/hra-news-and-announcements/hra-given-go-ahead-for-feasibility-study-hra-assessment-for-approval-of-research-in-the-nhs/

— Under-reporting of research can lead to avoidable harm to patients and can waste limited healthcare and research resources.[38]

— Greater access to appropriately controlled data for valid scientific inquiry offers significant scientific benefits and helps ensure scientific validity, particularly for large studies where replication is more difficult.

— It helps to develop hypotheses and improves trust in clinical and health research.

23. Transparency is an important issue for all those who conduct, fund, participate in and utilise the results of clinical trials in industry, academia, the NHS, charities and elsewhere. Solutions will therefore require the involvement of a wide range of stakeholders. The increasing number of cross-sectoral collaborations between these groups means that responsibility for transparency is increasingly shared.

24. Single studies rarely provide definitive evidence to answer important clinical questions.[39] Looking at a series of studies helps to address the effect of chance and other variation in results. It is usually necessary to combine results of studies to obtain reliable answers. If only research with extreme, or favourable, results reach the public domain, a biased conclusion regarding interventions will be drawn. Transparency about the methods and results of all research is the best guard against such biased conclusions.

25. Much discussion about transparency to date has focused on clinical trials to develop pharmaceuticals. However, clinical and health research is also conducted in other areas where transparency is important such as those involving surgery; devices; psychological, educational or organisational interventions; and understanding the causes and mechanisms of disease.

26. The wide range of types and size of clinical and health research means that developing appropriate and generalisable guidelines and regulations will require considerable thought.

Clarity around transparency

27. Transparency in clinical and health research can cover many different sorts of activity some of which are undertaken at the present time and some of which are not, these include:

— public registration of trials, including their methods and protocols;

— public posting of progress of trials and summaries of results;

— publication of trials in journals;

— public posting of clinical study reports; and

— providing access to individual patient level data.

28. Clarity about which aspect of transparency is being discussed is important as each presents different issues. It can also be helpful to distinguish between data, information and knowledge as is described in the recent Royal Society report "*Science as an open enterprise*".[40]

29. Currently sponsors of clinical trials involving pharmaceuticals in the UK are expected to provide the MHRA and the relevant ethics committee with a report 12 months from the end of a trial.[41] Funders often require the wider publication of trial results as part of their terms and conditions, and research ethics committees ask how researchers plan to publish their data and results before approving projects. Many medical journals endorse the CONSORT statement that encourages transparent reporting and describes ways in which this can be achieved.[42] The European Union Drug Regulatory Authorities Clinical Trials (EudraCT) database of all recent EU clinical trials of investigational medicinal products does not collect the results of clinical trials and there is no single place where clinical trial results are published. However, we are aware of plans to collect results and make them publicly available.[43]

Models for transparency

30. The Academy believes that clinical and health research should be presented in a form that is intelligible, assessable, reliable and usable.[44] The gold standard mechanism to achieve this goal is peer-review, which often takes place through journals. The results of clinical and health research should be placed in the public domain through peer-reviewed media such as scientific journals. Validated research summary reports and clinical study reports with patient level data removed should be posted on a public web-based database, after regulatory approval and where relevant. The resource implications of this proposal are considered in paragraph 33. Further consideration should be given to mechanisms to allow access to more detailed data to address issues such as patient confidentiality, particularly in small studies or for studies of rare diseases, and to ensure that data is intelligible, assessable, reliable and usable.

[38] Chalmers I & Glasziou P (2009). Avoidable waste in the production and reporting of research evidence. Lancet 374, 86–89.

[39] Ioannidis JPA (2005). *Why Most Published Research Findings Are False*. PLoS Med **2(8)**, e124. doi:10.1371/journal.pmed.0020124

[40] Royal Society (2012). *Science as an open enterprise.* http://royalsociety.org/policy/projects/science-public-enterprise/report/

[41] Association of Medical Research Charities (2013). *Registration of clinical trials*. http://www.amrc.org.uk/home/

[42] Further information about CONSORT is available from: http://www.consort-statement.org/

[43] Association of Medical Research Charities (2013). *Registration of clinical trials*. http://www.amrc.org.uk/home/

[44] Royal Society (2012). *Science as an open enterprise.* http://royalsociety.org/policy/projects/science-public-enterprise/report/

31. Careful consideration should be given to the storage and management of more detailed data from clinical and health research to tackle issues such as applications from countries that do not have as robust regulatory and governance frameworks as the UK.

32. As discussed in paragraph 24, when important issues of treatment or outcome effect have been studied in several trials, reliable systematic reviews are the preferred method for presenting summary data. Results from a single study may be misleading. This should be considered when thinking about open access to data of individual trials.

Resource requirements

33. Any initiatives or regulation around transparency should be proportionate and seek to maximise net patient and social benefit. One important consideration is the resources required to achieve the different sorts of transparency discussed earlier. This will need to be balanced against the benefits that greater transparency could bring, for example by preventing research in areas shown to be unproductive. Thought needs to be given about who should pay for creating and maintaining the requisite infrastructure and for any costs to researchers for uploading data. This is a particular challenge for non-commercial funders that often have less resources than industry. The issue of resource requirements for transparency are considered in the Royal Society's report on "*Science as an open enterprise*".[45]

Roles and responsibilities for clinical trials transparency

34. GSK recently committed to a system of transparency where clinical study reports, are made publicly available through their clinical trials register.[46] In a separate initiative, GSK will also provide a system to request access to anonymised patient level data for further research, with requests reviewed by a committee that GSK has announced will be composed of independent experts. GSK hopes that this will be a first step to a model whereby researchers can access trial data from multiple sponsors from industry, academia and charities to conduct further research. This initiative has been welcomed by many, although some have argued that responsibility for providing access to clinical trial data that has been authorised for marketing should be independent from the sponsor. The regulator might fulfil this role as this might engender greater public trust, although EU/UK regulators might not have the full dataset and this would only cover trials submitted as part of the market authorisation dossier. Furthermore, the UK regulator is only responsible for some types of medical intervention that might be the subject of clinical trials, such as drugs, but not others, such as changes to health education.

35. The European Medicines Agency's (EMA's) commitment to make clinical research data more available is welcome and we are keen to participate in the multi-stakeholder conversation about how this might be achieved.[47] We also welcome the BMJ's recent commitment to only publish trials where there is access to data on "reasonable request".[48]

The role of registries

36. Appropriately accredited public trials registries offer a useful mechanism for monitoring and encouraging transparency around clinical trials. There is a legal responsibility for all trials applying for clinical trial authorisation to be registered on the private EudraCT clinical trials database.[49] We are aware of a number of different registries in different countries and different fields so are keen that these initiatives are coordinated and coalesce to avoid duplication of effort and to increase simplicity (see paragraphs 6 and 44).[50] Patient friendly information should be available for all trials that are open for recruitment as is currently the case for all cancer trials recruiting people in the UK through Cancer Help, and via the UK Clinical Trials Gateway.[51,52] Evaluative tools such the services provided by the company Research Fish and Research Council UK's Gateway to Research can also help monitoring.[53,54]

Negative results

37. While the results of much clinical and health research with positive results are currently available, the results of much research with negative results or research that closed early are not.[55] This has major

[45] Royal Society (2012). *Science as an open enterprise.* http://royalsociety.org/policy/projects/science-public-enterprise/report/

[46] Further information on GSK's announcement can be found at: http://www.gsk.com/media/press-releases/2013/GSK-announces-support-forAll-Trials-campaign-for-clinical-data-transparency.html

[47] EMA (2012). *Access to clinical trials data and transparency workshop report.* EMA, London.

[48] Godlee F (2012). Clinical trial data for all drugs in current use. http://www.bmj.com/content/345/bmj.e7304

[49] Association of Medical Research Charities (2013). *Registration of clinical trials.* http://www.amrc.org.uk/home/

[50] Examples of registers include: Clinical Trials.gov: http://www.clinicaltrials.gov/ EudraCT: https://eudract.ema.europa.eu/ and Current Controlled Trials: http://www.controlled-trials.com/

[51] Further information is available from: http://www.cancerresearchuk.org/cancer-help/

[52] Further information on the UK Clinical Trials Gateway is available from: http://www.ukctg.nihr.ac.uk/default.aspx

[53] Further information on Research Fish is available from: https://www.researchfish.com/

[54] Further information on RCUK's Gateway to Research is available from: http://www.rcuk.ac.uk/research/Pages/gtr.aspx

[55] For the purposes of this response the term "negative results" refer to those studies where there is no evidence of the intended effect but are nevertheless scientifically useful.

consequences for unbiased assessment of the totality of evidence on a clinical or public health question. Non-publication can result from factors such as:

— competition for space in journals; and

— lack of capacity or willingness by researchers in industry and public service to spend time preparing such research for publication.

38. The Academy is a supporter of Universities UK's Research Integrity Concordat that commits to ensuring rigour, transparency and open communication when reporting research data, including the sharing of negative results.[56] The publication of negative results can help:

— ensure that time and resources are not spent pursuing unproductive areas of research; and

— identify alternative uses for drugs or highlight patterns in responders and non-responders that might indicate sub-populations where the drug might be more effective.

39. A non-journal based portal with peer-review to ensure quality might help facilitate the publication of negative results. We are also aware of, and welcome, journals dedicated to publication of negative findings, such as the Journal of Negative Results in Biomedicine, or commitments by journals to publish negative results, such as from PLOS ONE.[57,58]

Ensuring timely publication

40. Publication of clinical and health research in journals should happen as swiftly as practically possible once studies are complete and the results validated. However, we believe that setting a single deadline for publication of results of all clinical and health research in journals would not be helpful because:

— Researchers require time to rigorously analyse their findings.

— A single study may generate several papers that each may take time to prepare.

— Different journals have different times for peer-review.

— A paper may not be accepted by the first journal to which it is submitted.

— Researchers should have some initial degree of exclusivity to results otherwise there will be significantly less incentive to conduct important studies as the reward will be accrued by others.

41. As discussed in the previous section, we welcome the HRA's plans for research ethics committees to follow up publication plans with researchers and hope these will be proportionate.

42. We are aware of calls for retrospective registration and reporting of the full methods and results of all trials.[59] Resources could be a key constraint in this regard and are considered further in paragraph 32. The Academy believes that the focus should be on developing mechanisms to ensure rapid prospective posting and publication of current and future trials as this can be practically addressed more swiftly.

Tackling clinical trials transparency and data disclosure internationally

43. As a result of globalisation clinical trials are increasingly conducted both within and between more countries than ever before. Transparency therefore needs to be tackled at the international level. This would:

— improve coordination;

— increase simplicity;

— reduce duplication; and

— help ensure that the UK remains scientifically competitive.

44. We are aware that national and regional regulators, such as the MHRA and US Food and Drugs Administration (FDA), are already in regular communication on the matter of clinical trials transparency. Moreover, the Academy is discussing joint work on this issue with the US Institute of Medicine (IOM), our sister academy in the USA. There is an opportunity for the UK to take an important role in this area through engagement with others at an international, particularly European, level. However, we also understand that there are already many international measures that require the registration of trials and posting of results. It is therefore important to avoid duplication, particularly with UK specific solutions, see paragraphs 6 and 36.

This response was prepared by Christian Markus Hüber (Medical Science Policy Intern) and Laurie Smith (Medical Science Policy Manager). A draft was considered by Council and the final draft was signed off on their behalf by the President.

[56] Universities UK *et al* (2012). The concordat to strengthen research integrity. http://www.hefce.ac.uk/whatwedo/rsrch/rinfrastruct/concordat/

[57] Further information is available from: http://www.jnrbm.com/

[58] Further details of PLOS ONE is available from: http://www.plosone.org/

[59] Further information is available from: http://www.alltrials.net/

Declaration of Interests

Many of the Academy's Fellows and experts who contributed to this response are involved directly or indirectly with academia, life sciences industries and the NHS. Further details are available upon request.

The Academy of Medical Sciences

The Academy of Medical Sciences promotes advances in medical science and campaigns to ensure these are converted into healthcare benefits for society. Our Fellows are the UK's leading medical scientists from hospitals and general practice, academia, industry and the public service.

The Academy seeks to play a pivotal role in determining the future of medical science in the UK, and the benefits that society will enjoy in years to come. We champion the UK's strengths in medical science, promote careers and capacity building, encourage the implementation of new ideas and solutions—often through novel partnerships—and help to remove barriers to progress.

February 2013

Appendix 1

CONTRIBUTING EXPERTS

We are grateful to the following individuals for their inputs into this response:

- Professor Sir John Bell FRS HonFREng FMedSci, Regius Professor of Medicine, University of Oxford.
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- Professor Sir Alasdair Breckenridge CBE FRSE FMedSci.
- Professor Sir Iain Chalmers FMedSci, Co-ordinator, James Lind Initiative.
- Professor Sir Rory Collins FMedSci, Professor of Medicine and Epidemiology and Co-Director of the University of Oxford's Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), University of Oxford.
- Professor Janet Darbyshire CBE FMedSci, Emeritus Professor of Epidemiology, University College London.
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- Professor Stephen Evans, London School of Hygiene and Tropical Medicine.
- Professor Lesley Fallowfield FMedSci, Director of SHORE-C and Professor of Psycho-Oncology, University of Sussex.
- Professor Gary Ford, Jacobson Chair of Clinical Pharmacology, Newcastle University.
- Professor Michael Parker, Professor of Bioethics and Director of the Ethox Centre, University of Oxford.
- Professor Sir Michael Rawlins FMedSci, Chairman, National Institute of Clinical and Health Excellence.
- Professor Genevra Richardson CBE FBA, The Dickson Pool School of Law, King's College London.
- Professor Caroline Savage FMedSci, Vice-President and Head of the Experimental Medicine Unit, GSK.
- Professor Robert Souhami CBE FMedSci, Foreign Secretary, Academy of Medical Sciences.
- Professor Sir John Tooke PMedSci, President, Academy of Medical Sciences.
- Professor Patrick Vallance FMedSci, President, Pharmaceuticals R&D, GSK.
- Professor Sir Simon Wessely FMedSci, Vice-Dean and Professor of Psychological Medicine, Institute of Psychiatry, King's College London.

Written evidence submitted by Roche

1. *Introduction*

1.1 Roche is a leading manufacturer of innovative medicines in a range of therapeutic areas, including cancer, rheumatoid arthritis and infectious diseases, such as hepatitis C and influenza. Many of our treatments have changed the standard of care in difficult to treat conditions, extending and enhancing the lives of millions of patients.

1.2 We operate two autonomous research units, as well as 150 research partnerships all over the world, to foster diversity of research and translate science into medicines. In 2012 we invested nearly 8.5 billion Swiss Francs in research and we now have 72 new molecular entities in clinical development. Last year there were 2,280 clinical trials in operation involving Roche medicines, involving 35,720 healthcare centres across the world. In total, 326,642 patients were involved in these trials.

1.3 Clinical trials are critical for determining the safety and efficacy of new medicines and the clinical value of diagnostic tests. They also provide important information on the cost effectiveness of a treatment or diagnostic test and how a treatment improves quality of life. This information is shared with regulatory authorities and payers in order to gain marketing approval and, ultimately, reimbursement. Roche also publishes the results of our clinical trials through numerous channels, such as peer reviewed journals and online, as we recognise that healthcare professionals, researchers, patients and the public are also interested in knowing about potential new therapies.

1.4 We therefore have a good deal of expertise in the issues associated with conducting clinical research, including ways in which data and findings can be published. As such, we welcome the Committee's inquiry and this opportunity to contribute evidence. As previously outlined in a letter to the Chair, we would be happy to provide oral evidence. Given the recent publicity relating to our decision around disclosure of patient-level clinical trials data on oseltamivir (Tamiflu), we have also extended an offer to the Committee to share in detail Roche's data on this medicine, as well as to answer any specific questions the Committee may have regarding the data and to discuss the reasons for the approach we have taken.

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

2.1 As one of Europe's largest sponsors of clinical trials we see the changes being introduced through the new clinical trials regulation as positive. A single portal for a submission, with harmonised decision-making is a major simplification and the proposal to introduce a timeline for the ethical committee approvals is most welcome.

2.2 The main barriers to conducting clinical trials in the UK are not the same as across the EU. From our experience in conducting significant numbers of trials throughout Europe it is clear that the clinical trials environment varies hugely between EU member states. Different countries interpret and implement international regulatory requirements in different ways, some with a much less legalistic approach than others. The UK has taken an excessively rigid approach, and conducting clinical trials in the UK is becoming increasingly costly and bureaucratic.

2.3 Barriers and enablers to conducting clinical trials in the UK can be categorised as follows:

— **Cost**: the cost of conducting clinical trials in the UK can be much higher than in other countries. The reason for this appears to be twofold. The UK has a particularly intensive approach to implementing regulation compared to other countries, and the NHS does not see clinical trials as part of its day to day operation, but instead a marginal activity which is priced accordingly. Whilst standard of care interventions (such as the set number of scans a patient with a particular condition would normally receive) are charged at standard tariff prices, any additional activity required to meet rigorous clinical trial standards tends to be priced much higher—often up to 100% higher.

— **Time**: establishing trials in the UK and getting levels of recruitment up is often a more time consuming process than in other EU countries. Local inconsistency is the main source of delay. Each NHS organisation interprets compliance with regulations differently, and this manifests itself in wide variations in local processes to gain approval. Furthermore, the wide-ranging remits of organisations such as ethics committees can lead to many clinical trials being delayed. There is a perception that the relatively slow recruitment to trials in the UK is indicative of how trials are perceived in the NHS, and this makes arguing the case for centring trials in the UK a more challenging one.

— **Quality**: whilst the quality assurance standards in the UK are extremely comprehensive, the NHS is inherently a risk-averse environment and this filters down to individual provider units such as radiotherapy and pharmacy. This risk-aversion will increasingly have an opportunity cost in terms of being able to host the most advanced, high quality clinical trials. In addition, because the NHS is often a "low and slow" adopter of innovative new medicines, the standard of care is not always of the same quality as in comparable EU health economies, and this makes the NHS a less attractive clinical trials environment. Similarly, there is lower motivation to undertake trials in an environment where the population is unlikely to benefit from the outcome.

These views are not held by Roche alone, and were confirmed by the Academy of Medical Sciences in their 2011 report *A new pathway for the regulation and governance of health research*, which concluded that "a complex and bureaucratic regulatory environment is stifling health research in the UK."

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

3.1 The HRA has been given a significant and appropriate role in protecting patients and the public in health research. However, there are concerns that it has not been given the resources to achieve its role effectively and therefore may be at risk of either scaling back its remit or slowing down its work and the research and trials that rely upon it. The HRA should be appropriately funded or given access to alternative funding routes.

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

4.1 Bringing a new medicine to market involves conducting extensive clinical trials, often involving thousands of patients. Pharmaceutical companies therefore generate a huge amount of data on a particular medicine. This data is gathered to meet the requirements of Health Authorities globally, including the provision of patient-level data to the US Food and Drug Administration (FDA), and support them in reviewing the safety and clinical effectiveness of a medicine. Much of these data will also be reported in peer-reviewed publications and many manufacturers publish summaries of all their trials, both positive and negative.

Publication of trial data

4.2 Since 2007 Roche, along with other pharmaceutical companies, committed to disclose protocols of trials and the subsequent trial results in a public registry (ClinicalTrials.gov) and have published these on our own registry (Roche-trials.com) since 2005. In addition, any medicine for which marketing authorisation is sought is subject to full disclosure to regulatory authorities around the world, in accordance with local regulations. The vast majority of health authorities request specific and extensive information on a medicine when reviewing its approval. The EMA bases its approval of a medicinal product or a new indication on clinical study reports and can also include full data listings of anonymised data and aggregated summary data. Once approved, safety data is supplied on an ongoing basis and in annual summary reports (periodic safety update reports). The US FDA also receives the same data as the EU, but in addition receives the electronic patient-level data files, which it has the capacity to reanalyse.

Tamiflu

4.3 Roche has recently been the subject of concerns raised about transparency of clinical trial data following our inability to agree with a group of academic reviewers the release of patient-level clinical trials data on Tamiflu. We stand behind the robustness and integrity of our data supporting the efficacy and safety of Tamiflu, which has been shared with all relevant regulators according to their requirements and guidelines. When considering the case of Tamiflu, it is important to note that:

— Tamiflu has been reviewed and approved by regulatory authorities in over 80 countries and over 95 million patients have received this medicine since it was first licensed and made available.

— Clinical trials and real-life experience from flu pandemics have shown that Tamiflu is effective in reducing the severity and duration of symptoms in those infected with flu and decreases the risk of developing the illness if there is contact with an infected individual.

— Various analyses of Tamiflu show a benefit in reducing the duration of symptoms, fever and time to return to normal sleep, health and activities, as well as reducing occurrence of lower respiratory tract complications (including bronchitis) requiring antibiotics in infected patients.

— Tamiflu is recommended as a flu antiviral by public health bodies worldwide including the US Centers for Disease Control & Prevention (CDC), the European Centre for Disease Prevention & Control (ECDC) and the World Health Organization (WHO).

— The US FDA has just extended the license for Tamiflu, now approving its use in children two weeks of age and over. This recent approval further substantiates the safety and efficacy of Tamiflu.

4.4 Over the past 15 years Roche has been the sponsor for 81 trials into Tamiflu. Of these, one was terminated before any patients were enrolled, and 74 are now completed. Of the 74 completed Roche sponsored trials, 71 (or 96%) are in the public domain either as a primary publication or secondary publication or on Rochetrials.com. Arrangements are underway for the three sponsored studies which are completed but not yet in the public domain to be posted.

4.5 Roche receives requests regarding the release of clinical trial data from academic and independent institutions worldwide. As part of this, we request an analysis plan and signed confidentiality agreement. Given some of the complexities inherent in making available patient-level data which was generated many years ago on the basis of consent forms which were never intended to enable such access. In addition the merit for any request should be assessed to ensure that the pre-planned analyses are based on clearly defined scientific and clinically relevant questions.

4.6 In relation to an initial request from the Cochrane Acute Respiratory Infections Group for access to data on Tamiflu, we provided large volumes of information in 2009 which we believe was sufficient to answer their questions. The reviewers questioned and did not sign a confidentiality agreement. In circumstances where concerns are raised about the detail of a confidentiality agreement, it is usual to investigate alternative arrangements that protect patient confidentiality, commercial sensitivities and provides them with the reassurance they require. In this instance, no such discussion was had, a mutually acceptable position was not reached and therefore patient-level data was not released to the review group.

4.7 Roche has subsequently shared Tamiflu data with another academic group under the scope of an agreement covering these necessary issues.

4.8 We maintain the highest ethical standards in the conduct of our clinical trials and transparency of our interactions with all external parties for all of our medicines. We recognise, however, that following the debate about Tamiflu, there is legitimate policy interest in our data. Roche is confident in the data supporting Tamiflu and that and this is why we have offered to share in detail Roche's data on Tamiflu with the Committee, answer any specific questions it may have and discuss the reasons for the approach we have taken.

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

5.1 The medicines licensing system was established for very good reasons. It is vital that new treatments are assessed to ensure that the benefits to patients outweigh any potential risks for the condition in question. For this reason, and in order to maintain public confidence in medicines, the relevant licensing authorities need to remain the gatekeeper for drug approval. Provision and review of patient data should be conducted in a legitimate, independent and appropriately resourced environment to avoid the risk of offering false hope to patients or, conversely, giving rise to public health scares and consequences. Accordingly, the complete liberalisation of access to all data on medicines, without sensible assessment mechanisms in place, would not be without difficulties. Inappropriate data analysis and interpretation can lead to inconsistent messages regarding a given medicine and how best it should be used, and there are examples, such as the scares around MMR vaccines, that highlight the importance of handling data in a responsible way.

5.2 That being said, there is also legitimate interest from healthcare professionals, researchers, patients and the public into issues relating to the efficacy and safety of medicines, as well as in understanding what new therapies are in development. Accordingly, we recognise the importance of transparency and we support efforts to enable greater transparency of clinical trial results. We also understand that pharmaceutical companies have an important role to play in both facilitating and supporting this.

Role of pharmaceutical companies in supporting transparency

5.3 It is important to note that the demands for access to patient level data have increased significantly in recent years. Unfortunately many of the trials of today's medicines were conducted many years ago when the imperative for transparency of patient-level data was somewhat less. As a result, they were not always conducted in a way which supported easy disclosure of patient-level data and, in some circumstances, the wording of the patient consent forms makes this very difficult to achieve. We believe this challenge lies at the heart of much of the current debate about the transparency of trials and is something that we are committed to addressing.

5.4 We support moves to increase transparency and believe that these are best achieved on a cross-industry basis. In doing so, it will be important to consider how transparency can be improved:

- Prospectively, ensuring that clinical trial conduct and patient consent is delivered in such a way which maximises the transparency about medicines of the future.
- Retrospectively, ensuring that more data are available on medicines in standard use today for which trials were conducted some years ago.

5.5 This is why we, along with many other stakeholders, offer our support to the European Medicines Agency (EMA) in their commitment to the proactive publication of data from all clinical trials supporting the authorisation of medicines. As a member of one of the EMA advisory groups, we are keen to see the results of deliberations on how proactive publication of data can be taken forward. We understand that a draft EMA policy will be available in June 2013 allowing us to prepare for the full implementation of the policy which will come into place on 1 January 2014.

5.6 Additionally, Roche is developing a policy and a process to make patient level data available: either to external researchers where a confidentiality agreement is in place and the scientific validity of the request has been reviewed by an independent third party, or for the scientifically valid request to be analysed by a third party. It is our intention to make this raw data available, but to be rigorous about the scientific standards of the requests and the quality of the analysis. We believe this to be in the interest of the trial participants and the patients and prescribers who use the medications.

Additional scrutiny of Tamiflu

5.7 In the specific case of Tamiflu, and in addition to the offer we have extended to the Committee to review and discuss the data we hold, we are taking steps to facilitate further independent review. We are seeking to establish an independent multi-party advisory board comprising expert clinicians, academics and independent institutions to look at the data on Tamiflu, identify any medically relevant unanswered questions and agree on a statistical analysis plan to address these. Given the Cochrane Acute Respiratory Infections Group's interest in Tamiflu, it may wish to be part of this advisory board.

Real world data

5.8 Roche believes, when considering the overall benefit-risk of a medicine, all available data should be taken into account. This includes both formal clinical trial data as well as "real world" data generated during a medicine's routine clinical usage. This approach offers important insights into how a medicine can be used to maximum effect, supports evaluations of cost effectiveness, informs pricing and enables authorities to ensure that treatment is delivering value for money.

5.9 There are already good examples of real world surveillance of drug efficacy, although more can and should be done. For example, the WHO conducts detailed global surveillance of influenza resistance to anti-virals such as Tamiflu. Clinical trials and reallife experience from the 2009–10 flu pandemic have shown that Tamiflu is effective in reducing the severity and duration of symptoms in those infected with flu and decreases the risk of developing the illness if there is contact with an infected individual.

5.10 Equally, efforts are underway to collect data on the usage, efficacy and safety of anticancer medicines in routine NHS use, through the development of the Systemic Anti-Cancer Therapy (SACT) database, which will collect data on every cancer patient who receives cancer drug therapy in England.

5.11 We would welcome the Committee's recommendations on how best the collection and use of real world data can be improved as part of wider efforts to enhance the transparency of data.

6. *Lessons from other countries*

6.1 We provide health authorities around the world with all the data they request when assessing the benefits and risks of our medicines. However different national licensing authorities take different approaches to assessing and analysing data.

The vast majority of health authorities request specific and extensive information on a medicine when considering whether to grant marketing authorisation. The U.S. Food & Drug Administration (FDA) specifically requests anonymised patient datasets whereas the European Medicines Agency (EMA) does not. The FDA re-programmes and reanalyses the data in order to verify the analysis performed by the company. The EMA rather interrogates the sponsor and requests additional analysis or reanalysis from the company directly.

6.2 There are benefits and drawbacks to both this approach and that adopted by the EMA. The more information that is supplied to regulatory bodies, then the greater the cost that is associated with analysis and securing approval. Ultimately these costs will need to be borne either directly (through additional funding to the regulator) or indirectly (through higher medicines costs) by the taxpayer. It is for policymakers to determine whether or not this additional cost is justified by the benefits which may be incurred by submission of anonymised patient-level data.

February 2013

Written evidence submitted by Cancer Research UK

1. Every year around 300,000 people are diagnosed with cancer in the UK. Every year more than 150,000 people die from cancer. Cancer Research UK is the world's leading cancer charity dedicated to saving lives through research. Together with our partners and supporters, Cancer Research UK's vision is to bring forward the day when all cancers are cured. We support research into all aspects of cancer through the work of over 4,000 scientists, doctors and nurses. In 2011–12 we spent £332 million on research. The charity's pioneering work has been at the heart of the progress that has already seen survival rates in the UK double in the last forty years. We receive no government funding for our research.

2. Clinical studies are a vital strand of Cancer Research UK's work. We currently fund over 240 clinical studies in the UK; we are one of the largest funders of clinical research in Europe. In 2011–12 over 37,000 patients were recruited to clinical studies supported by CR-UK.

3. We take an active role in ensuring that regulation associated with clinical studies is proportionate to allow patients to participate and benefit from the results of clinical research. In February 2012, together with the Academy of Medical Sciences, Cancer Research UK brought together leading figures from across the health research sector to discuss the evolving regulatory landscape.[60] Cancer Research UK has also led on coordinating a joint statement between academia and industry funders, to feed into revisions of the EU Clinical Trials Directive.[61]
We would therefore welcome the opportunity to provide oral evidence to the committee.

4. Our key points are as follows:

- Cancer Research UK is broadly supportive of the draft Clinical Trials Regulation and its aim to streamline and improve the regulatory environment for clinical trials of investigational medicinal products in Europe. We believe that certain aspects of the Regulation could be amended further in order to facilitate more effective running of clinical trials in the UK.
- The Health Research Authority (HRA) has already demonstrated its competency in regulating research in the UK.
- We are particularly pleased that in October 2012 the HRA announced a feasibility study to test the potential benefits of a simplified and streamlined HRA assessment for all research in the NHS. This feasibility study should remain a key focus for the HRA; as if successful it has the potential to significantly impact on the environment for running clinical studies in the UK.
- Cancer Research UK welcomes efforts to improve transparency in research, especially the publication of negative data from all sectors involved in clinical studies.
- We would support requirements for clinical studies to publish a summary of results within a year of when the data analysis is planned in their protocol, which is submitted as part of regulatory approval to set up a clinical study.
- Solutions to increase transparency must be discussed and implemented at an international level in order to improve standards for studies and benefit patients. Without these key discussions it is possible that isolated action at either the UK or EU level could further discourage clinical research from being located in Europe, without benefitting patients.

5. We have used the term "clinical study" when referring to all types of clinical research undertaken in the NHS in the UK. We use the specific term "clinical trial" only when referring to a clinical trial of an investigational medicinal product, which is currently regulated by the EU Clinical Trials Directive. The term "clinical study" encompasses "clinical trials" and studies that look at other interventions such as screening tests.

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

6. The EU Clinical Trials Directive 2001/20/EC (CTD) set out with the best intentions to improve the regulatory landscape and the quality and safety of clinical trials in Europe. However it has been widely acknowledged that the CTD contributed to the general trend of decreasing numbers of clinical trials in Europe without providing benefits to patients. Research conducted by Cancer Research UK at the time found that "CTD had resulted in a doubling of the cost of running non-commercial cancer clinical trials in the UK and a delay to the start of trials" and research staff were "unable or unwilling to open trials in non-UK centres because of the different interpretation of the CTD by member states."[62] Between 2003 (before the Directive) and 2007 (following the Directive) the time to set up a study increased by 65% and the staffing requirements increased by 75%.[63]

[60] Transforming the regulation and governance of health research in the UK. May 2012 http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@pol/documents/publication/cr_087422.pdf

[61] Proposal for an EU Regulation on Clinical Trials: A joint statement from non-commercial and commercial organisations, December 2012 http://prodcontrib.cancerresearchuk.org/cancer-info/publicpolicy/workingwithgovernment/europe/ssLINK/CTRJOINTSTATEMENT

[62] The impact of the "Clinical Trials" directive on the cost and conduct of the non-commercial cancer trials in the UK. J Hearn and R Sullivan. European Journal of Cancer 43 (2007), 8–13.

[63] Ibid.

7. Cancer Research UK is broadly supportive of the draft Regulation adopted by the European Commission on 17 July 2012 and its aim to streamline and improve the regulatory environment for clinical trials of investigational medicinal products in Europe. Our assessment, based on consultation with our Clinical Trials Units, is as follows:

- As a Regulation this legislation will achieve one of its principal goals in harmonising the regulatory system for clinical trials across Europe.
- Provisions in the new Regulation will improve the set-up and running of multinational trials. For example, we welcome the legislation's explicit introduction of co-sponsorship as well as the introduction of a single European portal for applications.
- Cancer Research UK's main concern is how the Regulation will work in practice. Provisions such as the single European application portal have the potential to greatly improve the application process and reduce trial set up times. However we have requested more information to understand how the new systems will operate and what resources will be allocated to it.
- The Regulation has introduced a risk adapted approach. This means that the levels of monitoring and reporting associated with a trial are adapted to suit the level of knowledge about a medicine being tested. For example a medicine which is being used within its existing licence would require less assessment compared to a treatment being tried in man for the first time. We welcome this move as the previous "one size fits all" approach meant that many academic trials had a disproportionate amount of regulatory oversight.
- Set timelines for approvals have been introduced into the legislation which should provide a marked improvement over existing timelines in some member states.

8. We believe that certain aspects of the Regulation could be amended further in order to facilitate more effective running of clinical trials in the UK. We have put forward amendments to both the Medicines and Healthcare products Regulatory Agency (MHRA) and the European Parliament:

- To reduce the scope of the Regulation so that clinical studies which require additional monitoring but do not pose any additional risk to patients would not fall under the Regulation.
- To ensure that only medicinal products fall within the scope of the Regulation.
- To clarify language around the terms clinical trial and clinical study.
- To risk adapt the safety reporting mechanisms so that treatments which are considered standard use do not need to submit particular types of safety reporting.

9. The purpose of these amendments is to improve the efficiency of running clinical trials and make the Regulation proportionate to the type of work being conducted by academic researchers.

10. If clinical trials cannot take place due to excessive regulatory requirements then no patient benefit can be derived at all. Amendments to the proposed Regulation must be carefully considered to make sure they do not have the same unintended consequences.

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

11. Clinical studies do not solely involve the testing of a medicine; many studies involve testing new devices, non-medicinal products and surgical interventions. The Health Research Authority has responsibility for regulating and approving many elements of clinical studies, however many important regulatory requirements sit with other bodies such as the MHRA.

12. The Health Research Authority's role in relation to clinical studies is through the approval of the ethical aspects undertaken by National Research Ethics Service.

13. The Health Research Authority's current role in relation to clinical studies is through the approval of the ethical aspects undertaken by National Research Ethics Service. Since its formation in December 2011, the HRA has demonstrated its competency in regulating research in the UK. It has also shown that it is capable of leading a programme of work to streamline and improve regulation and governance of clinical research in the UK. We are particularly pleased that in October 2012 the HRA announced a feasibility study to test the potential benefits of a simplified and streamlined HRA assessment for all research in the NHS.[64] In our evidence to the Academy of Medical Sciences review of regulation and governance of health research in June 2010[65] we outlined that the biggest barrier facing clinical studies in the UK was the layers of governance associated with seeking permission from NHS Trusts to run studies. Our main recommendation was to develop a streamlined process for these NHS permissions, to be implemented at a national level. We strongly believe that the feasibility study being run by the HRA is the biggest step towards achieving this recommendation, with the ultimate vision outlined as:

[64] 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/

[65] Cancer Research UK submission to the Academy of Medical Sciences reviewof the regulation and governance of medical research. June 2010 http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@pol/documents/generalcontent/cr_053410.pdf

14. *"NHS organisations would be able to rely on the HRA assurance and devote their review to confirming their capacity and capability to host and deliver the research. RECs would be able to focus their expertise on projects raising ethical issues."*

15. To our knowledge there has not yet been data published outlining the impact of the HRA, however we remain confident that its establishment has been an important breakthrough in the regulation of UK clinical research. Our priority is that the HRA is able to continue to focus on developing a streamlined assessment. The draft Care and Social Support Bill currently passing through pre-legislative scrutiny will grant the HRA statutory footing and allow it to continue to develop independently from Government, and push forward with its programme of work.

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

16. Cancer Research UK welcomes efforts to improve transparency in research, especially the publication of negative data from all sectors involved in clinical studies, and supports the AllTrials campaign.[66]

17. Over the past 10 years Cancer Research UK has financed and endorsed 298 trials of more established treatments (late phase trials) organised by hospital trusts or universities and now completed. Of these, 183 have reported results to date and the remaining 115 trials have yet to be fully analysed. One of the reasons for this is that a trial cannot generally report until a pre-defined time point has been reached or a specified number of events have occurred. See appendix for a case study.

Results of clinical studies

18. Transparency is an important principle in research studies, from basic research through to clinical studies regardless of whether supported by academia or industry. We welcome efforts to improve transparency in research, especially the publication of negative data from all sectors involved in clinical studies. For example, we are involved in initiatives that take on drugs to further their development and publication of previous trial data on these compounds would speed up progress and reduce unnecessary duplication of effort.

19. Cancer Research UK has policies in place to support transparency in research studies. We require that trials funded through our Clinical Trials Awards and Advisory Committee undertake clinical trial registration and we monitor when these trials publish their results. Cancer Research UK runs the CancerHelp UK clinical trials database which aims to list all cancer studies recruiting in the UK—not just those supported by Cancer Research UK.[67]

20. CancerHelp UK works with trial teams to produce summaries of studies to provide useful, easily understandable information for the public. This helps patients with cancer identify which studies they could potentially participate in as well as giving information on both positive and negative studies that have been completed. The database currently includes details of approximately 500 studies recruiting people in UK, and more than 400 summaries of study results. In 2012 we added 83 results summaries, including 25 from studies that had received funding from Cancer Research UK and 15 that were sponsored by pharmaceutical companies.

21. We would support requirements for clinical studies to publish a summary of results within a year of when the data analysis is planned in their protocol, which is submitted as part of regulatory approval to set up a clinical study. It should be noted however that the planned analysis could be many years after recruitment to the study has ceased. Timings of analyses are not generally scheduled in terms of months and years but instead are event-driven. If a summary of results is not available within a year of the planned analysis then an explanation should be provided and publicly available. It may also be necessary to build in an annual reporting mechanism for studies that fail to report in a year, to ensure there is continued pressure to publish.

Patient level data

22. We believe that the issue of releasing patient level data is separate to that of releasing the summary of results from a clinical study.

23. There are important issues relating to patient consent and confidentiality to take into account when considering transparency of clinical studies data beyond the publication of summary results.

24. Requests to access patient level data from clinical studies need to be considered very carefully. We support the responsible sharing of patient level data, with investigators who have set out clear plans for how they will interrogate data through peer-reviewed studies.

25. On the issue of patient level data, the need for transparency must be balanced against the following concerns:

— patient consent and confidentiality; patients may have only provided consent for their data to be used in a certain way; any measure to promote transparency would need to respect this historic consent;

[66] http://www.alltrials.net/supporters/cancer-research-uk/
[67] http://www.cancerresearchuk.org/cancer-help/trials/

— the risks that information could be misrepresented which could undermine public understanding of a treatment or research finding;

— maximising usefulness and minimising risks by balancing the level of detail in the data (eg aggregated findings versus patient level data) with how widely these data are shared (eg publicly available versus controlled access); and

— the need to ensure the environment incentivises the funding and delivery of clinical studies, for example by granting a researchers a period of exclusivity for the use of their data.

26. It is important to ensure that full consideration has been given to ensuring solutions work across the range of clinical studies, not just trials of investigative medicinal products (currently covered by the EU Clinical Trials Directive).

27. This is a complex area so it is important that any action the Government takes is well thought through, aligns with actions taken at an international level, and doesn't inadvertently affect the ability to conduct research that will benefit patients.

Ethics

28. Ethics committees (which the HRA oversees in the UK) have a significant role in upholding the transparency of study data and other ethical concerns about missing data.

29. The Declaration of Helsinki makes it clear that the:

> *"Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports."*[68]

30. This is a guideline that should be upheld by ethics committees and deliberated upon when a study is being considered for approval. Many of the concerns raised on the issue of data transparency for clinical studies could conceivably fall within the remit of ethics committees as it their role to ensure the ethical conduct of research studies as well as ensuring the results of the study being used to advance medical knowledge.

31. We welcome the Health Research Authority pilot to scope the feasibility of ethics committees ascertaining if researchers have failed to publish their previous research projects. It will be important that this extra check will not extend the time it takes to gain ethics approvals. The community should be consulted on what ethics committees would constitute appropriate and robust assurance from Sponsors and researchers. We therefore look forward to engaging further with the HRA as their pilot develops.

32. Cancer Research UK would not support a system where ethics committees automatically refused study approval to researchers based on failure to publish previous work. We believe such a system has the potential to be onerous and ineffective. We believe that the time taken for ethics committees to conduct comprehensive analysis of the principle investigator, investigational team, Sponsor or even on an IMP would cause severe delays in research without resulting in sufficient gains in transparency.

Clinical Trials Regulation

33. The draft Clinical Trials Regulation (as proposed in July 2012 and not taking into account any proposed amendments) supports greater transparency than exists under the current Clinical Trials Directive:

— Article 78 of the current draft of the Clinical Trials Regulation states that a new database will capture all information relating to clinical trials in Europe and makes it compulsory for this to be made public while protecting patient and commercial confidentiality.

— Article 33 also makes requirements for Sponsors to notify regulators of the start and end of the trial.

— Article 34 (3) states that "within one year from the end of a clinical trial the sponsor shall submit to the EU database a summary of the results of the clinical trials" with the exception that results can be delayed when scientifically justified.

34. We view these as useful steps towards ensuring that all trials are registered and therefore can be followed up to ensure that the results have been published. While definitions could be clearer on the exact nature of the data that would be published and what exactly the legislation could define as commercially confidential, the Regulation does appear to give legislative backing to support a greater level of transparency than existed under the Directive.

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

35. The push for transparency must also involve the international research community if it is to be successful. Solutions to increase transparency must be discussed and implemented at an international level in order to improve standards for studies and benefit patients. Without these key discussions it is possible that isolated action at either the UK or EU level could further discourage clinical research from being located in Europe,

[68] World Medical Association, Declaration of Helsinki, Article 30

without benefitting patients. Discussion with the US in particular should be encouraged due to its size and the influence the American market has on the global pharmaceutical industry.

February 2013

APPENDIX

CASE STUDY: INTERCONTINENTAL TRIAL

Intercontinental was a trial looking at intermittent versus continuous hormone therapy for prostate cancer that had continued to grow but had not spread—it was an international trial supported by Cancer Research UK.[69]

Doctors thought that hormone therapy given intermittently rather than continuously may work just as well and may also reduce side effects. The main aims of this trial were to compare intermittent and continuous hormone therapy to see the difference between how long the men lived and how it affected their quality of life.

Recruitment of patients:

Sample size—1,386
Start 01/10/2002
End 30/11/2005
Publication date (N Engl j med 367;10 nejm.org, 6 September 2012)

The Independent Data and Safety Monitoring Committee recommended halting the trial after a planned interim analysis showed that the trial had already offered the required results, ie that giving intermittent hormone therapy was not worse than giving continuous hormone therapy. This demonstrates why it is can be difficult to say when an analysis publication should happen.

The trial team found that the amount of time that men lived was not reduced when they had intermittent therapy. And that for many of the men side effects were reduced and could lead to an improved quality of life. The men were followed for an average of around seven years.

There are a number of reasons why trials may report later than expected as well. For example, when testing new therapies it may not be possible to predict participants' response in advance leading to delays in the trial.

Results should be reported as swiftly as possible to ensure that effective treatments get to patients quickly and any evidence of ineffectiveness is known to the medical community, patients and the public.

Supplementary written evidence submitted by Cancer Research UK

More than 35,000 full trial summaries are viewed on Cancer Help each month—more than 400,000 per year. This is our current quote based on last financial year's traffic. Overall the site traffic is on an upward trend.

May 2013

Further written evidence submitted by Cancer Research UK

The CancerHelp UK Clinical Trials Database is unique resource, providing information for the public about cancer trials and studies that recruit people in the UK.

Unlike trials registers which provide an internationally agreed set of data about the design, conduct and administration of clinical trials, the trial summaries on CancerHelp UK are written specifically with patients in mind.

The information is not intended to be as detailed as a Patient Information Sheet, as it is not part of the recruitment/consent process. But all summaries include information about the aims of the trial, who can take part, what taking part would mean—ie number of hospital visits and/or additional tests, and information about possible side effects. We conduct user testing and act on feedback to try to ensure the information is presented in an accessible and helpful way for our lay audience.

The summaries are written in plain English by our team of specialist nurses and all the information is reviewed and approved by the team or organisation running the trial before it is added to CancerHelp UK.

We aim to list all cancer trials and studies recruiting in the UK—not only those supported by Cancer Research UK. We currently have more than 1,500 studies listed on the site, including more than 500 trials that are open to recruitment, over 500 studies that are closed to recruitment but ongoing, and more than 400 trials with results.

We work with a wide range of organisations, including many pharmaceutical companies to prepare summaries of both open trials and of trial results.

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[69] A trial looking at intermittent versus continuous hormone therapy for prostate cancer that has continued to grow but has not spread (Intercontinental), CancerHelp UK website, http://www.cancerresearchuk.org/cancer-help/trials/a-trial-looking-at-intermittent-versus-continuous-hormone-therapy-for-prostate-cancer-that-has-continued-to-grow-but-has-not-spread

The database was started more than a decade ago and initially only detailed trials that were open to recruitment. But in response to feedback we received from users, we started adding brief summaries of trial results when we redesigned the website in 2009.

Since then, we have added more than 400 results summaries. About 18% of these are pharma trials—percentages are approximate as the number of trials on the database (and their current status) changes on an almost daily basis.

Of the 83 results summaries we added during the course of 2012, 15 were sponsored by pharmaceutical companies, 25 were for studies that had received funding from Cancer Research UK.

There are currently 50 closed trials listed on the database that do not have a full summary of results. We have added a brief explanation of why this is. For example, 41 of these trials were not able to recruit enough people, or were stopped early for other reasons. Out of the 400 results summaries we currently have in total, there are only nine trials listed for which we have been unable to obtain results or have a results summary approved.

The length of time between a trial closing to recruitment and us being able to add a summary of results varies enormously. There are some trials listed that closed to recruitment a number of years ago. We will have been in touch with the trial team about adding results, and may now be waiting for analysis to be completed or for a paper to be published. We can sometimes base a summary on an end of study report or a conference abstract, but if results are being published, we may not be able to add details to CancerHelp UK until the publication date has passed.

By working with teams that are involved in running clinical trials, we produce intentionally brief summaries that accurately reflect the findings of a trial and provide useful, easily understandable information for the public.

Cancer Research UK is committed to providing information for the public about cancer trials and their results. We are dependent on trial teams, including clinical researchers, academics and pharmaceutical companies working with us in a timely fashion in order to be able to do this.

May 2013

Written evidence submitted by the Faculty of Pharmaceutical Medicine

1. The Faculty of Pharmaceutical Medicine is a professional membership organisation and standard-setting body, with 1,450 members, who are practising pharmaceutical physicians or those with a professional interest in the speciality. It was founded in 1989, and is a Faculty of the Royal Colleges of Physicians of the UK.

2. Pharmaceutical medicine is a medical specialty concerned with the discovery, development, evaluation, licensing and monitoring of medicines and the medical aspects of their marketing. The Faculty's members work in diverse environments; from front line clinical trials, to pharmaceutical marketing and medicines regulation.

3. Our mission is to advance the science and practice of pharmaceutical medicine by working to develop and maintain competence, ethics and integrity and the highest professional standards in the specialty for the benefit of the public. The Faculty seeks, through its activities, to bring about an improvement in the health of the public.

4. The Faculty welcomes the opportunity to submit evidence to this important inquiry and we would be happy to supplement this written evidence with oral evidence to explore these issues in more detail.

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

5. The Faculty has recently responded to the MHRA "Consultation on the European Commission's proposal for a clinical trials regulation." The following comprises an abridged version of that response which we feel relevant to the specific questions posed here.

6. We believe that the general scope and aims of streamlining and harmonization are to be welcomed. However, while it is stated that Directive 2001/20 is to be repealed, the Faculty is concerned that in practice national laws, customs and practices will be slow to change. There is a danger that for a significant time period additional requirements and complexity are being created rather than replacement ones.

7. The proposal is very unclear as to precisely which functions remain with the 45 national competent authorities (NCAs), the ethics committees which are currently affiliated with research sites (and not, by design, the NCAs), both when an NCA may opt in, or after it uses a qualified opt out.

8. The Faculty can see some merit in having a central body review the overall ethical aspects of a study. Such a body can include relevant scientific experts and professional ethicists and give a degree of consistency. However, the Faculty has major concerns over a single body making ethical determination for the whole of the EU. This is not the process in the United States of America where the FDA approves clinical studies but independent institutional review boards making ethical determinations. The delegation of ethics approval to NCAs, or even a single referring NCA, if that is what is meant by Article 6, para 1, is itself unethical. A

referring NCA assessor in, say, London is highly unlikely to understand the cultural and medical position of a patient in, say, Valetta. If NCAs intend to retain local arrangements for Ethics Committees, then a layer of review has been added, not removed, by the Regulation; furthermore, there is the risk of mutually exclusive conditions for a clinical trial being imposed by the two reviews. We believe that there will be a risk to quality if the NCA ethics reviews supplant the local ones. If both are required, and the results conflict, then some compromise will be needed or the trial will not take place at all.

9. The Faculty believes that in practice there will remain a process of national and local review in many territories. The regional MREC is working well in the UK and a case could be made to adopt the same model Europe-wide with the same focus on ethics. This would deal with the regional differences and allow responsiveness to local populations. The clinical trials authorisation (CTA) submission of a multi-national trial within the EU appears optimized by the implementation of Voluntary Harmonization Procedure (VHP), though not all EU countries participate in VHP because of various national regulatory (and probably cultural) differences.

10. From the point of academic research, this regulation provides no reduction in paperwork. It threatens an additional layer of ethical review. From the point of view of industry-sponsored clinical trials, the imposition of the timelines, taken together with the various extensions available to the regulators, would seem to be a slower, rather than faster, process compared to what has hitherto been the case in the United Kingdom, Sweden, and The Netherlands (and possibly also elsewhere).

11. We believe that the EMA may lack the manpower and expertise for these clinical trial applications, which will be in large volume.

12. Hence the Faculty considers that these proposed revisions will need refining if they are to enhance the speed and effectiveness of clinical trials in the UK and EU. Indeed there should be more focus on the needs of all researchers, both academic and in industry, if we are to make the EU more attractive for conducting clinical trials.

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

13. The National Research Ethics Service has transferred to the HRA. One such service has been the in-line submission of studies. This Integrated Research Application System (IRAS) was launched in January 2008, and has since become a successful system with an excellent record of system availability. To date, IRAS has been available 24 hours a day, 7 days a week with less that 0.1% "downtime" for system upgrades and maintenance. The HRA will enable research ethics committee (REC) and MHRA electronic submissions through IRAS. This service has greatly simplified submission and will greatly enhance efficiency and should serve to improve the attractiveness of the UK as a country to conduct clinical trials in.

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

14. To provide clear direction to all pharmaceutical physicians the Faculty published its "Guiding Principles for Pharmaceutical Physicians" in 2006 and revised in 2010. This forms the basis for the ethical and professional standards of its members.

15. This document contains a section entitled "Sharing Findings" which states:

16. *"All studies should be performed to increase knowledge in some useful way, and there should be openness and honesty in the sharing of this knowledge with the wider world. Trial findings need to be communicated, whatever the outcome, for the benefit of the community at large. The sponsor should have a clear policy regarding trial publication which should be agreed with the clinical researcher prior to trial initiation, and neither the sponsor nor the researcher should seek to prevent publication or the admission of trial results within the public domain. Communications on clinical studies must be a correct objective representation of all the findings, allowing others, in their turn, to give well-balanced risk-to-benefit advice to patients and their families. It is especially important that negative results or adverse safety data are communicated to regulators and clinicians in a timely manner where this information may affect prescribing practices and the protection of patients."*

17. This is a clear direction to pharmaceutical physicians to ensure open access to study trials.

18. However, even though there is a requirement that all clinical trial data are submitted to regulatory agencies, there is clear evidence that not all clinical trial results have been made publicly available in medical or scientific journals. Research by Ross *et al*,[i] has demonstrated that most studies registered on the US-based ClinicalTrial.gov clinical trial registry and website had not lead to publication of study results; though nearly all had included all the data elements mandated by ClinicalTrials.gov, such as intervention and sponsorship. Looking at a sample of trials registered, less than half (311 of 677, 46%) of trials were published. Trials primarily sponsored by industry (40%, 144 of 357) were less likely to be published when compared with non-industry/non-government sponsored trials (56%, 110 of 198; $p<0.001$), but there was no significant difference when compared with government sponsored trials (47%, 57 of 122; $p = 0.22$). Evidently there is a long way

to go before the publication of all clinical trial data is achieved. However, it is obvious that the issue is not confined to the pharmaceutical industry and similar patterns of non-publication are found amongst non-industry and government sponsored trials.

19. Well known examples of clinical research where a lack of public dissemination of clinical trial data has been linked to an avoidable and detrimental health impact for patients treated with those drugs include vioxx and paroxetine. Over the last couple of years the ability and requirements to make results public has increased markedly especially with ClinicalTrials.gov. The ClinicalTrials.gov registration requirements were expanded after the Food and Drug Administration Amendments Act of 2007; more types of trials fell within scope for registration and there was a requirement for the submission of results for certain trials. This led to the development of the ClinicalTrials.gov results database, which contains information on study participants and a summary of study outcomes, including adverse events. The results database was made available to the public in September 2008. There are penalties for failing to register or submit the results of trials. However, it is often the case that not until meta-analyses of all clinical trials with a drug are conducted that some important safety signals emerge. These meta-analyses are often conducted by academics outside of industry and regulatory agencies; and they require full and complete access to the data on a drug to be reliable.

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

20. The amended Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) requires prospective trial registration with a statement that "Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject". In addition, many medical journals make it a pre-condition of acceptance for publication that a trial was registered. Relatively recent moves within the United States also make the provision of results from "applicable clinical trials" to ClinicalTrials.gov a requirement once the study has completed. The US FDA normally holds open public meetings with experts to discuss clinical trial data submitted as part of a new drug application though in other regions these types of meeting are normally closed sessions. Therefore there is public access to the occurrence of clinical trials and their key features are already well served via the requirements to enter clinical trial data into the US ClinicalTrials.gov clinical trial registry/website and, more recently, via the EMA supported EU Clinical Trials Register.

21. However the key question is how to enable the full set of raw clinical trial data to be made available to third parties to assess, review and analyse and not be restricted to just the trial sponsors and regulatory agencies. The Faculty has, for a long time, been supportive of greater transparency in clinical research and has promoted allowing third party access to clinical trial data. However this needs to be conducted in a fair and responsible manner. We believe that there is enormous potential for benefits to the broader research effort and public health if data could be more openly scrutinised by third parties. Under the current system, researchers are able to make their own assertions about the "significance" of their research and data. However, it may be that other researchers can spot potential in the data that was not originally recognised, or can combine historical data with new information to highlight unforeseen benefits. Collaboration and transparency between researchers will also lead to less duplication of efforts and wasting of resources.

22. Overall, the Faculty favours a policy of both prospective and retrospective disclosure of data, but with a system that ensures adequate safeguards for both the anonymity of trial subjects and maintains safety for potential patients. Whilst open access should be enshrined in any new process of searching the data sets, there would need to be an orderly and scientifically sound process to facilitate access. We recommend the establishment of a "gate keeper"; an independent body reviewing requests for data. Third parties would be required to submit a statistical analysis plan or at the very least clear questions that they wish to address. The identities of those third parties requesting data should not be anonymous to the "gate-keeping" body, but not necessarily made public. The cost of such a system could be shared by government, the sponsoring company and perhaps also the requesting party.

23. The Faculty would recommend that the following requirements should also be upheld for all clinical research:

24. *Sponsors and clinical investigators should make available the methods and results of their trial within one year of study completion.*

25. The task of policing this policy could fall on the Health Research Authority as an extension of the IRAS. The HRA is best placed to take account of local needs, but would need to integrate seamlessly with EMA, FDA and other national regulatory agencies, given the global nature of pharmaceutical product development.

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

26. Of note, the US FDA organises open advisory committee hearings for many new drugs, particularly where there is potential for significant public health impact, where FDA staff, external advisors and company representatives debate issues around the clinical trial results and implications for public health. The general public is also able to contribute to these meetings. The FDA assessment reports on the drugs reviewed become publically available on its website. The US ClinicalTrials.gov website and data registry now requires posting of the results of "applicable" clinical trials, this includes key clinical trials supporting marketing approval for

new drugs and subsequent clinical trials with them. We believe that this system works well and would be appropriate and applicable in the UK/EU.

27. The EMA does now support the EU Clinical Trials Register and provides a publically accessible (commercially confidential material having been redacted) version of its assessment report for new drugs on its website. The EMA could look to mirror FDA in holding open public meetings when issues pertaining to new drug applications are debated with the medical and scientific experts. Given the ease of accessing information via the internet, international nature of major pharmaceutical companies and the fact that results from all relevant trials are available in the EMA assessment report for a drug.

Reference

[i] Ross J S, Mulvey G K, Hines E M, Nissen S E, Krumholz H M (2009). Trial Publication after Registration in ClinicalTrials.Gov: A Cross-Sectional Analysis. PLoS Med 6(9): e1000144. doi:10.1371/journal.pmed.1000144

February 2013

Written evidence submitted by the Association of the British Pharmaceutical Industry (ABPI)

Introduction

A.1 The Association of the British Pharmaceutical Industry (ABPI) welcomes the opportunity to submit evidence to the Committee's inquiry into clinical trials. Clinical trials are vital in order to demonstrate efficacy and safety of new medicines and are a regulatory requirement for every new medicine. In addition, clinical trials provide important information on the best ways of treating diseases with new medicines. Treatments discovered and developed in the UK help to save lives, reduce suffering and improve quality of life for millions of people all over the world. The UK has traditionally been at the forefront of international medicines research—only the USA has discovered and developed more medicines.

A.2 ABPI is committed to greater transparency in clinical trial information and in particular, the reporting of the occurrence and results of clinical trials. We believe access to trial information is vital and in the best interests of patients and the practice medicine—and that summary clinical trial results should be made available for both new and existing medicines.

A.3 Many steps are already being taken towards this goal:

(a) Since 2012, current and future trials must be registered within 21 days of enrolling the first patient and results, positive or negative, must be published within one year of marketing authorisation (or study completion for marketed products).[70]

(b) ABPI is looking at a new, compliance monitoring system to ensure that the registration of clinical trials and publication of summary results takes place**.** A transparency toolkit will also be made available to assist companies with robust internal processes for compliance.

(c) For trials conducted in the EU from May 2004, summary reports will be made available via a central database (EudraCT), once the system has been upgraded by the end of 2013.[71]

(d) The ABPI has also produced guidelines to help improve access to clinical trial information including the ABPI Best Practice Model for the Disclosure of Results and Transparent Information on Clinical Trials and the Clinical Trial Transparency guidelines, produced with the Ethical Standards in Health and Life Sciences Group (ESHLSG) in 2012.[72] Both sets of guidelines are currently being reviewed.

A.4 We believe that one of the areas where more could be done is in the disclosure of information from past trials. The process of improving transparency is, however, an international one, governed by EU legislation. The industry in the UK is therefore working with partners in Europe and internationally to ensure that action is taken. We are working with our member companies and experts to participate in the European Medicine Agency's (EMA) working groups to find a real, effective and practical solution for the publication of summary results from clinical trials. As well as a global issue, this is also a complex issue. One challenge is to improve transparency while ensuring that disclosure policies protect patients: the consent a patient had provided at the time a study was conducted may not cover the general release of their data, even if the data had been effectively anonymised. In addition, it is important to protect both the integrity and effectiveness of the overall research and regulatory process and commercial information. The legitimate interests of companies in the protection of IP must also be protected in an appropriate way.

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[70] ABPI Code of Practice for the Pharmaceutical Industry Second 2012 Edition, http://www.abpi.org.uk/our-work/library/guidelines/Pages/code-2012.aspx

[71] European Union Drug Regulating Authorities Clinical Trials database, https://eudract.ema.europa.eu

[72] ABPI Best Practice Model for the Disclosure of Results and Transparent Information on Clinical Trials, (produced 2007, revised 2008), http://www.abpi.org.uk/our-work/library/guidelines/Pages/best-practice-model.aspx Clinical Trial Transparency guidelines, Ethical Standards in Health and Life Sciences Group, 2012, http://www.eshlsg.org/wp-content/uploads/ESHLSG-Clinical-Trial-Transparency-Principles-and-Facts.pdf

A.5 As well as improving transparency to clinical trial information, we believe that patients and the practice of medicine would benefit most when unnecessary regulatory hurdles to conducting clinical trials in the UK are removed. More progress is also required on attracting investment in research as the benefits of hosting clinical trials in the UK are well established, both for patients and society at large. Ambitious policy responses are therefore required for the UK to become and remain competitive as a centre for clinical research. We support the Government's efforts to streamline the regulation of clinical trials and to create a more positive environment for research in the NHS through the life sciences strategy.

A.6 From HIV to cardiovascular disease, neurological conditions to oncology, the pharmaceutical industry researches, develops and delivers medicines that radically improve patients' quality of life and bring a wide range of benefits to society. Clinical trials are a vital part of this and the UK pharmaceutical industry is committed to acting in the best interests of patients and to ensuring that patients continue to have access to the most effective treatments.

A.7 Please note that throughout this document, the term "clinical trials" refers to all interventional, commercial sponsor led clinical trials, except where otherwise specified.

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

1.1 Yes, ABPI agrees that the European Commission's proposed revisions to the Clinical Trials Directive make positive steps to address the main barriers to conducting clinical trials in the EU, which would be beneficial for the UK. The current Directive has seen variation between member states on processes for submission, assessment and authorisation of clinical trials, timelines and safety data reporting, for example.

1.2 Revising the Directive as a Regulation will create a simpler, more efficient and uniform legal and regulatory framework for the authorisation and conduct of clinical trials in Europe. ABPI supports the proposed single submission of a Clinical Trial Authorisation (CTA) through an electronic portal with a coordinated assessment process resulting in a single decision per Member State (encompassing Regulatory Authority and Ethics Committee opinions) and competitive timelines for decisions. ABPI calls on the UK Government to ensure the UK can meet these timelines to ensure competitiveness.

1.3 At a national level, a significant administrative hurdle is the need to obtain separate NHS research and development (R&D) approval when the clinical trial is conducted in an NHS hospital or enrolling NHS patients. This is not addressed by the proposed Clinical Trials Regulation, but the Health Research Authority (HRA) has proposed to test a system for a single unified assessment for all research within the NHS (see response to Q. 2 for an assessment at a national level).

1.4 Overall, it is important that the Commission's proposals remain as intended for this legislation through the EU co-decision process and that all parties aim for agreement at first reading to avoid potential delays as a result of the upcoming European Parliament elections.

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

2.1 ABPI strongly supported the creation of the HRA in 2011 to streamline regulation and to protect and promote the interests of patients and the public in health research. Streamlining regulation and making the UK a more attractive location to conduct clinical trials is at the core of the HRA's remit. Just over a year after its establishment, we believe it is too early to judge the effectiveness of the HRA in a comprehensive manner. Certainly, more can and should be done to make the UK a more attractive location to conduct clinical trials.

2.2 The HRA provides the Integrated Research Application System (IRAS), a UK-wide e-submission system through which applications for regulatory and governance approvals for health research are made. It is also the Appointing Authority for Research Ethics Committees (RECs) in England and provides the National Research Ethics Service (NRES), which regulates and guides ethics committees.

2.3 In addition, the Department of Health has agreed to the HRA's proposal to test the potential benefits of a simplified and streamlined HRA assessment for all research in the NHS. The devolved nature of the NHS means that trials often require many separate grants of permission, particularly where research is to be carried out across multiple sites, run by different NHS organisations. Securing several different permissions is an administrative burden for trial sponsors and does not provide additional protection for patients. A single HRA assessment would combine and replace aspects of the current review by NHS Research and Development and RECs. A single HRA assessment could potentially improve both study set-up times and the quality and consistency of ethical review, as well as improving transparency around the process.

2.4 ABPI believes the HRA should focus on building and maintaining competitive timelines for starting research studies in the UK, with particular emphasis on delivering the commitment to recruit the first patient within 70 days of receiving a valid research application, while consistently ensuring the delivery of patient recruitment to time and target.

2.5 The HRA also has a clear remit focused on protecting patients and would be well placed to ensure that precise information is given to Ethics Committees and trial participants on where to find trial registration details and ultimately, summary results.

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

3.1 The pharmaceutical industry supports enhanced transparency of clinical research and safety information. Already, current and future trials must be registered within 21 days of enrolling patients and summary results, positive or negative, must be published within one year of marketing authorisation or within twelve months of study completion for marketed products.[73]

3.2 It is widely reported, however, that some clinical trial information is not in the public domain. It is true that compliance with the requirement to register clinical trials and posting of their summary results could be further improved, and we propose mechanisms to achieve this in our response to Question 4.

3.3 The charge that pharmaceutical companies withhold clinical trial information is commonly associated with a report published in 2012.[74] This report relates to a study of all trials completed in 2009 which met the criteria for mandatory registration and summary results posting on www.clinicaltrials.gov under FDA regulations from 2007. The authors reported that 22% of all trials meeting the criteria were registered and had summary results posted; the figure was 43% for industry-sponsored trials and 9% for academic trials.

3.4 At the Thirteenth Annual Pharmaceutical Regulatory and Compliance Congress and Best Practice Forum held in the United States in November 2012, a presentation by Dr Ann Meeker-O'Connell from the US Food and Drug Administration (FDA) challenged the results of the above mentioned study, finding several flaws in the analysis. The US FDA's preliminary review of Prayle's results found that instead of 77.9% of trial summary results being overdue, 34.6% trial results were overdue by January 2011. Updating this analysis to May 31 2012, 21.1% of trial results were overdue, a compliance rate of 78.9%.[75]

3.5 ABPI is undertaking its own research to ascertain the extent to which pharmaceutical companies publish the results of clinical trials sponsored by them, irrespective of prevailing requirements. All company sponsored clinical trials conducted in patients for all new active substances (NAS) (excluding vaccines and combination products) approved by the European Medicines Agency (EMA) during 2009–11 inclusive are being evaluated. This involves:

- Checking of the European Public Assessment Report (EPAR) for all studies conducted in patients in the individual Marketing Authorisation Application (MAA).
- Searching for all registered trials in the major international registries and company clinical trial registers.
- Searching PubMed for all publications (limited to clinical trials), viewing the abstract field and matching to trial registry identifiers where they appeared in the abstract.
- Cross-matching trial identification numbers from all sources, and minimizing duplication as far as possible.
- Checking the dates that the studies were entered in a publicly available clinical trial registry (noting those that were not entered).
- Ascertaining which studies have reported results (either in the academic literature or in a section of the registry) by one year after the later of the date of first approval of the product or the date the study was completed.
- Referring queries back to the companies concerned.

3.6 The research is still ongoing, but ABPI found that for the 12 new products approved in 2010, the levels of trial registration and publication clearly exceed those quoted in Prayle *et al*, and are more in line with the FDA's preliminary findings—see table below.[76] Our analysis shows that the publicly available evidence base for new medicines has improved in recent years. The research also suggests that clinical trials conducted prior to the existence of mandatory requirements or industry guidelines were less likely to be posted on registries and less likely to be published individually; this was particularly the case for smaller, early phase trials. In addition, problems commonly arise where products changed ownership after licensing deals or company mergers and acquisitions.

[73] ABPI Code of Practice, 2nd Edition (2012), http://www.pmcpa.org.uk/thecode/Pages/default.aspx
International Federation of Pharmaceutical Manufacturers and Association's (IFPMA) Joint Position on Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (2010), http://clinicaltrials.ifpma.org/clinicaltrials/fileadmin/files/pdfs/20100610_Joint_Position_Publication_10Jun2010.pdf

[74] Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study, Prayle *et al*, 2012, http://www.bmj.com/content/344/bmj.d7373

[75] PhRMA Press release, http://phrma.org/media/releases/phrma-statement-clinical-trials-bad-pharma and personal communication

[76] op cit. Prayle *et al*.

ABPI analysis of clinical trial registration and publication of summary results for all company sponsored clinical trials in patients for the 12 new active substances approved by EMA in 2010

Year	*Trials registered and summary results posted/published within 12 months (%)*	*Trials registered and summary results posted/published (as of 31 January 2013) (%)*
2010	115 of 145 (79%)	176 of 191 (92%)

NOTE: Of 213 trials identified as complete as of end of January 2012, 68 were non-evaluable due to the absence of one or other of the key assessment dates (eg, the precise date of study completion is missing or summary results have been posted, but the date of posting is not available). For some of these products, this includes trials conducted before any mandatory requirements for reporting summary results were in place. We are conducting a similar analysis for all NAS approved by EMA in 2009 and 2011.

3.7 It is important to stress that regulatory authorities have access to all the relevant information as part of the approval process for new medicines, and regular updates thereafter. A Freedom of Information (FOI) request can be made for any document within the MAA for any approved product. Certain documents should however be redacted to prevent personal data (as protected under European and national data protection laws) and commercially confidential information being disclosed, in consultation with the MAA holder.

3.8 Work is already underway to improve access to clinical trial data for existing medicines. Summary reports for clinical trials since 1 May 2004 will be entered on the EudraCT database when it has been upgraded to accept them later this year. EudraCT is the European Clinical Trials Database of all clinical trials within the scope of the EU Clinical Trials Directive.

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

4.1 There are a number of steps which can be taken to ensure that clinical trial information can become more open in the future. Some immediate steps which ABPI recommends are:

(a) The global nature of clinical development means that an **international approach** is required. International agreement is needed on which trials to include in transparency measures (for example, all trials in humans, including healthy subjects, or all trials in patients) and on definitions of terms such as "study completion". Good Clinical Practice (GCP) is an international quality standard that is provided by the International Conference on Harmonisation (ICH), an international body that defines standards which governments can transpose into local legislation for clinical trials. ICH could be a mechanism to achieve harmonisation of an international approach. In the interim, ABPI recommends that **MHRA Good Clinical Practice inspections should be able to assess compliance** with trial registration and publication of summary results requirements.

(b) For all trials, the patient informed consent agreement between a trial participant and the sponsor should include a **statement from the sponsor that the summary results will be made publically available**. Precise information must be given to trial participants on where to find trial registration details and ultimately, summary results. Investigators and Ethics Committees should all receive summary results not later than posting dates of the results on the registry. These are activities which HRA should ensure are implemented immediately for all clinical research in the UK.

(c) **One global portal to which all clinical trials registries can be linked** would be ideal. For now, www.clinicaltrials.gov and www.clinicaltrialsregister.eu should be used. Companies may wish to also maintain their own clinical trial register, which should cross-reference the entries in the international registries with the unique trial identifiers. Companies could state where disclosures can be found on their websites, as part of their compliance statements. Medical journal editors should demand that the unique trial identifier is mentioned in the **abstract** of journal publications.

(d) Already, Marketing Authorisation Applications **must be accompanied by all relevant clinical trial information**. ABPI recommends that for an MAA to be valid, the EMA in Europe and MHRA in the UK should require that all trials submitted as part of the application have been entered into an international registry, and the unique trial identifier from the registry must be listed against each trial.

(e) It is important to understand **what kind of information is required to be disclosed**, and what kind of information is being called for. Currently, semi-structured summary information for Phase II-IV clinical trials for licensed medicines can be disclosed through www.clinicaltrials.gov within 12 months of completion. With an upgrade of EudraCT planned to be completed in 2014, trials summary report information for Phase II-IV adult clinical trials conducted in the EEA for licensed drugs are to be disclosed within 12 months of completion and paediatric clinical trials of any origin when included in a Paediatric Investigation Plan are to be disclosed within six months of completion.

ABPI is closely following the progress of the five working groups set up by EMA to advise on the specific mechanisms that will govern whether and how final clinical study reports (CSR) and all available clinical trial information could be accessed by researchers and other interested parties. EFPIA, ABPI's European equivalent, has set up five parallel groups, each led by an industry representative who sits on the respective EMA group. The output from this work is critical as it will ensure that there is a consistent and clear understanding of what level of information should be released, in what format and when. ABPI will respond to the outputs of the EMA working groups in Q2 2013.

(f) **Compliance is, of course, critical**. ABPI is preparing a **clinical trial transparency toolkit** (comprising good practice guideline, process flowchart, template SOP, compliance checklist etc) to assist companies to comply with their obligations. These will be available on the ABPI website during Q3 2013. In addition, ABPI will appoint a third party service provider to monitor compliance with current and future industry codes of practice on clinical trial transparency. **ABPI will take on the responsibility for reporting non-compliance in relation to trial registration and posting of summary results to the Prescription Medicines Code of Practice Authority (PMCPA), or where applicable to the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA).**[77]

4.2 All of the above initiatives should be taken for new clinical trials. There is also the additional issue of improving disclosure of information from past trials for existing medicines, where there are significant complexities over release of information. The EMA and EFPIA are currently looking at all of these issues as part of their work. The complexities include:

(a) **Patient consent:** complete annoymisation of patient data may not always be possible. Even if patient data is anonymised and all patient identifiers are removed, some patients may not have given their consent to release of their data from past trials.

(b) **Orphan (or rare) diseases:** it is much more difficult to protect patients' identities for clinical trial information for medicines for orphan diseases.

(c) **Different data formats:** clinical trial information has been presented in quite different formats over time and between different companies and any system for release of this information would need to take this into account.

(d) **Paper archives:** much information for past clinical trials is held in paper format. Making all information available would require this information to be reproduced in electronic format.

(e) **Volume of information:** releasing all information for all trials would be an enormous undertaking. It is not unusual for a full CSR to be several thousands of pages in length. www.clinicaltrials.gov already has over 140,000 registered trials.

(f) **Ownership of information:** many medicines are bought and sold as part of licence deals or company acquisitions across the world. In some cases, there is insufficient clarity over responsibilities in connection with management of clinical trial information within legal agreements.

(g) **Start date:** a grandfathering clause date would need to be set before which it would be impractical and of questionable benefit to release clinical trial information for medicines. A mechanism for deciding this date needs to be agreed.

(h) **Different regulatory regimes:** clinical trial legislation and requirements have changed over the years, resulting in different sets of information being collected and analysed in different ways, especially across different EU member states prior to the EU Clinical Trials Directive.

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

5.1 The international governance framework for clinical trial transparency already exists and is workable if appropriate attention is paid to detailed implementation. In the US, the FDA has made greater strides in this regard. The regulation is clear and the database employed, www.clinicaltrials.gov, is widely acknowledged as being user-friendly and easy to navigate for companies and researchers alike.

5.2 The most significant barrier to clinical trial transparency has been, and still is, monitoring and enforcement. Given the current trend towards greater transparency in all walks of life, the time is ripe to put in place robust measures to make clinical trial information easily accessible for patients, researchers and healthcare providers, as outlined in the response to question 4.

About the Association of the British Pharmaceutical Industry (ABPI)

The ABPI represents innovative research-based biopharmaceutical companies, large, medium and small, leading an exciting new era of biosciences in the UK.

[77] Prescription Medicines Code of Practice Authority http://www.pmcpa.org.uk/Pages/default.aspx International Federation of Pharmaceutical Manufacturers & Associations http://www.ifpma.org/

Our industry, a major contributor to the economy of the UK, brings life-saving and life-enhancing medicines to patients. Our members supply 90% of all medicines used by the NHS, and are researching and developing over two-thirds of the current medicines pipeline, ensuring that the UK remains at the forefront of helping patients prevent and overcome diseases.

The ABPI is recognised by Government as the industry body negotiating on behalf of the branded pharmaceutical industry, for statutory consultation requirements including the pricing scheme for medicines in the UK.

February 2013

Supplementary written evidence submitted by the Association of the British Pharmaceutical Industry (ABPI)

I am writing to you to provide an update on ABPI's evidence to the Committee's inquiry into clinical trials, following the completion of our research into the extent to which pharmaceutical companies disclose the results of clinical trials they sponsor. ABPI is submitting this research for publication very shortly; however, in the meantime, we would like to share with the Committee the final results for new active substances approved in 2010 as well as the aggregate results for 2009–11 inclusive.

This update refers to the information in paragraphs 3.5 and 3.6 of our written evidence to the inquiry, which contained the preliminary results of the research. The preliminary aggregate results were also referred to during the oral evidence session on 22 April.

ABPI undertook its own research in order to ascertain the level of completeness of the evidence base for recently approved medicines, by checking the extent to which results were disclosed for company sponsored clinical trials in patients, irrespective of prevailing requirements.

Year	*Trials registered and summary results posted/published within 12 months (%)*	*Trials registered and summary results posted/published (as of 31 January2013) (%)*
2010	116 of 144 (81%)	182 of 195 (93%)
Aggregate (2009–2010–2011)	616 of 807 (76%)	781 of 882 (89%)

Please note that the final disclosure percentages have changed slightly compared to those in the evidence provided to the Committee following additional information received from companies regarding trial results that were publically available prior to 31 January 2013.

We would be very happy to discuss these results with the Committee in more detail if requested, and were pleased to have had the opportunity to submit evidence to this important inquiry.

June 2013

Written evidence submitted by the Health Research Authority (HRA)

In this submission, the Health Research Authority (HRA) is responding in general terms to the call for evidence but in particular to the matter: What is the role of the HRA in relation to clinical trials and how effective has it been to date?

BACKGROUND AND REMIT

1. The HRA is a Special Health Authority with a remit to promote and protect the interests of patients and the public in health research.

2. The HRA is one of a number of bodies with responsibilities for the regulation and governance of research in the UK. However, it is in the unique position, as described below, to consider the overall framework of both the regulation and governance of research, and linked key roles for those responsible for funding, sponsoring, hosting, publishing and responding to research.

3. The HRA is widely recognised as having transformed the systems for ethical review in the UK by providing an efficient, proportionate and effective system for NHS Research Ethics Committees (RECs) which approve research, including clinical trials, within the research governance framework. The HRA has also already taken responsibility for the Gene Therapy Advisory Committee (GTAC) and will take on further functions at the end of March when the National Information Governance Board closes and responsibility for approving the processing of confidential patient information transfers to the HRA.

4. The Government intends to legislate to establish the HRA as a non-departmental public body, and the draft Care and Support Bill has now been published for pre-legislative scrutiny.

The HRA—Making it Easier to do Good Quality Ethical Research in the UK

5. As well as making it easier to do good quality ethical research in the UK, the HRA has set out an ambitious programme of work to deliver practical solutions and inform further improvements to the framework for managing and supporting research in the NHS. To this end, the HRA has established a Collaboration and Development Steering Group to oversee a set of projects to improve the environment for research in the UK. Recognising that the HRA has a lead role, it will need to work effectively with partner organisations to deliver improvement and unify processes for application and approval, so that tasks are worthwhile, proportionate and undertaken once by the most appropriate organisation to remove unnecessary activity and duplication, and the associated delays and inefficiencies.

6. The HRA received around 6,000 applications from across the UK last year, 1,000 of which were Clinical Trial Investigational Medicinal Products and needed expert review from the Medicines and Healthcare products Regulatory Agency (MHRA), which is coordinated and managed through a Memorandum of Understanding. In addition, a further 1,000 applications now proceed through the REC Proportionate Review Service, and are completed in an average of eight days.

7. The HRA is currently testing the potential benefits of a simplified and streamlined HRA assessment for all research in the NHS, including clinical trials, in one of a portfolio of projects under the HRA Collaboration and Development Steering Group. The assessment would combine and replace aspects of the current review by NHS Research and Development (R&D) and RECs. Scoping work for the project has suggested that a quality-assured HRA assessment could potentially improve both study set-up times and the quality and consistency of ethical review. NHS organisations would be able to rely on the HRA assurance and devote their review to confirming their capacity and capability to host and deliver the research, whilst RECs would be able to focus their expertise on projects raising ethical issues. If successful, this radical simplification across R&D and ethics review would potentially provide a simplified platform for other improvements planned by the HRA and other partners.

Working with others to Support Research

8. The HRA recognises that to deliver its ambition to make it easier to do good quality research in the UK it needs, not only to work in collaboration with other bodies, but also to influence and lead change with them. The collaborations forged through the National Research Ethics Service (NRES, now part of the HRA) and Integrated Research Application System (IRAS) partnership demonstrate the HRA's successful track record of improving the UK research environment.

9. The HRA also has well-established partnerships with the MHRA, the Human Tissue Authority, the UK Health Departments, and other organisations regulating and governing research.

10. The HRA coordinates a UK-wide steering group to ensure that identified solutions are adopted widely to maximise further improvement. The HRA chairs the UK Ethics Committee Authority (UKECA), which has responsibility for establishing, recognising and monitoring ethics committees under the Medicines for Human Use (Clinical Trials) Regulations 2004.

Influencing EU Regulations for Clinical Trials

11. The HRA is an active member of the MHRA steering group, which is formulating the UK response to the revision of the EU regulations for clinical trials, and with them contributes to negotiations in Europe.

Transparency in Research

12. The HRA is committed to transparency, in the conduct of its own business and in promoting transparency in research and improving public confidence in research. As part of the IRAS application process, researchers are asked to provide information about the registration of their study on a publicly accessible database, and their plans for dissemination of results; and these aspects are reviewed by RECs.

13. As well as publishing research summaries for all applications, the HRA is developing a policy framework for transparent research. It is engaging key stakeholders in developing the framework to describe the HRA's role in promoting transparency of research, through registration, publication, dissemination, access to data, access to tissue and providing results to study participants.

14. The HRA fully supports the European Commission's ambition, as part of the revision of the EU Clinical Trials Directive, to increase and improve transparency in clinical trials.

Declaration of Interest

The author has no declarations of interest.

February 2013

Written evidence submitted by INVOLVE

KEY POINTS

- Public involvement in research is critical to its quality and relevance but also to ensuring that it is conducted to the highest standards and in the public interest
- Lack of disclosure of clinical trial results has been a perennial issue of concern to patients and the public.
- Reducing research regulation is equally important to patients but not if it is at the expense of issues of importance to them
- We welcome the work being done by the Health Research Authority (HRA) to address issues around bureaucracy but also transparency of reporting etc. We welcome the HRA's forward-thinking attitude to patients and the public.
- All research funders should commit to making sure that research participants receive the results of trials they have taken part in as well as how the research has improved knowledge into their condition.
- We welcome the work that NIHR is doing in partnership with INVOLVE and others to make information on open trials and the results of trials more openly accessible through the provision of plain English summaries.
- The UK Clinical Trials Gateway (UKCTG) is a potentially important vehicle for making clinical trial results and data more publicly available.

INVOLVE welcomes the opportunity to submit written evidence to the House of Commons Science and Technology Select Committee inquiry into clinical trials and disclosure of data.

INVOLVE is the national advisory group for the promotion and advancement of public involvement in all forms of health and social care research. Established in 1996 we have been funded by the National Institute for Health Research (NIHR) since 2006 and remain one of the few publicly funded organisations for public involvement in research across the world.

The perspectives of patients and the public are crucial to any discussion on clinical trials. They are key as both participants in trials and ultimately as the people for whom the research is aimed to benefit.

Active public involvement in research and research governance is vital to ensure that the interests of patients and the public are considered alongside those of researchers and clinicians. For example they can bring a patient perspective on important issues such as consent, anonymity, risks, safety, transparency and the acceptability and relevance of research. Whilst the public as well as researchers recognise the importance of streamlining and reducing bureaucracy this needs to be done in a way that is acceptable to patients and for patient benefit.

INVOLVE's primary focus is on improving and strengthening public involvement in the design and delivery of research. Nonetheless, over the last decade, we have built up considerable knowledge and expertise in the issues and concerns of patients and the public about the conduct and impact of research more generally. This includes the registration of clinical trials and reporting of trial results.

It has been a perennial complaint of clinical trial participants that they are very rarely told the results of trials they have taken part in and how it has benefited medical research into their condition. Where they take it upon themselves to track down results and any accompanying data they often find it impossible to do so. As patients and the public become more knowledgeable about their condition through the web and other sources, we believe it is imperative that ways are sought to improve transparency in this area so that patients, with their doctor, can make appropriate treatment decisions informed by the latest evidence available.

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

At our recent INVOLVE Conference Sir Iain Chalmers presented evidence published in an article in the Lancet that research is underreported with for example over 50% of studies not publishing in full and over 50% of planned study outcomes not being reported. (Chalmers, I and Glasziou, P. (2009), Avoidable waste in the production and reporting of research evidence, 374: 86–89)

For the public to trust and have confidence in research and to improve patient care and treatment, there needs to be far greater openness and transparency in the publishing and accessibility of research findings. Researchers should be required to make all research findings publicly available as well as to feed back findings to participants. Patients who participate in clinical trials do so with the wish to improve treatments and outcomes for the future. If such research isn't published then both their time and contribution as well as any learning for future research and treatment is wasted.

It is disappointing that, to the best of our knowledge, the pharmaceutical industry has taken no proactive steps in recent months to meet with and discuss the concerns of patients and patient groups on this subject. In our view this has only compounded the perception among many patients and the public that the industry is not acting in their best interests. We would welcome and hope that the Select Committee will encourage a more open dialogue among all relevant parties.

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

The Health Research Authority and NRES have to balance protecting and promoting the interests of patients and the public alongside addressing unnecessary bureaucracy in research governance.

Since the establishment of the HRA in 2011 they have been proactive in their aim to create a unified approval process and to promote proportionate standards for compliance and inspection within a consistent national system of research governance. They have also recently announced plans to develop an HRA policy framework for transparent research, looking at registration, publication, dissemination, access to data, access to tissue and providing information on study results to participants.

Since 2006, INVOLVE has worked closely with NRES to support and develop the role and contribution of the public to ethical review and research governance. With the establishment of the HRA they have continued to work with ourselves and others to ensure that patient and public perspectives are integral to the way that they operate and are in the process of developing their strategy for public involvement. We also welcome the steps that HRA is taking to improve the evidence available on public attitudes to research regulation generally with its recently announced Sciencewise public engagement project.

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

The NIHR is working to improve guidelines and policies to ensure that all NIHR funded research is reported fully and publicly available when the research has been completed. Similar guidance and self regulation is needed for the pharmaceutical industry and other funders. However, in addition there is a role for the Health Research Authority and MHRA working with patients and the public to regulate and monitor the reporting and publishing of research.

In view of the new statutory duties on all NHS organisations to advance and promote research (Health and Social Care Act 2012, and the Government's welcome drive to increase research participation among patients, we would also support any steps to ensure that patients are told the results of trials they have taken part in and thanked for their role in making research happen. This sort of commitment can only help to encourage more patients to choose to take part in research.

Finally, the UK Clinical Trials Gateway (CTG)—one of the few patient-facing pledges in the Government's Life Sciences Strategy—has the potential to be the central point for accessing and recording the progress of all clinical research, providing publicly available information on current research as well as the outcomes of the research in an accessible language and format.

A recent NIHR commissioned survey showed strong support for the idea of the Gateway among patients and the public. Nonetheless respondents identified a range of improvements and modifications to UKCTG with transparency a common theme. For example, in recent months INVOLVE has been leading work as part of an overall drive to include both plain English summaries of all studies as well as plain English summaries of the findings of research. This would help to raise public awareness of both the nature of research being undertaken as well as the extent of reporting of research findings.

February 2013

Written evidence submitted by the Medical Research Council

Introduction

1. The Medical Research Council (MRC) is a UK-based non-governmental organisation funded by a grant-in-aid by the UK tax payer. The mission of the MRC is to improve human health and support economic growth through supporting the delivery of world class medical research. The MRC has a long-standing interest in the development and implementation of clinical trials; and is a major funder of academic clinical trials in the UK and internationally. The MRC is grateful for the opportunity to provide evidence to the Committee and is strongly committed to transparency in registration and publication of clinical trials.

The MRC and Clinical Trials Funding

2. The MRC funds a wide spectrum of medical research from basic and preclinical work through experimental medicine studies to early proof of efficacy trials. It also provides support for a range of population based epidemiological and public health studies. In considering the area of this inquiry it is important to have clearly agreed terminology. The term "*Clinical trial*" includes trials of *investigational medicinal products* (IMPs) as defined in the current UK and EU legislation. However, the Committee will be aware that there are also clinical trials that assess the safety or efficacy of medicines not defined as IMPs or of devices or other interventions, such as surgical techniques or behavioural therapies. There are also *clinical studies*—a term that MRC uses to describe other research involving people, often with the aim of understanding the pathways to disease or health but not assessing the safety or effectiveness of interventions. The need for clarity in these

definitions is very important in determining the optimal means of ensuring transparency of clinical trial findings and assessing whether these are appropriately adopted.

3. The MRC has a long history of funding early and late phase clinical trials conducted in the UK and internationally. In 2006 there was an alignment of the remits of the MRC and the National Institute for Health Research (NIHR) in clinical trials funding in England. The MRC has responsibility for funding first-in-man and early phase trials and NIHR has responsibility for funding later phase trials through the Health Technology Assessment (HTA) panel with intermediate (efficacy and mechanism) trials being funded under the joint MRC-NIHR EME programme. The MRC also funds Global Health trials, in coordination with DFID, at both early and later stages.

Clinical Trial Findings and Data

4. In relation to questions about publication and transparency it is again important that consistent terminology is used to allow clarity as to what is required from all involved in any aspect of clinical trials. The MRC considers it is important to differentiate between:

(a) Clinical trial findings or outcomes—the final outcomes of the trial after appropriate statistical analysis. These should be published in accordance with the CONSORT guidelines,[78] where these apply, and this is a requirement for MRC funded clinical trials.

(b) Research Datasets—these range from aggregated to anonymised to complete identifiable datasets for each participant. The MRC requires researchers to allow access to their research data in accordance with the Data Sharing Policy.[79]

MRC Funded Clinical Trials: Registration and Publication

5. The MRC is committed to promoting the highest standards of good practice in the conduct of the research that it funds. Prior to the adoption of the EU Clinical Trials Directive the MRC led the way in providing guidance on Good Clinical Practice for Clinical Trials (published in 1998) which included requirements for Independent Data Monitoring Committees and Trial Steering Committees for clinical trials. These two committees provide a very important role in independent review of clinical trial data, analysis and outcomes. The MRC was a founder member and has Board representation on ISRCTN—one of the first global clinical trial registers which accepts registration of all clinical trials assessing efficacy of any intervention (not restricted to IMPs) in people. The MRC also funds the CONSORT group which provides authoritative guidelines on transparent clinical trials reporting.

6. The MRC requires access to funded research data and sharing through policy requirements and supports this through the MRC Data Sharing Initiative.[80] The MRC has been a lead partner in development of Open Access to research publications. The MRC initially developed the MRC-DH Clinical Trials toolkit[81] (now hosted by NIHR) and continues to provide authoritative advice and guidance on best practice in all areas of clinical research through the MRC Regulatory Support Centre.[82]

7. These initiatives support our commitment to best practices in transparent reporting and access to research data, however, there may be further needs to address gaps in this area and the MRC is committed to providing resource to address these, acting with relevant partners and stakeholders.

8. The MRC policy on publication of clinical trial (and other clinical study) results states that:

> *Results of MRC-funded clinical studies (whether positive or negative) must be published within a reasonable period (generally within a year of completion) following the conclusion of the study. Results should be reported in accordance with the recommendations in the CONSORT statement [Schulz et al. BMJ 2010;340:c332]. Data should be made available in line with the MRC Policy on Data Sharing.*

9. In the MRC data sharing policy it is stated that:

> *The MRC expects valuable data arising from MRC-funded research to be made available to the scientific community with as few restrictions as possible so as to maximize the value of the data for research and for eventual patient and public benefit. Such data must be shared in a timely and responsible manner.*

10. Advances in information systems, grant coding and tracking are making confirmation of registration of clinical trials more accurate and less resource-intensive. In order to establish a current baseline for registration and reporting of MRC funded work we are undertaking an initial review of registration and publication of outcomes for MRC funded clinical trials. The baseline position from this review will also provide the opportunity to identify whether and how MRC policies and compliance review might need to be more explicit or stringent in relation to registration and publication. It is likely that there is scope for improvement in ensuring

[78] http://www.consort-statement.org
[79] http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/datasharing/index.htm
[80] http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/datasharing/index.htm
[81] http://www.ct-toolkit.ac.uk/
[82] http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/RegulatorySupportCentre/index.htm

a joined-up approach from initial clinical trial registration to recording final outcomes and publications. The MRC is committed to supporting improvements that may be required, in partnership with other funders and sponsors across the spectrum of clinical trial funding.

Responses to the Questions of the Science and Technology Committee

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

11. The proposed revisions will address only interventional clinical trials of IMPs and so are not relevant to non-IMP clinical trials. The main regulatory barriers to clinical research in the UK have been reviewed by the MRC in partnership with other funders and academic societies. The MRC, on behalf of RCUK, submitted two responses to the Academy of Medical Sciences Working Group[83] which published the report "*A New Pathway for Regulation and Governance of Health Research*".[84] The MRC supported the recommendations in this Report which identified that there are barriers to conducting clinical trials in the UK that arise from the current Clinical Trials Directive. However, further significant barriers do not stem from the Clinical Trials Directive, but from other aspects of the complex regulatory framework for clinical trials and other clinical research in the UK. This is particularly marked for clinical trials that occur across several sites and for those that require access to patient data for follow-up of outcomes. The underpinning issues include a lack of clarity on roles which are often duplicative; requirements for multiple NHS R+D approvals; and the particularly complex framework relating to access to and use of NHS patient data for clinical research.

12. The proposed revisions to the EU Regulations have been welcomed by the MRC and partner organisations.[85,86] As drafted, they will address many of the barriers that have arisen from the current Clinical Trials Regulations. In particular, the revisions allow for a more risk-proportionate framework and improved harmonisation of review of multinational trials.

13. However, there are remaining issues in relation to the scope of the revised legislation, for example, in its definition of interventional clinical trials; in the delineation of risk categories and the requirements for reporting adverse events. Many of the proposed amendments to the draft legislation from the Rapporteur are welcome in addressing these issues although there is a risk that some of the amendments will further increase the regulatory burden without improving protections for patient safety, rights and well-being. In particular we are concerned at an emphasis on publication of Clinical Study Reports (CSRs) as an assurance of transparency. Such reports are provided for marketing submissions but not for the vast majority of clinical trials in the academic sector where their provision can take at least three months. Therefore, requiring this for each academic clinical trial would be a significant burden on academic funders.[87] The CSR is unlikely to provide any more relevant information than ensuring publication of outcomes and access to appropriate final data, including the statistical analysis plan. The MRC will be submitting comments on the proposed amendments to the draft Regulations and can provide these to the Committee once available.

14. The proposed revisions will not address other regulatory barriers to research in the UK as outlined above, for example, access to records or Registers for follow-up of participants of a clinical trial. This currently requires approval from an NHS research ethics committee, from NHS R+D at each NHS Trust or body involved as well as the local Caldicott guardian and/or s251 approval. These approvals are not coordinated so duplicative or contradictory views can be provided and the timescale for completion of approvals is often long. We are extremely concerned that proposed amendments from the LIBE Rapporteur on the draft European Regulations on Data Protection may make such research much more difficult, if not impossible.

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

15. The role of the HRA includes the role previously delivered by the National Research Ethics Service (NRES) in coordination of governance and guidance for the NHS research ethics committees (RECs) which provide review of clinical trials. In addition, the HRA will oversee the s251 approvals process through which researchers request access to NHS health records when explicit consent is not in place. The HRA is a relatively new body and so there has been a very short period over which to judge its effectiveness.

16. Prior to establishment of the HRA, NRES fulfilled a commendable role in developing consistency across RECs; providing governance and streamlining approvals such that a single REC approval applied to all clinical trial sites in the UK. In addition, development of the Integrated Research Approvals System (IRAS) is widely recognised as a very positive step to a single portal for applications for approvals of research studies.

[83] Academy of Medical Sciences review of regulation and governance of medical research: Call for evidence: June 2010—http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC007048 and August 2010: http://www.rcuk.ac.uk/documents/submissions/RegulationMedicalResearch_Aug2010.pdf

[84] http://www.acmedsci.ac.uk/index.php?pid=99&puid=209

[85] Joint statement on the Clinical Trials Regulation: http://www.acmedsci.ac.uk/p47prid118.html

[86] MHRA consultation on the draft EU Regulation for Clinical Trials for Medicinal Products: December 2012: http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC009007

[87] The MRC Clinical Trials Unit completes an average of eight trials a year. Provision of a CSR for each would require up to £100,000 per annum.

17. To date the HRA has shown a commitment to continue the positive approach of NRES and also to commence a review of the processes and requirements for research approvals in the UK. The proposed pilot on facilitating NHS research approvals is very welcome. The effectiveness of the HRA in improving the clinical trials environment will be predicated upon its ability to conduct such a review; to ensure that its findings can be implemented and effective collaboration with other regulators, in particular MHRA. An optimal approach that will streamline research approvals in the UK while protecting participant safety and rights may require amendments to legislation or Codes of Practice as well as significant changes in how other Regulators and NHS Trusts deal with local and central research approvals.

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

18. There have been widely publicised examples of large fines imposed on pharmaceutical companies for not making relevant data available to Regulatory authorities. Where this has occurred there are potential risks to public health and to the progress of medical research in identifying new effective and safe therapies. Regulators need the most complete information available to take a balanced view as to the risk/benefit ratio of the use of a drug. In addition, other researchers benefit from knowing results from previous trials in order to avoid duplicative approaches. There may also be unidentified benefits of treatments in clinical trials that could be found from access to appropriate datasets. These last two benefits need to be balanced with the commercial interests of companies in proprietary data whereas the requirement of disclosure to regulators is absolute.

19. There have also been recent announcements of steps that companies are taking to increase transparency and access to trial data. One example is the recent announcement by GSK of its intention to allow access to clinical trial data.[88]

20. The MRC collaborates in research funding with industry partners and considers this a valuable and important approach to medical research. Such collaborations are funded under an MRC Industry Collaboration Agreement (MICA) which includes agreement on publication of results and data in accordance with standard MRC policies with the potential to recognise a period of exclusivity for commercially privileged information.[89]

21. It should be noted that there are also failures of non-commercial trials to publish outcomes or make data available in an appropriate and timely way. The factors and consequences of non-publication may differ from those relating to commercial trials. However, there is good evidence that trials which give negative results have been under-reported, leading to bias in the available body of evidence towards positive outcomes of new interventions. One consequence of this is seen when meta-analyses clarify from large, authoritative trials that the benefits of an intervention are lower than originally supposed, or absent altogether—revealing a waste of time and resources invested in conducting unnecessary further trials.

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

22. In order to ensure transparency for the public, regulators and other researchers, the MRC strongly agrees with the need for all clinical trials to be registered on publically accessible registers. This applies to all clinical trials of investigational medicinal products as an absolute minimum. However, there should also be registration of non-IMP interventional trials, as provided by, for example, ISRCTN. Other approaches to enhance registers and make them more accessible are also valuable—for example the NIHR sponsored Clinical Trials Gateway. The MRC, with other Research Councils also makes publically available the full portfolio of funded research alongside information on outputs.[90]

23. It should also be mandated that the outcomes of all clinical trials are published in peer-reviewed journals or otherwise made publically accessible—this is a requirement of MRC clinical trial funding. Further, there needs to be clear linkage of publications of the results to the registration in order to facilitate discovery of the relevant data and also to provide a straightforward check on compliance. There also needs to be a means for clinical trial findings that are not accepted for peer-reviewed publication or that are not completed be made publically available.

24. The MRC is committed to ensuring that clinical trials are registered and that outcomes are accessible and will provide additional support for this. It is important that approaches to registration and publication of findings are easily accessible to all ensuring that a full overview of open clinical trials is available to patients as are the outcomes of all clinical trials relevant to their condition. There are improvements that could be made to the current approaches to these and the MRC will support the development of improvements needed in this regard in relation to its remit in clinical trials support.

25. Once optimal systems are in place to allow discovery of which clinical trials have been undertaken and what their outcomes are, there also need to be mechanisms to ensure compliance with requirements for all clinical trials be recorded in this way. The MRC has identified that in order to implement effective monitoring of compliance there needs to be appropriate and consistent definitions of projects to be tracked; effective

[88] http://www.bmj.com/content/345/bmj.e6909
[89] http://www.mrc.ac.uk/Fundingopportunities/Grants/MICA/Specification/MRC005438#P26_1314
[90] RCUK Gateway to Research: http://gtr.rcuk.ac.uk/

systems to track projects from funding to trial registration to outcomes and sufficient resources to complete the analysis. Many of the challenges can be addressed through improvements to evaluation and IT systems.

26. The MRC strongly supports the requirement for researchers to facilitate access to appropriate clinical trial data to inform and support further research and to review clinical trial findings. The mechanisms by which such access should occur are currently under discussion and expert reports from the Caldicott review, the Royal Society and European Medicines Agency (EMA) are due to be published in the first half of 2013 and will inform conclusions on the preferred model. It is clear that such access needs to provide a straightforward and timely route to disclosure of usable datasets that do not breach participant confidentiality; vitiate their consent or undermine data integrity. One approach, that MRC has endorsed, is to use "safe havens" to store, collate and provide access to single or combined datasets. There are also examples of Centres of Excellence that facilitate access to requested data without transferring to a safe haven—as is the case for the MRC Clinical Trials Units. Whichever mechanisms are adopted, it is important to ensure that the data made available are high quality, reliable and provided in a usable format within a reasonable timeframe. The MRC has supported development of "safe havens" and appropriate standards of research data for sharing through the MRC Data Sharing Initiative.

27. The question of whether these datasets should be made openly and publically available without any access "gatekeeper" or redaction is more complex. The key factors to be considered include the information and consent provided to and given by clinical trial participants; the risks of inadvertent identification of participants (particularly pertinent to smaller sample groups; rare diseases or stratified approaches). There is also the risk that data may be used for methodologically flawed research which may be linked to the original research group or funder to give an impression of quality or authority; or which might be used to promote agendas which the trial participants would not have consented to. In addition, there is a serious risk of deliberate misuse, such as deductive identification of trial participants to link to their health details or outcomes. The MRC's view is that the use of neutral "safe havens" or Centres of Excellence to curate and provide data through an independent access procedure provides the best way of balancing the need to respect the concerns of participants; to ensure governance and ownership of research is clear; and to realise the benefits from broadening access to clinical trial data. The MRC has welcomed the increased emphasis on the potential benefits of research participation for patients in the NHS Constitution and recognises the desire of many people to be more aware of research outcomes and current clinical trials relevant to their condition. The MRC would welcome enhanced measures to make information about relevant clinical trials more easily available to patients, clinical teams and carers at the point of care.

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

28. The position in the EU is being reviewed by EMA building on its workshop in November 2012. The MRC does not have further specific examples to provide at this point.

February 2013

Written evidence submitted by Dr Ben Goldacre

1. I am a medical doctor, currently working as a Research Fellow in Epidemiology at London School of Hygiene and Tropical Medicine. For the past 10 years I have written about problems in science for the Guardian, and in two books: Bad Science, and Bad Pharma. I am also a co-founder of alltrials.net, a widely supported non-profit campaign group seeking to improve access to clinical trial results.

2. Background

3. Healthcare professionals and patients need the results of clinical trials to make informed choices about which treatment is best. Currently, drug companies and researchers are allowed to withhold the results of clinical trials, on treatments currently in use, from doctors and patients if they wish to. This means that we are misled about the benefits and risks of treatments. We can be misled into prescribing an expensive new drug, for example, when in reality an older cheaper one is more effective. As a consequence, patients are exposed to avoidable harm, and money is wasted unnecessarily.

4. Withheld results are a problem for both industry and academic trials. The best currently available evidence, from the most current systematic review, estimates that only half of all trials are published, and trials with positive results are twice as likely to be published. A systematic review is the most robust form of evidence, since it is an unbiased overview of the evidence. This systematic review is published by the NHS NIHR HTA programme.

5. http://www.hta.ac.uk/fullmono/mon1408.pdf

6. The ongoing problem of withheld trial results has not been adequately addressed by any of the initiatives in place today. The FDA Amendment Act 2007, for example, requires that results for a subset of trials (one research site in the US, studying a currently licensed drug, etc) are posted at clinicaltrials.gov within one year of completion. This legislation is widely cited as evidence that the problem of missing trials has been fixed.

However there was no routine public audit of implementation, and when one was finally conducted, and published in the BMJ in 2012, it found that this law has been ignored by four trials out of five.

7. Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. BMJ. 2012;344:d7373.

8. http://www.bmj.com/content/344/bmj.d7373

9. In any case, this and other interventions would have done little to improve medicine today, even if they were effective. This problem cannot be addressed prospectively, by ensuring access to trials finishing after 2008, or after 2013: around 85% of medicines prescribed in the UK are "generic", and came to the market a decade ago or more. It is the evidence from this era of clinical trials that we need most—2003, 1999, 1993—to ensure prescribing today is safe and effective. In almost all cases (although perhaps not for aspirin trials six decades ago) this information still exists. Doctors and patients should be given access to it to make informed decisions.

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

11.

12. I am working with colleagues on low cost randomised controlled trials, seamlessly embedded in routine clinical care, using the General Practice Research Database, and have submitted a response with them on the separate issue of administrative barriers to doing clinical trials more efficiently in the UK.

13. So far ethics committees have not sought to address the issue of withheld trial results. This is problematic, as it is one of the key ethical problems in medical research. Patients participate in trials in the belief that they are helping to improve knowledge and treatments for future patients. Where trial results are withheld, those patients have been misled. I understand that Janet Wisely, the new head of the HRA, is keen to engage on this issue. In my view there are certain elements that should be laid down in the legislation for this body.

14. Research ethics committees should ensure that researchers do not have a previous track record of leaving trial results unpublished, before granting them permission to conduct further studies on trial participants. This can be done at almost no administrative cost, by simply requesting a signed statement from the lead medic or primary investigator that they are not witholding the results of any trials more than one year after completion. Similarly the HRA should insist on a commitment to publication, then publicly monitor and audit compliance. Again this would not require any significant administrative or investigative activity: an ethics committee can simply make a diary note, write to the primary investigator, and ask for a link to results publication, whether in an academic paper or on a results registry, one year after completion of the trial.

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

16. I have addressed this in an attached memorandum, as suggested, because it is adapted from an earlier document which I initially drafted as a briefing note for Earl Howe, and then as a briefing note for alltrials.net.

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

18. In my view there has been a widespread systemic failure by regulators, industry, universities, policy makers, and medical and academic professional bodies to take ownership of this problem. As a consequence we have seen an incomplete patchwork of interventions that have failed to address the core issue—we need doctors and patients to have access to all results of all trials on all currently used treatments. Instead we have engaged with peripheral details.

19. "Clinical trial registries" are a clear illustration of this problem. Registers are public lists that contain a small subset of all the trials that have been conducted on a medicine. They are incomplete by design. The European Clinical Trials Register is a list of trials conducted within Europe over the past few years. It is not a list of all the trials that have been conducted on all the medicines currently available in Europe. It should be, or it should at least strive to be. Clinicaltrials.gov, similiarly, is mostly trials conducted in the US, mostly from the past ten years, and with compulsory registration only since 2007 (though even here compliance is uncertain). These limitations reflect the early administrative origins of these registries. They are not what trial registries should be, or need to be, to inform evidence based clinical practice, and to achieve the clear goal of access to all results.

20. The European Clinical Trials Register should simply be a list of all the trials ever conducted, on all the medicines currently prescribed in Europe. It should include results. Where and when these trials were conducted is irrelevant. It is clear to me, from my experience of talking to the public, journalists, doctors, policy makers and academics about these problems, that many people believe a trials register to be just this: a complete list of all the trials that have been conducted. This is indeed what they should be.

21. There are many stories of how companies have refused to hand over information. These in turn have generated discussions about what levers are available, and how we can force companies (in particular) to hand over trial results. I am struck that we have never tried simply asking, in a systematic fashion. The European Medicines Agency could say: "You have a marketing authorisation to sell your medicine in Europe. We maintain a list of all trials ever conducted on all uses of all medicines currently prescribed, so that doctors and patients can make informed decisions. Here are the forms: please tell us about all the trials you hold, or are aware of."

22. However there are many other stages where influence could be brought to bear. IQWiG, the German equivalent of NICE, has developed a reputation for demanding high standards of evidence before approving a drug for use, and also for requiring all trial results to be shared with them, and then making those public. It is through this mechanism that we have become aware of major problems with currently used medicines such as reboxetine.

23. http://www.bmj.com/content/341/bmj.c4737

24. We could use this more robust approach in the UK. We could also insist that a treatment is only available for prescription after all the trial results have been made publicly available.

25. Universities could also insist that all results are published, and that all collaborative contracts between academics and industry include the right to publish, and the right of access to data.

26. There is also the matter of culture. I am concerned that the impact of withheld results on patient care is currently a cultural blindspot in medicine and academia, even despite systematic review evidence showing that half of all trials do not go on to be published. It is a peculiar paradox that we spend so much money on each individual trial, investing huge effort to ensure that they are free from bias, carefully appraising their strengths and weaknesses, then allow so many of them to be simply deleted from the record. This non-publication reintroduces all the biases we spend so much time and money avoiding back into the evidence base.

27. We need wider recognition that this is a serious problem, and that it gravely undermines our attempts to practice evidence based medicine and make informed decisions. If a researcher selectively deletes the unflattering data points from one single trial, in order to massage the results and get the result they want, they are rightly regarded as being guilty of research misconduct. This is a serious business, since they are misleading doctors and harming patients. However, if a group of researchers delete whole trials from the overall research picture, then there are no reputational or professional consequences, even though we know that this will distort the apparent benefit of the treatment, just as surely as one researcher fraudulently manipulating the results of a single trial.

28. This could be addressed in part through medical and academic membership bodies. They could demonstrate leadership on this issue, state clearly that withholding the results of clinical trials is research misconduct, and impose sanctions or even ejection where appropriate.

29. I am concerned that currently most major UK medical and academic bodies have done the opposite. Many are currently signatories to a pair of documents produced by the "Ethical Standards in Health and Life Sciences Group" that give false reassurance around the issue of withheld trial results. The ESHLSG is co-chaired by the ABPI (the UK pharmaceutical industry body) and the Royal College of Physicians. Engaging with industry on ethical challenges is plainly a good thing. However the ESHLSG documents appear to make misleading statements about the problem of withheld results. For example they make extensive reassuring comments about current regulations, while failing to disclose the best currently available evidence, from fully published academic papers, in leading peer reviewed journals, which demonstrates that these regulations have been routinely ignored. I believe this issue may be covered in more detail in a submission by the "Bad Guidelines" group, but I am happy to give more details.

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

31. No. The European Clinical Trials Register is incomplete even by its own standards, with many trials still withheld from the public form of the register, and the EMA has failed outright to deliver on key objectives, such as their promise to carry results on their register by 2012. The US registry at clinicaltrials.gov is incomplete by design, as discussed above—it is not retrospective, and does not cover all trials on a treatment—and even for its limited remit the FDA Amendment Act 2007 has not been adequately implemented, with trial results still routinely withheld, as shown by Prayle *et al*, 2012 referenced above. Even if similar legislation was perfectly implemented, and muscularly enforced, any beneficial impact of getting trial results from now onwards would only be felt in several decades' time.

32. We need to ensure that doctors and patients have access to all results of all trials that have ever been conducted on all treatments currently in use, in order to make informed decisions about which treatment is best. We need serious working groups to discuss how to achieve this objective, urgently.

33. We need a credible public process to explore the details of the costs involved to industry and academia of retrospective disclosure, in either summary results form or Clinical Study Reports, where those exist. The EMA now discloses Clinical Study Reports on the small proportion of trials that they hold, and the European Ombudsman said that the administrative burden of doing so—and of removing some identifiable patient

information where appropriate—is not significant. GSK have also committed to releasing Clinical Study Reports, in signing up to alltrials.net

34. I would also suggest a pilot of full disclosure, either for some commonly used drugs, or for some commonly used classes of drugs. This would allow us to identify any costs, the changes to the evidence base for current decisions, and therefore the public health benefits.

35. I believe Sir Iain Chalmers, co-founder of the Cochrane Collaboration, has made a submission on how he has been told this problem is being fixed for three decades now. There are many who use the reassuring language of "engagement" on missing trials, but act inconsistently. We should not lose momentum on this important public health issue.

36. Declaration of Interests

37. I am currently a Research Fellow in Epidemiology at London School of Hygiene and Tropical Medicine. I earn income as a doctor, academic, writer and broadcaster. In my work I discuss problems in science, including publication bias, which is a major theme in my book Bad Pharma. I am a co-founder of alltrials.net with the BMJ, Oxford University Centre for Evidence Based Medicine, the James Lind Library and Sense About Science. Alltrials.net is a non-profit campaign group to improve access to clinical trial results with extremely broad support.

February 2013

APPENDIX

MISSING TRIAL DATA

Ben Goldacre (adapted from alltrials.net briefing note, grateful for assistance and support from alltrials.net team).

1. Healthcare professionals and patients need the results of clinical trials to make informed choices about which treatment is best. Currently, drug companies and researchers are allowed to withhold the results of clinical trials, on treatments currently in use, from doctors and patients if they wish to. This means that we are misled about the benefits and risks of treatments. We can be misled into prescribing an expensive new drug, for example, when in reality an older cheaper one is more effective. As a consequence, patients are exposed to avoidable harm, and money is wasted unnecessarily.

2. This problem is very well documented, and widely discussed within the professional academic literature. It has not been adequately engaged with by policy makers.

3. The Scale of the Problem

4. The current best estimate is that around half of all the clinical trials that have been conducted and completed have never been published in academic journals, and trials with positive results are twice as likely to be published as others. This figure comes from a systematic review conducted in 2010 by the NHS NIHR Health Technology Assessment programme. A systematic review is an unbiased overview, that covers all the research that has ever been done on a particular question in science. This is the most robust form of evidence, and it is risky to permit unsystematic "cherry picking" of other evidence.

5. http://www.hta.ac.uk/fullmono/mon1408.pdf

6. This problem occurs for industry and non-industry trials, internationally, at all stages of drug development, and for trials of all sizes.

7. The majority of drugs in current use were approved several years ago. Around 85% of prescriptions in the UK are for generic medications: these generally came on the market more than ten years ago. For this reason, it is unsatisfactory to fix the problem with greater access to the results of all trials starting from now. The rates of missing data over past few decades have the greatest detrimental impact on current clinical practice, and this missing data will continue to do harm for decades to come, as those drugs will continue to be used.

8. However, evidence collected since the NHS NIHR HTA review shows that the problem also persists at very high rates. Results from individual studies rather than systematic reviews should be interpreted with caution. With that caveat, here are three prominent recent studies (assembled by Dr Carl Heneghan for the alltrials.net briefing document):

(a) Ross J S, Tse T, Zarin D A, Xu H, Zhou L, Krumholz H M. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. BMJ. 2012 Jan 3;344:d7292. doi: 10.1136/bmj.d7292.

(b) "Among 635 clinical trials completed by 31 December 2008, 294 (46%) were published in a peer reviewed biomedical journal, indexed by Medline, within 30 months of trial completion. The median period of follow-up after trial completion was 51 months (25th–75th centiles 40–68 months), and 432 (68%) were published overall."

(c) "Despite recent improvement in timely publication, fewer than half of trials funded by NIH are published in a peer reviewed biomedical journal indexed by Medline within 30 months of trial completion. Moreover, after a median of 51 months after trial completion, a third of trials remained unpublished."

(d) Bourgeois FT, Murthy S, Mandl KD. Outcome reporting among drug trials registered in ClinicalTrials.gov. Ann Intern Med. 2010 Aug 3;153(3):158–66. doi: 10.1059/0003–4819–153–3–201008030–00006.

(e) "Overall, 362 (66.3%) trials had published results. Industry-funded trials reported positive outcomes in 85.4% of publications, compared with 50.0% for government-funded trials and 71.9% for nonprofit or nonfederal organization–funded trials ($P < 0.001$). Rates of trial publication within 24 months of study completion ranged from 32.4% among industry-funded trials to 56.2% among nonprofit or nonfederal organization–funded trials without industry contributions ($P = 0.005$ across groups)."

(f) Deborah A Zarin, M D, Tony Tse, Ph.D., Rebecca J Williams, Pharm.D., M.P.H., Robert M Califf, M D, and Nicholas C Ide, M S. The ClinicalTrials.gov Results Database—Update and Key Issues. N Engl J Med 2011; 364:852–860March 3, 2011DOI: 10.1056/NEJMsa1012065

(g) "We characterized the 79,413 registry and 2178 results of trial records available as of September 2010. From a sample cohort of results records, 78 of 150 (52%) had associated publications within two years after posting."

(h) "ClinicalTrials.gov provides access to study results not otherwise available to the public. Although the database allows examination of various aspects of ongoing and completed clinical trials, its ultimate usefulness depends on the research community to submit accurate, informative data."

9. There have been no changes to legislation since the 2010 NHS NIHR HTA systematic review was conducted.

10. Failed Initiatives

11. Two major failed initiatives are commonly cited as evidence that the problem of "missing trial results" no longer exists: journals requiring registration before publication, and FDA legislation requiring results to be posted on clinicaltrials.gov within one year of completion.

12. ICMJE and Journals Requiring Registration before Publication

13. Trialists are encouraged to register the existence of their trials publicly, to ensure that there is a clear record of trials in progress. Although this does not guarantee reporting of results, it allows some public scrutiny of whether completed studies have been published.

14. In 2005, after concern that trial registration was not being used, the International Committee of Medical Journal Editors said they would only publish trials that had been registered at inception. The intention was to force trialists to register trials. There was no public audit of this promise, however, and in 2009 it was shown that half of all trials published in major medical journals after this requirement had been announced had not been properly registered, and a quarter had not been registered at all.

15. *Mathieu S, Boutron I, Moher D, Altman D G, Ravaud P. Comparison of Registered and Published Primary Outcomes in Randomized Controlled Trials. JAMA. 2009 Sep 2;302(9):977–84.*

16. http://jama.jamanetwork.com/article.aspx?articleid=184503

17. This is perhaps not surprising, since academic journals have their own conflicts of interest around: publishing positive findings (positive results may get higher citations, and these will increase an academic journal's "impact factor", the widely used index of journal quality); and publishing industry findings (such as revenue from reprints and adverts).

18. Failure of the European Medicines Agency Clinical Trials Register

19. The EMA was asked to produce a clinical trials register in 2001, and then in legislation in 2004. It is important to be clear that a register contains notice of the existence of a trial, and some aspects of the trial's design, but not its results. For many years the contents of this "transparency tool" were held by the EMA in secret. Since March 2011, after public criticism, the EMA has made a publicly accessible register. However, despite claims that this is complete, in reality, details of the existence of several thousand trials are still currently withheld from the public, while the EMA considers whether they should be disclosed. There should be a presumption that details about all trials on the register are to be disclosed.

20. Furthermore, unlike the US register at Clinicaltrials.gov, information about all Phase 1 trials are held in secret. This is despite the inquiry into the TGN1412 trial stating that Phase 1 trials should be made more widely available, to prevent harm to trial participants (pp86–87).

21. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_073165.pdf

22. There is currently no facility on the EMA register to allow researchers to disclose the existence of their registered Phase 1 trials, even if they wish to do so.

23. The EMA has also stated on many occasions that it would produce a publicly accessible database of trial results in 2012. It is now 2013 and they have not done so.

24. Finally, it is perhaps worth noting that in my (BG) anecdotal experience of checking specific trials, the contents of the EMA register can be in error, or at least shown to be inconsistent with the contents of other registers, when trials have been posted on more than one register.

25. FDA Legislation Requiring Results to be Posted on clinicaltrials.gov within one Year of Completion

26. The US government FDA Amendment Act 2007 requires that, for all trials with at least one site in the US, researching a currently licensed drug, etc., all results must be posted on the website clinicaltrials.gov within a year of completion of a trial. This law is widely cited as evidence that the problem has been fixed. However there has been no official public audit of compliance, and no publicly accessible structured data on due dates for results.

27. An audit was conducted independently and published in the British Medical Journal in 2012. This is the best currently available evidence, and it shows that only one in five trials has met this reporting requirement (compliance was 40% for industry funded trials, and 10% for mixed industry and independent trials). Despite this very low compliance, no fine has ever been levied against any company or researcher for failing to post results. Even if a fine had been levied, it is $10,000 a day, or $3.65 million a year: this is trivial for a large organisation.

28. *Prayle A P, Hurley M N, Smyth A R. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. BMJ. 2012;344:d7373.*

29. http://www.bmj.com/content/344/bmj.d7373

30. Even if this law had been implemented, it would not have fixed the problem. It would only require publication of trials completing after 2008, whereas prescribers mostly use medicines approved over several previous decades, and so we rely on evidence from trials done much earlier than 2008 to make decisions about which *current* treatment works best. It also misses many trials conducted outside the USA, which is increasingly common now that trials, including post-marketing trials, are commonly run by Contract Research Organisations in Brazil, Russia, India, China etc.

31. Tamiflu and Access to Clinical Study Reports

32. Tamiflu (oseltamivir) is a drug the UK government has spent £500 million stockpiling. The manufacturer, Roche is currently withholding important information about trials on this drug from the Cochrane Collaboration, the large international non-profit academic collaboration that produces rigorous systematic reviews of reliable evidence on the effects of drugs and other forms of healthcare interventions for doctors and patients.

33. http://www.plosmedicine.org/article/info:doi%2F10.1371%2Fjournal.pmed.1001201

34. http://www.bmj.com/tamiflu

35. Tamiflu is not an isolated case, and the evidence above shows that this problem is widespread throughout the whole of medicine. Tamiflu is, however, the most thoroughly documented case, because of the extent of the research by the Cochrane Acute Respiratory Infections Group.

36. There is one specific issue here: for several Tamiflu trials, while there are brief summaries available in the public domain, these do not contain sufficient information to make an informed judgement about the reliability of the trials, and whether they were methodologically rigorous. This is why the Cochrane researchers have sought access to the full Clinical Study Reports. Roche have publicly promised in writing that they would share these documents, in December 2009, but have since refused to do so. Their recent suggestion that they would convene a committee to look at this issue addresses none of the relevant issues around transparency, and they continue to withhold data.

37. www.bmj.com/tamiflu

38. In 2010 the European Medicines Agency made a commitment to release more CSRs on request, after a change of personnel, and a finding of maladministration against the Agency from the EU Ombudsman over their withholding information from Cochrane researchers. However the EMA only holds documents for very recently approved treatments, and does not hold all the full CSRs on Tamiflu.

39. Researchers and Industry are not the only ones at Fault

40. *Universities* have failed to ensure that contracts with companies sponsoring trials run by academics allow the academics to publish the results of trials, regardless of whether the company is happy with them.

41. *Ethics committees* that approve research projects have failed to protect patients, because they have not insisted that researchers publish results, and they do not check to see if researchers are withholding the results of previously approved trials. This may currently be being addressed by the Health Research Authority.

42. *Medical membership bodies* have failed to act on this issue, and have failed (with one exception) to state publicly that withholding the results of clinical trials is research misconduct.

43. These all represent opportunities to help address the problem of missing results for future trials.

44. It is also worth noting that non-publication of trial results presents a major ethical breach: patients participate in research, experiencing inconvenience and sometimes risk, in the belief that their participation will improve our understanding of which treatment works best. If the results of trials are withheld, then the participants have been misled.

45. Journals

46. Researchers and industry sometimes claim that medical journals will not publish negative trial results. This was a modest problem in another era of medicine, but was fixed a decade ago. The most current NHS NIHR HTA systematic review (cited above) found that overall journals were not the main barrier to publication. With the advent of open access journals where the business model is not dependent on the need to sell subscriptions with high profile "positive" papers, there are now several open-access academic journals—such as the open-access journal Trials, and journals from BioMedCentral and the Public Library of Science—that will publish trials regardless of whether the results are positive. All researchers may struggle to get their academic paper into their first choice of high end academic journal. But academic journals are no longer the key barrier to publishing trial results; they are no barrier to posting results on clinicaltrials.gov; and they are no barrier to sharing Clinical Study Reports.

47. Why do Doctors need to see Results as well as Regulators?

48. A medicine does not simply "work" or "not work". Some drugs work very well, some work less well than other drugs, but are still better than nothing. A medicines regulator decides if a drug should go on the market at all, and they have a low bar for approval. This is good: we need some less effective drugs to come on the market. For example, a patient may have idiosyncratic side effects from the best available drug for their condition, in which case it is useful to have a less effective drug to try next.

49. Doctors and patients need all the information about all the clinical trials that have been conducted on drugs (and other treatments) in order to make informed decisions. A clinical decision ("should this patient receive this drug?") is very different to a regulator's decision ("overall, is it in the interests of society that this drug should be on the market for use at all?").

50. Furthermore, regulators can sometimes miss important problems with medicines. For example, as with Tamiflu, the problems with the drugs Vioxx and Rosiglitazone—both now effectively off the market—were spotted by academics and clinicians rather than regulators. This is not because regulators are incompetent: these are difficult problems, so it is good to have many eyes working on them.

51. It is also good for patients if the evidence behind regulators' decisions can be independently assessed, to ensure regulators have made good decisions. Science is built on transparency: on people critically appraising the methods and results of scientific research to decide whether they agree with each others' conclusions. This is the absolute core of science, it is how we have progressed as a society: the motto of the Royal Society is "nullius in verba", "on the word of nobody". Decisions about which treatment is best for a patient are some of the most important scientific decisions ever taken.

52. Data on Individual Patients who have participated in Clinical Trials

53. This is a separate issue but also important. Better systems for sharing clinical trial data about individual patients would create more transparency, permit more accurate assessments of drugs by doctors and patients, and enable more accurate identification of any subgroups of patients who might respond to a treatment, to a greater or lesser extent than average.

54. Sharing data is very valuable because it facilitates more accurate estimates of the effects of interventions. This is well demonstrated by the work of the Early Breast Cancer Trialists' Collaborative Group, which has demonstrated leadership in this field by conducting highly accurate and informative systematic reviews and meta-analyses using individual patient data from a large pool of clinical trials to inform breast cancer treatment supported by research funding agencies around the world.

55. *Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10–801 women in 17 randomised trials. The Lancet. 2011 Nov;378(9804):1707–16.*

56. http://www.thelancet.com/journals/lancet/article/PIIS0140–6736(11)61629–2/abstract

57. Analyses such as this present challenges in ensuring confidentiality for individual patients (although these can be overcome, and the work of the YODA data sharing project at Yale presents one interesting early proposal of how to manage these issues). This is a different issue, however, to claiming confidentiality about the existence and aggregate summary results of the trials themselves; or withholding information about their design, methods, and conduct.

58. Existing Promises to Share Clinical Trial Data

59. GSK has indicated it will share data on Relenza, its influenza treatment, with the Cochrane Acute Respiratory Infections Group working on Tamiflu. This has not yet happened.

60. GSK has also offered to share more data from its earlier phases of drug development, since 2007, with named researchers, behind closed doors, after review by a GSK panel, to enhance collaboration and innovation. Again, while this is positive, it has not yet happened, and it is unclear what the processes will entail.

61. GSK has signed up as a supporter of alltrials.net, and has committed to share CSRs for medicines currently in use, going back to the founding of GSK by merger a decade ago. This information has not yet been shared, and will take time to produce. However, all of GSK's commitments are extremely important positive steps.

62. The EMA has indicated that it intends to share individual patient data given to them as part of the licensing process for a drug (which is not all trials on that drug). It is presently unclear how this will work. At the EMA meeting to discuss options, industry representatives made clear that they felt industry should be allowed to control access to data and to decide who would be allowed to inspect the data. It was also suggested that this transparency should only be permissible for trials starting in 2014 or later.

63. Because drugs continue to be used for many decades, this will do nothing for the evidence base of currently used treatments, and will have little impact for a decade, if not longer. This is especially the case since many of the most widely used drugs have been on the market for some time, and good treatments continue to be used for as long as they are the best in their class.

64. What needs to Change?

65. All involved parties need to work to ensure that *all results of all clinical trials—past and future—on all treatments in current use* are available to doctors and patients, so that they can make informed decisions about treatments. At present, although this problem is thoroughly documented and ongoing, many in industry seek to deny it exists. NICE, regulators, and medical membership bodies have all failed to accept ownership of the problem or show leadership in addressing it.

66. There is no UK legislation requiring the results of all trials on all drugs in current use to be made available to doctors and patients. There *is* legislation requiring disclosure of adverse events and other monitoring of clinical trials conducted within the UK, such as regulation for "good clinical practice" in the conduct of trials, by the MHRA. This legislation does not address biased under-reporting of clinical trials and should not be confused with the issue of missing results.

67. This problem can be addressed through many means.

68. In Germany, the equivalent of NICE (IQWiG) has developed a reputation for requiring high standards of evidence before recommending the use of drugs. It has also refused to allow drugs to be used until companies have disclosed all trial results to them, which IQWiG has then made public. It is through this mechanism that we have become aware of major problems with currently used drugs such as reboxetine.

69. http://www.bmj.com/content/341/bmj.c4737

70. This more robust approach could and should be replicated in the UK. One option is to insist that a treatment can only be used by the NHS if all information about all trials conducted on it are made publicly available to doctors and patients; or that a company's treatments can only be used by the NHS if all information about all trials on all their drugs are made publicly available. This may be more powerful, or practical, if similar agreements can be sought with other countries in the EU or elsewhere.

71. The current form of the draft EU Clinical Trials Regulation is weak, and does not adequately address the problem of missing results for medicines currently in use. This must be addressed urgently as the Regulation is being considered by the European Parliament now.

72. Research ethics committees must address publication bias for all future trials by insisting on commitment to publication, and publicly monitoring and auditing compliance. Ethics committees could also insist on evidence of publication of researchers' previous trials before giving permission for additional research, for example by requesting a signed assurance from the primary investigator or key medical personnel.

73. Finally, Universities should insist on the rights of access to data and the right to publish results in all collaborative contracts.

Written evidence submitted by the Wellcome Trust

KEY POINTS

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

INTRODUCTION

1. The Wellcome Trust is pleased to have the opportunity to provide evidence to this important inquiry, and we welcome the fact that the Committee is looking at this topic. We fund clinical trials through both our Science Funding and Technology Transfer schemes, but do not act as a sponsor.

2. We consider that the opening up of clinical trials to greater scrutiny is an important part of the research pathway, as it provides an important means of validating research results. However, it is important to distinguish between enabling access to research findings, and making available the detailed data which underpins those findings, which presents additional issues that we discuss throughout this response.

3. We support the disclosure of findings from research involving clinical trials; the Trust's policy position on clinical trials has just been updated and requires all trials to be registered on our clinical trials register. We also require the researchers we fund to maximise access to research data with as few restrictions as possible, although we recognise there are further discussions to be had with regard to the resourcing, infrastructure and curation necessary to achieve this. We have also signed up to the AllTrials petition, which calls for the outcomes of all clinical trials to be made publically available.

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?*

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

SINGLE SUBMISSION, AUTHORISATION AND DECISION PROCESSES

5. Current approval processes for multicountry clinical trials result in multiple assessments across Member States with duplication of work and divergent and inconsistent approaches. We therefore support a system of single submission followed by a coordinated authorisation process for multinational trials. This should reduce the burden on researchers both directly—by removing duplication between multiple submissions—and indirectly by ensuring greater harmonisation in decision making and the application of common requirements across Member States.

6. We also support a system of single authorisation and single decision within the UK. This is a natural progression from the current move towards greater streamlining. A strong relationship between the Medicines and Healthcare products Regulatory Agency (MHRA) and Health Research Authority will be needed to deliver this and we are pleased that these organisations have already had preliminary discussions. Clarity is needed on which elements of the regulatory and governance system would come under this single authorisation and decision, particularly whether this extends to NHS R&D permissions. In order for the UK to provide a competitive environment for the conduct of clinical trials, it is vital that further regulation and governance checks at the local level do not significantly extend authorisation and decision timelines.

7. The single submission and authorisation process will be based on an IT system that will provide a single entry point for the submission of data relating to clinical trials, called the EU Portal. The smooth development and operation of this EU portal will be critical to the success of the single submission, authorisation and decision processes and to deliver the aim of the Regulation to reduce bureaucracy. Sufficient and sustained funding will be needed to develop and deliver the EU portal. We recommend that the Government should seek assurances from the Commission that the EU portal will be ready by the time the Regulation is implemented and that sustainable resourcing will be provided to support the EU portal. We also suggest that the Commission could gather feedback on and learn from the experience of implementing other EU portals, such as the European Database on Medical Devices.

Risk Proportionality

8. The current "one size fits all" approach to clinical trials is not appropriate since different trials carry a different level of risk and benefit. The Regulation must therefore deliver a proportionate regulatory framework that enables regulatory requirements to be adapted according to the risks of the trial. We welcome steps towards greater risk proportionality in the Regulation compared to the Directive since this will help to reduce the regulatory burden on sponsors and regulators, without compromising the safety of participants or the robustness of trial data.

9. The Regulation proposes a two category approach to risk-adaptation, with further scope for risk adaptation that is independent of these categories. The current MHRA approach to risk adaptation uses a three category approach and also demonstrates how much can be achieved through guidance rather than legislation. We encourage the Government to seek further clarity on the amount of flexibility inherent in the Regulation and to undertake a thorough analysis of the risks and benefits of a two category approach in order to assess whether the level of risk adaptation in the Regulation is sufficient compared to the UK's current three category system.

Scope and Definitions

10. We are pleased that the scope of the Regulation has not been increased compared to the Directive. However, the broad scope has created difficulties for some academic trials in the past and we are concerned that this will not be addressed by the Regulation.

11. We note that trials of some products available without prescription, such as vitamins, minerals and food supplements may be captured in the scope of the Regulation based on the interpretation of "medicinal product" as defined in Directive 2001/83/EC. Robust trials of these products are often conducted in academia and are important to increase our understanding of their safety and efficacy. However, trials of these products will not usually fall in the low-intervention category, even though they are widely available without prescription, since they do not have a marketing authorisation. It would be helpful for the Government to seek clarification from the Commission on whether trials of these products are intended to be included in the scope of the Regulation. If the Commission intends to exclude these products, amendments are needed to clarify this. If the Commission intends to include these products, amendments will be needed to ensure these trials are regulated proportionately.

12. Article 2(2)e states that a study is deemed a clinical trial when a clinical study "involves diagnostic or monitoring procedures in addition to normal clinical practice". This has the potential to draw many studies involving the monitoring of standard treatments into the scope of the Regulation, even where the monitoring was a single blood test. The requirements of the Regulation would act as a barrier and disincentive to the conduct of these important studies. This has been a concern under the current Directive[91] and it is important to consider whether this can be addressed in the Regulation. Studies excluded through an amendment would still be covered by the scope of NHS Research Ethics Committees and therefore patient safety would not be compromised, while this approach has potential to foster more research into standard treatments.

13. A lack of clarity in the definitions for key terms in the current Directive has led to inconsistent interpretation in Member States. We welcome the approach of describing the scope of the Regulation through the definition of "clinical trial", rather than relying on the definition of what is excluded ("non-interventional trial"). We think this approach provides greater clarity compared with the approach in the Directive. However, we consider the introduction of a definition of "clinical studies" to be confusing since this term is often used synonymously with "clinical trials". It is important that the definition of "clinical study" is amended to reduce the potential for confusion.

Standards and Requirements

14. We support the approach taken in the current UK Medicines for Human Use (Clinical Trial) Regulations that the International Conference on Harmonisation guidelines on Good Clinical Practice (ICH-GCP) should not be a legal requirement and that instead appropriate GCP standards should be written into the protocol. We are pleased that the Regulation is also flexible with respect to good clinical practice standards since this allows sponsors to determine appropriate requirements for their trial. Any move towards less flexibility is likely to have a detrimental impact on academic clinical trials that are not able to operate to ICH-GCP standards.

15. We welcome the Regulation's moves towards greater transparency around clinical trials, for example on the requirement for registration of trials where information is submitted in the application dossier (Article 25(6)); the requirement to publish summary results of the trial (Article 34(3)); and to make information in the EU database publicly available (Article 78).

16. Provisions for emergency clinical trials are also welcome but must be reviewed to ensure that they are consistent with the current UK Medicines for Human Use (Clinical Trial) Regulations so as not to undermine the UK's strong position in this area.

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

Other Barriers

17. Evidence suggests that obtaining R&D permissions at the NHS sites where research is to take place are the greatest regulatory and governance barrier to research studies, including clinical trials of investigational medicinal products.[92] These permissions are independent of the regulation of clinical trials, but it is vital that this rate-limiting step is addressed. We therefore warmly welcome the HRA's pilot project in this area, as noted in paragraph 18.

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. We have welcomed the establishment of the Health Research Authority, and the provisions in the draft Care and Support Bill to establish it as an independent non-departmental public body. The HRA has a central role to play in the streamlining of research approval processes and promoting common standards for compliance and monitoring. We have been encouraged by the start made by the HRA, particularly the establishment of the pilot project for a system of streamlined assessment of research in the NHS. We have also been impressed by the HRA's proactive approach to engage with key stakeholders and other regulators from the outset to discuss and develop its role.

19. The HRA has also showed willingness to engage on the issue of clinical trial transparency and we understand that they are considering this at the moment as part of the organisation's work, particularly with regard to requirements of research ethics committees in the area of transparency and publication, and monitoring of compliance. The joint committee which is currently carrying out pre-legislative scrutiny on the draft Care and Support Bill, which will establish the HRA as a non-departmental public body, is also considering the issue as part of the broader remit and functions of the organisation. We believe that the HRA can play a significant role in promoting and contributing to discussions around these issues, and welcome the fact that the HRA is moving forward with a number of activities including the single assessment pilot mentioned previously and statements in support of research transparency, as well as broader discussions with stakeholders.

20. It is important to note, however, that the HRA is just one of a number of players in this area, and other organisations and stakeholder groups have a similarly important role to play in these discussions in order to embed the principle of transparency throughout the regulatory pathway (see also the discussion of responsibility in paragraph 24, below).

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

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

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

22. There are several methods by which clinical trials can be made more open to scrutiny. The most important of these is trial registration, which is a crucial first step in opening up clinical trials for examination. Information about clinical trials should be placed in an appropriate accredited registry, including details of the interventions and outcomes being measured. This should also include a lay summary of the trial, including aims, interventions, methods and outcomes, in a form which can be easily understood by a non-specialist or lay reader.

23. We also support efforts to publish summary results of clinical trials available, and welcome the requirement for this in the Clinical Trials Regulation (see paragraph 15). We recognise that it may be more difficult to publish negative findings in peer reviewed journals, but do not think this should be a long-term barrier to making all results and outputs available. We consider that, where appropriate, a range of approaches to making research findings available should be considered, such as websites, data repositories and trial registries.

24. Full disclosure of the data underlying research outcomes represents a larger challenge, as data must be made available in a form that is both accessible and useful, while protecting the confidentiality of research participants. This in turn presents challenges around putting in place the appropriate infrastructure and curation to facilitate this while protecting individual identifiable data, and there are also issues of resourcing and cost. Researchers and research sponsors will need to consider whether appropriate facilities are in place to manage, store and provide access to large volumes of data, whether sufficient expertise is contained within the research team, and whether additional tools or facilities will be required to enable access. There may also be cases in which it is useful to have more tightly controlled access to fuller datasets, for example to protect intellectual property or data exclusivity, or to safeguard research participants. None of these challenges are inherently insurmountable, but they require careful consideration.

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

25. Responsibility for ensuring that clinical trials are made more open to scrutiny lies with a number of stakeholders, including researchers, research sponsors, funders, publishers, regulators and industry. All stakeholders have a responsibility to explore methods of increasing transparency of clinical trials and to work together to promote common standards and mechanisms. It is important also to consider the role of research ethics committees here and how their role in scrutinising research proposals relates to the monitoring of research transparency. Although the HRA is not itself a regulator, there may be a role for it as it develops in the promotion of common standards around research transparency. There is also a role for the MHRA where the release of clinical trial results and data has a direct bearing on safety assessments for medicines and devices.

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

26. Clinical trials are an increasingly global activity, and so it is important to consider trial transparency in this context and to take a global approach. This does, however, bring its own challenges around resourcing and infrastructure, discussed above. It also raises the question of where responsibility should lie, for example in the country or countries where the trial takes place, or in the country where the sponsor is located, should this be different.

27. The UK saw its global share of patients recruited to clinical trials fall from six to two to three% between 2000 and 2006.[93] Steps are being taken to address this decline and ensure that the UK creates and maintains competitive environment for clinical trials for the benefit of patients and the economy. The proposal for a Clinical Trials Regulation will also improve the regulatory environment in the EU. It is important that measures to promote transparency and sharing of clinical data are considered within this wider context. Seeking global, rather than country-specific, solutions to transparency will maximise the benefits to society and while ensuring that the UK maintains its competitive advantage.

March 2013

APPENDIX A

WELLCOME TRUST STATEMENT TO THE ALLTRIALS PETITION ON CLINICAL TRIAL TRANSPARENCY

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

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

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

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

Written evidence submitted by GlaxoSmithKline

INTRODUCTION

— GSK is a global healthcare company that researches and develops a broad range of innovative products. We make medicines, vaccines and consumer healthcare products that are used by millions of people around the world, allowing them to do more, feel better and live longer.

— Our focus on responsible, values-based business underpins everything we do including how we conduct and report our research. Business decisions are guided by our GSK values to: commit to transparency; show respect for people; demonstrate the highest integrity in our conduct; and be patient-focused. The activities described in this paper demonstrate our commitment to embed greater openness within the fundamental ways in which we work.

[93] www.ukcrc.org/index.aspx?o=2874

— We are committed to being transparent with clinical trial data to help advance scientific understanding and inform medical judgment. Since being the first company to launch an internet-based clinical study register in 2004, we have expanded our approach and provided earlier access to greater information. This evidence submission describes recent commitments to publically disclose Clinical Study Reports (CSRs) and provide researchers with an opportunity to access anonymised patient level data to undertake further research. Our commitments acknowledge the contribution made by the individuals who participate in clinical research. All those involved in the conduct and publication of clinical research have a role to play in ensuring that the data they generate are made available to help bring patient benefit.

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 proposals in the Regulation are broadly welcomed and should reduce the time and number of approvals needed to set up clinical trials**. New timelines for the submission and review of a single Clinical Trial Application (CTA) for multi-country trials could speed up the initiation of clinical trials, without compromising the safety of research participants. The new process and timelines should be supported, with no additional complexity added as the proposals progress through the legislative process.

1.2 GSK supports in principle the establishment of an EU database containing information on applications for and results of clinical trials. Further clarity is needed on the content of the EU Database and mechanisms to protect personal information and any commercially sensitive information.

1.3 **UK-specific assessments, including NHS R&D approval, need to be delivered within the same timelines established in the Regulation**. Barriers to conducting trials in Europe should be reduced by the Commission's proposals. To protect the UK's competitiveness and capture the benefit to patients of taking part in trials, additional UK approvals need to be made in parallel to the legislated requirements of the Regulation. The progress started by the Health Research Authority, MHRA and National Institute for Health Research in streamlining UK decisions needs to be maintained.

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 role of the Health Research Authority should remain focused on removing complexity and delays in the UK approval process.** We welcome the HRA's commitment to begin testing plans in Spring 2013[94] to combine and replace aspects of the current reviews by NHS R&D and Research Ethics Committees (RECs) into a single assessment. The effectiveness of the HRA needs to be measured against its ability to deliver a simplified and streamlined process.

2.2 The HRA was established to correct past practice of layering new, well-intended checks and approvals onto the UK approval pathway.[95] Any role for the HRA in monitoring compliance against transparency commitments (eg reviewing past publications) needs to avoid adding delays to UK research approvals. Sponsors and funders of research should review past compliance with disclosure commitments when assessing new research projects.

2.3 **The positive start made by the HRA in addressing unnecessary complexity should be allowed to continue; a number of significant challenges remain.** Efforts by the Department of Health, NIHR and the HRA to streamline research approvals are to be applauded. Approval timelines across NHS sites remain variable and many improvements remain planned or in pilot form, however early evidence shows a reduction in approval times.[96] We want to work with investigators, NIHR and Trust R&D staff to improve the UK performance in embedding high quality commercially funded research as a core function of the NHS. To increase the number of UK patients in trials and the effectiveness of the HRA, a number of outstanding issues need to be addressed:

— The efficient and reliable start up of trials, with patient recruitment completed to time and target.

— The further streamlining of cost and contract negotiation with NHS Trusts.

— The failure to deliver full electronic submissions for NHS RECs and the MHRA—a system that had been presented as being integral to creating a unified process—appears a backwards step.[97] Further clarity is needed on how the HRA will work closely with MHRA and NIHR.

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

3.1 Patient safety is always our priority. We evaluate the benefits and risks of our medicines at all stages of research and after a new product is approved for sale. Pharmaceutical companies are legally required to disclose

[94] 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/

[95] The Academy of Medical Sciences (2011). "A new pathway for the regulation and governance of health research" http://www.acmedsci.ac.uk/download.php?file=/images/project/130734957423.pdf

[96] Data presented at the NOCRI/ABPI/BIA R&D Conference in November 2012.

[97] http://www.hra.nhs.uk/hra-news-and-announcements/future-of-iras/

results from clinical trials to the appropriate regulatory authorities. After approval, companies have a continuing obligation to provide regulators with updated safety information from clinical research and other sources.

3.2 **GSK fully supports steps to drive greater transparency of clinical trial data and to help medical research by allowing scientists to study the detailed results of clinical trials and increase understanding of current and new medicines. Ultimately this should improve patient care**. We recognise that there are concerns about the extent to which all clinical trials (both industry and academic trials) are published and whether published information accurately reflects the conduct of the study. This evidence submission focuses on our ongoing commitment to promote greater transparency.

Evidence of disclosure and compliance with policies

3.3 **Our commitments reflect a desire to promote transparency, facilitate further research and ensure that the data provided by research participants are used to maximum effect in the creation of knowledge and understanding**. Detail on our commitments is in our Public Policy on "Public Disclosure of Clinical Research"[98] and information on recent initiatives under question 4. In summary our policies are:

- Public trial registration: when studies are initiated, protocol summaries are posted on internet registers.[99]
- Disclosure of results:
  - Result summaries are posted on public registers and studies submitted for publication in journals—irrespective of the outcome of the study.[100]
  - We will not wait until approval or termination of the medicine before posting results summaries or submitting manuscripts to journals.[101] Publication of results takes place within timelines from the completion of studies.
- Public disclosure of Clinical Study Reports (CSRs): In February 2013, we committed to post CSRs, with personal information removed, once the trial has been published and the medicines have been approved or terminated from development (see 4.2).[102]
- Access to anonymised patient level data: we will shortly be launching a system to enable researchers to request access to underlying patient level data to conduct further research (see 4.3).[103]

3.4 **We have embedded processes to monitor our performance against our own targets. In many cases these targets go beyond the industry minimum or practices in other sectors**.[104] Steps to disclose information and measure compliance have become an integral part of the trial process:

- By the end of 2012, our public Clinical Study Register contained 5,000 results summaries and received an average of 11,000 visitors a month.
- Since committing in 2009 to seek publication of all human research as manuscripts in the scientific literature we have submitted over 2,100 publications.[105] In 2012 we raised internal visibility of these obligations, increased use of internal metrics and provided additional support in publication planning, development and reporting.
- We are committed to getting information out to the scientific community in a timely fashion. For manuscripts submitted in 2009–12 we have seen a marked decrease in time from the end of the trial to the submission of a manuscript. Likely drivers for this include use of tracking systems and internal communication of metrics.

Impact on public health and further scientific research

3.5 When patients volunteer for clinical trials it is a legitimate expectation that the results will be used to help others. To accelerate the discovery of new medicines and vaccines, we make collaboration part of our business model. Our Open Innovation strategy is designed to promote change beyond GSK by sharing expertise, resources and intellectual property and know-how with external researchers and the scientific community.

[98] http://www.gsk.com/content/dam/gsk/globals/documents/pdf/GSK-on-disclosure-of-clinical-trial-information.pdf

[99] For example: http://www.clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ and/or our own register http://www.gsk-clinicalstudyregister.com/

[100] This commitment includes all our clinical trials (phase I-IV) as well as our observational studies and meta-analyses that evaluate our medicines. The GSK Clinical Study Register, created in 2004, includes studies since the formation of GSK in 2000 and some earlier studies where results inform medical judgement.

[101] Our approach is to post result summaries on the GSK Clinical Study Register with 8–12 months of the completion of studies and to submit a manuscript to a peer reviewed journal within 18–24 months.

[102] http://www.gsk.com/media/press-releases/2013/GSK-announces-support-forAll-Trials-campaign-for-clinical-data-transparency.html

[103] http://www.gsk.com/media/press-releases/2012/GSK-announces-further-initiatives-to-tackle-global-health-challenges.html

[104] For example, our commitment to seek publication of all our clinical research goes beyond the existing industry-wide (IFPMA) obligation to submit all Phase 3 results and others of significant medical importance for publication. Our commitment to post on our register phase I studies, observational studies and meta-analyses that evaluate our medicines goes beyond what is required by regulations in the US and EU.

[105] This figure includes primary, secondary and discretionary publications.

Providing access to information, sharing knowledge and reducing duplication is fundamental to the common goal of advancing science.

3.6 Our transparency efforts are not limited to clinical trials. From 2009, we have included all our observational studies and meta-analyses that evaluate our medicines on the GSK Clinical Study Register. In January 2009, in recognition that information from terminated research programmes can inform the scientific community and help reduce exposure of study participants to similar compounds in other clinical trials, we extended our disclosure commitment to all our studies of terminated compounds.

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

4.1 Providing access to further detail on the methods and results of trials promotes trust, avoids unnecessarily enrolling patients in trials and enables others to conduct further research. This subsequent research may be in new areas or enable others to identify important findings of relevance to GSK medicines. We look to provide access to information in ways that protect individual privacy and promote the responsible use of data. Since being the first company to launch an internet-based clinical study register, we have looked to meet changing expectations by expanding our approach and providing earlier access to greater information. The sections below describe recent steps to enable greater scrutiny of clinical trial information by providing further information in addition to protocol and result summaries and journal publications.

Public access to Clinical Study Reports (CSRs)

4.2 **In February 2013, GSK committed to post CSRs, with personal information removed, on our public register once the trial has been published and the medicines have been approved or terminated from development**.[106] CSRs are formal study reports that provide detail on the design, methods and results of trials and form the basis of submissions to regulatory authorities. To ensure patient confidentiality is maintained, the core CSR will be posted after removing patient information. While there are practical challenges, we also intend to publish CSRs for clinical outcomes trials for all approved medicines dating back to the formation of GSK. This will require retrieval and examination of each CSR to remove confidential patient information. Given the volume of studies, this work will be completed in a step-wise manner, with priority given to the most commonly prescribed medicines.

Access to anonymised patient level data

4.3 **In October 2012, GSK announced that we would create a system to enable researchers to access anonymised patient level data from published trials of our approved or terminated medicines**. Researchers will be able to request data from global patient studies conducted since 2007 and over the next two years we will include global patient studies going back to the formation of GSK. We will also include all patient studies we start in and after 2013.

4.4 This initiative will enable researchers to examine data more closely, to conduct further research to help optimise the use of medicines and ultimately improve patient care. Requests for access to data will be reviewed by an independent panel of experts. The panel will undertake a high-level review of proposals to help ensure that data is used in a scientific and responsible manner. To protect individual privacy, anonymised patient level data will be accessed in a secure IT environment. There will be controls in place to restrict the ability of researchers to download the anonymised data. Researchers will sign a data sharing agreement requiring them to publish their research and only use the data for the agreed purpose.

4.5 We recognise that our commitment is a first step. There may be other ways for further research to be conducted using these data and our approach may evolve as we gain experience. **We hope this initiative and what we learn will catalyse the development of a broader system where access to anonymised patient level data from all clinical studies conducted by industry and academia are made available for further research.**

European Medicine Agency (EMA)

4.6 We welcome the EMA's efforts towards greater transparency. Their ongoing consultation explores how clinical trial information, including clinical study reports, can be "proactively published" once the decision making process on an EU marketing authorisation is complete.[107] The CSRs provided to the EMA include patient level information in the appendices and main report. We encourage the EMA to identify an appropriate solution that protects patient confidentiality, ensures that the subsequent use of information is aligned with the original consent provided by patients and promotes the responsible use of data. We continue to provide input into the EMA consultation. One option may be for the EMA to progress in a step-wise manner, beginning with the publication of the core CSR (including aggregated information, but not the patient-level data in the report and appendices).

[106] http://www.gsk.com/media/press-releases/2013/GSK-announces-support-forAll-Trials-campaign-for-clinical-data-transparency.html

[107] http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&mid=WC0b01ac0580607bfa

Who should be responsible?

4.7 **Solutions need to be developed in collaboration with patients, regulators, journals and researchers from all sectors.** We hope that our commitments will catalyse the development of further efforts across industry and academia. It is important that steps to greater transparency include all patient trials, including the many studies conducted in academia.

4.8 Information needs to be provided in an accessible and usable manner and we caution against the further proliferation of public registers, which duplicate information and impose variable requirements. Embedding cultural change across organisations and raising visibility of transparency obligations may also reap benefits. We seek to promote transparency when entering research collaborations, including, for example, adding a requirement to the standard NHS model Clinical Trial Agreement that (unless it is an exploratory trial) the Sponsor shall submit the trial for listing in a public registry within 21 days of initiation of patient enrolment.

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

5.1 **The steps we have taken are global commitments that reflect the fact that clinical trials are conducted all over the world, with any one study often involving sites in multiple countries**. Introducing country-specific requirements could delay the approval of research and will impact on only a small subset of global trials. We hope the experience gained through our own initiatives will be of value in developing global approaches that promote further research to learn more about how medicines work in different patient populations and to help optimise the use of medicines with the aim of improving patient care.

March 2013

Written evidence submitted Professor Karol Sikora

Karol Sikora is Medical Director of Cancer Partners UK a group creating the largest independent UK cancer network. He was Professor and Chairman of the Department of Cancer Medicine at Imperial College School of Medicine and is still honorary Consultant Oncologist at Hammersmith Hospital, London. He is Dean of the new Medical School at the University of Buckingham.

The ability of technology to improve health is assured. But it will come at a price—the direct costs of providing it and the care costs of the increasingly elderly population it will produce. We will simply run out of things to die from. New ethical and moral dilemmas will arise as we seek the holy grail of compressed morbidity. Living long and dying fast and cheaply will become the mantra of 21st century medicine. Medicine's future will emerge from the interaction of four factors: the success of new technology, society's willingness to pay, new healthcare delivery systems and the financial mechanisms that underpin them. Clinical trials on cancer drugs continue to lead to significant advances in the treatment of this disease. Full disclosure of all data including all the molecular diagnostics used to stratify patients on trial entry is vital.

The New Diagnostics—Imaging and Molecular Probes

The reduction in waiting times throughout global healthcare systems has improved the speed of cancer diagnosis, but there are still delays in obtaining imaging, such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans. Furthermore, expert histopathology is critical to getting a precise diagnosis and capacity problems in many diagnostic laboratories are causing delays to getting started on treatment. The key to the future in all healthcare systems is up-front personalisation of therapy based on good diagnostics. Oncologists have actually been very good at this despite limited data. In breast cancer, adjuvant chemotherapy is personalized by the risk of recurrence. Sophisticated clinical tools such as *www.adjuvantonline.com* have, for some years, used clinical and pathology derived data to optimise the choice of drugs following surgery for breast cancer. But for most cancers we need something better.

Molecular signatures of response to high cost targeted drugs that are easily determined by tissue analysis are urgently needed. All hit well-defined molecular targets for which functional assays are available. After all, such assays for herceptin in breast cancer and crizotinib in lung cancer are an essential part of their discovery process. The activity of downstream signaling cascades can now be determined in clinical samples, provided repeat tissue samples can be obtained after drug administration. Such assays could provide not only the very signatures required, but also effective surrogates of early response. And there are examples where translational data could lead to new targeted drug combinations where two pathways are blocked simultaneously.

Within the next five years, phase III trials will look very different to today. Only patients whose tumours express the relevant biomarker pattern suggestive of response to a new agent will be entered. After 24 hours of drug administration, validated response surrogates will be measured. Those patients testing negatively will be removed from the study and offered either alternative medication or supportive care. By such a dual selection programme, the active arm of the new phase III programme will be fully enriched for responding patients, making drug development faster, cheaper, and more beneficial for those enrolled.

The costs of the diagnostics for personalized medicine may be high, but the potential for savings on the drug bill is enormous. No payer is going to ignore this. The days of marketing cancer drugs like a supermarket commodity are over. Developing ways to optimise responses through companion diagnostics and short-term surrogate biomarkers are now going to be essential.

New Drugs

This is an exciting time for those involved in cancer research and care. But the cost of getting a single drug to market now exceeds $1 billion per compound. More sophisticated molecular diagnostics are being developed, which will shortly be able to personalise care, increasing its cost-effectiveness. Giving the right medicine to the right patient will eventually drastically reduce the overall costs of care, but we are not there yet.

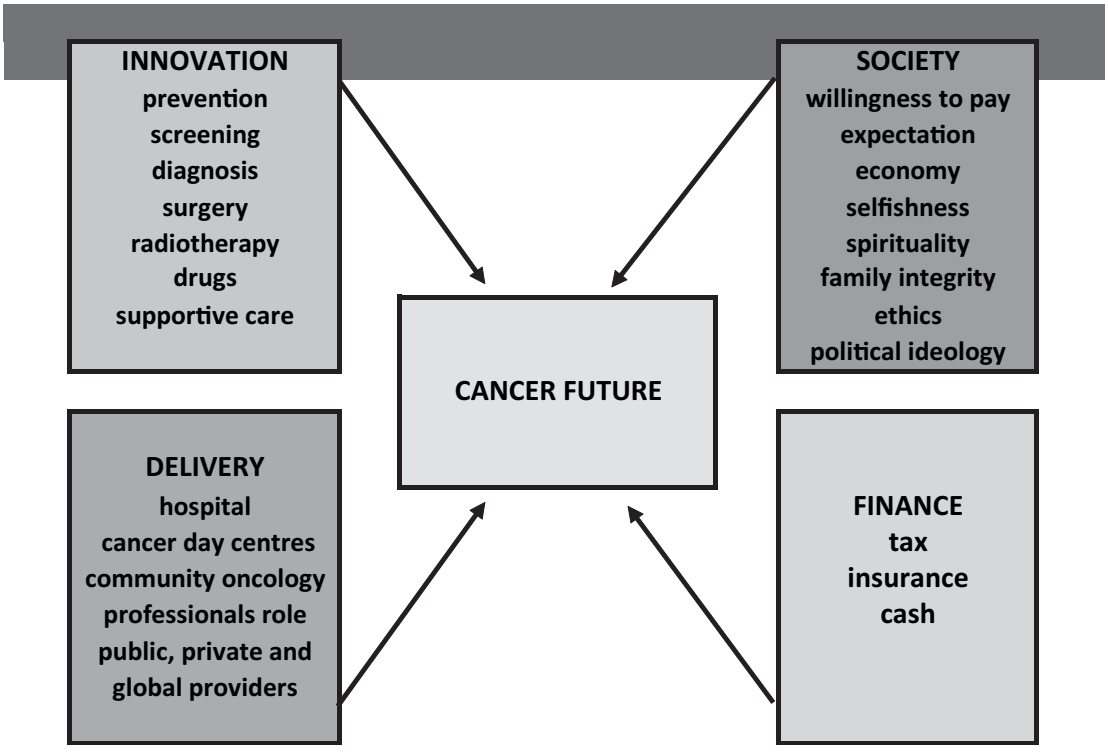
There's a lot of excitement about chemotherapy now based on human genome programme, bio-informatics, robots for high throughput screening, computer drug design and whole platforms such as the kinases for which to create drugs. New biomarkers identifying pharmaco-dynamic end points are now available so we can actually measure if the drug is hitting on its target by just taking a sample of tissue from the patient. We now have surrogate end points and molecular signatures to predict response to different agents. The pathology of the future is not going to be about microscopic morphology, it will be about identifying molecular patterns that rationally guide therapy.

There are currently just over 800 drugs in clinical trial for cancer of which about 500 are against very specific molecular targets. By 2022 there will be 2,000 compounds and probably by 2025 there will be 5,000 compounds. There are patterns evolving as the drug industry really has very little imagination. At the moment the main theme is small molecules. Monoclonal antibodies, cancer vaccines and gene therapy are on trial on a smaller scale but the emphasis on small molecules.

Conclusion

Over the next decade, I believe we are going to continue to make tremendous strides in the treatment of cancer. And local treatments with surgery or radiotherapy will dramatically improve with new technology. It will become more prevalent throughout society as we all get older. But will also become more treatable. It will move from being a fatal to a chronic disease like diabetes or hypertension. So it will be even more essential to understand their value to altering the natural history of cancer in a meaningful way with full disclosure of their developmental pathways. The future of cancer care has four main components—technical innovation, societal change, optimal delivery of care and financial mechanisms to pay for everything.

May 2013



Written evidence submitted by the Science Media Centre

1. Introduction

The Science Media Centre (SMC) was set up in 2002, in the aftermath of public controversies on BSE, GM crops and MMR, and in response to recommendations in the House of Lords Science and Technology Select Committee's 2000 report on science and society. Its aim is to support and encourage more experts to engage with the media more effectively in times of crisis and controversy, in order to ensure that the public get access to accurate and evidence-based information through the news. In over 10 years of responding to stories such as the Northwick Park clinical trial disaster, claims of cloned human beings, the HPV vaccine scare, swine flu, antibiotic resistance, hybrid embryos, and the recent horsemeat scandal, we have built up a huge body of expertise.

As an organisation we support openness and transparency in science generally, but we do not have a view on how clinical trials could be made more open to scrutiny or who should be responsible for making that decision; we have limited our comments to the aspects of the inquiry where we have experience, namely the portrayal of information and results from clinical trials in the media, and the opportunities and challenges this brings.

2. Reporting Science in the Media

Science is at the heart of almost all the major challenges we face as a society: how to treat incurable diseases, how to feed the growing population, how to tackle climate change. Despite the rapid rise of social and new media, surveys continue to show that the public get most of their information about science from the mass media, including television and newspapers.[108] This likely includes information about clinical trials, and many of the news stories the SMC deals with include reporting of clinical trials; from research into cutting edge new treatments to trial safety and regulation.

The MMR scare of the late 1990s is one of the most well-known examples of how media reporting can influence the public on science and health issues. Vaccination rates dropped from 92% to 80% after the scare, and cases of measles in England and Wales rose from 56 in 1998 to 1,370 in 2008;[109] the recent measles epidemic in Wales highlights the lasting effects of the story. While the media was not solely responsible for the scare, and lessons have been learned by all concerned, some of the underlying values still remain in parts of our newsrooms: the appetite for a scare story, the desire to overstate claims made by one individual, the reluctance to put one alarming story into its wider context, "journalistic balance" that conveys a divide among experts where there is none, and so on. The recent Leveson Inquiry provided a chance to reflect on the impact of the culture and practice of the press, and underlined the huge potential the media still have to influence public opinion on a wide range of issues.

3. Clinical Trials in the Media

Despite the large number of clinical trials carried out all over the world, the vast majority only hit the headlines when they become controversial or produce surprising, counterintuitive or unexpected results. There are obvious examples such as the trial at Northwick Park Hospital of the experimental drug TGN1412 in 2006 that ended after several participants developed severe immune reactions; or trials on the use of new cutting edge technologies such as embryonic stem cell treatments for spinal cord injury. For obvious reasons, and in reflection of a similar bias seen elsewhere in clinical trial reporting in academic journals, the media also tend not to report those clinical trials that replicate previous results, nor those that produce negative findings, despite their possible scientific importance.

The way in which many parts of the news media cover clinical trials illustrates several of the newsroom values mentioned above: the appetite for controversy and the focus on individual cases without placing them within their wider context. Media articles can overestimate the importance of results, suggesting that early stage safety trials imply a treatment is much more successful or near to fruition than it might actually be. For example, an early stage safety—not efficacy—trial of stem cells for treating blindness was reported in the Independent last year under the following headline: "Once they were blind, now they see. Patients cured by stem cell miracle."[110] Former science reporter Gary Schwitzer has come up with seven words that should never appear in medical news reporting: Cure, Miracle, Breakthrough, Promising, Dramatic, Hope, Victim. This is probably overly idealistic, as many of these words are what draw readers to medical stories in the first place, but Schwitzer's article is worth reading as a summary of where science stories can mislead readers.[111]

Last year the SMC submitted evidence to the Leveson Inquiry on the issue of science reporting in the media.[112] Following this, the Centre worked with journalists, subeditors and scientists to produce a set of

[108] BIS Public Attitudes to Science 2011: http://www.bis.gov.uk/policies/science/science-and-society/public-attitudes-to-science-2011

[109] Figures from the Health Protection Agency—http://tinyurl.com/5uylxdc

[110] http://www.independent.co.uk/news/science/once-they-were-blind-now-they-see-patients-treated-with-cells-from-human-embryo-6293706.html

[111] http://www.healthnewsreview.org/toolkit/tips-for-understanding-studies/7-words-and-more-you-shouldnt-use-in-medical-news/

[112] Science Media Centre Evidence to the Leveson Inquiry: http://www.levesoninquiry.org.uk/wp-content/uploads/2012/01/Witness-Statement-of-Fiona-Fox.pdf

guidelines for good health and science reporting. These include putting a study into its proper context (for example, stating whether something is a Phase I or Phase IV trial), and the need to make clear its size and nature. Central to our guidelines is that extraordinary claims require extraordinary evidence. These guidelines are included at the end of this document and have been welcomed by many.

The need for accurate and fair reporting of clinical trials applies as much to science communicators and press officers as to journalists. Many misleading stories about clinical trials and related studies can be traced back to a misleading press release. It is important that those publicising clinical trials to the media and the public do not oversell the importance and potential impact of a trial; there is a responsibility to not press release early stage trials without very good reason.

However, the SMC also see issues in the headlines as an opportunity to inform the public and policymakers about key issues, and encourages experts to engage, irrespective of how complex or controversial a story becomes. The UK is lucky to have a huge number of excellent specialist science and health journalists, across news outlets from tabloids to major broadcast organisations, and much of the coverage of clinical trials, whilst sometimes subject to a degree of hype or unwelcome headlines, is also full of accurate, evidence-based information as a result. These specialists are a dedicated and skilful group of journalists who, despite the pressures of the newsroom and editorial lines, take pride and responsibility in getting science stories right. The previously mentioned article in the Independent may have carried a very strong headline that over-claimed for the impact of the trial, but it was full of lots of detailed information about the trial in question. The current science media environment is a very different one to that which saw the confusion and media frenzy over MMR at the end of the 1990s.

May 2013

The Science Media Centre is an independent venture working to promote the voices, stories and views from the scientific community to the news media when science is in the headlines. Over 80 supporters including scientific institutions, media groups, charities, universities, corporate organisations and individuals fund the Centre, with donations capped at 5% of the running costs to preserve its independence. Science Media Centre is a registered charity (no. 1140827) and a company limited by guarantee (no. 7560997). Registered in England and Wales.

10 BEST PRACTICE GUIDELINES FOR REPORTING SCIENCE & HEALTH STORIES

The following guidelines, drawn up in consultation with scientists, science reporters, editors and sub editors, are intended for use by newsrooms to ensure that the reporting of science and health stories is balanced and accurate. They are not intended as a prescriptive checklist and of course shorter articles or NIBs will not be able to cover every point. Above and beyond specific guidelines, familiarity with the technicalities and common pitfalls in science and health reporting is invaluable and every newsroom should aim to employ specialist science and health correspondents. Wherever possible the advice and skills of these specialists should be sought and respected on major, relevant stories; the guidelines below will be especially useful for editors and general reporters who are less familiar with how science works.

- State the source of the story—eg interview, conference, journal article, a survey from a charity or trade body, etc—ideally with enough information for readers to look it up or a web link.
- Specify the size and nature of the study—eg who/what were the subjects, how long did it last, what was tested or was it an observation? If space, mention the major limitations.
- When reporting a link between two things, indicate whether or not there is evidence that one causes the other.
- Give a sense of the stage of the research—eg cells in a laboratory or trials in humans—and a realistic time-frame for any new treatment or technology.
- On health risks, include the absolute risk whenever it is available in the press release or the research paper—ie if "cupcakes double cancer risk" state the outright risk of that cancer, with and without cupcakes.
- Especially on a story with public health implications, try to frame a new finding in the context of other evidence—eg does it reinforce or conflict with previous studies? If it attracts serious scientific concerns, they should not be ignored.
- If space, quote both the researchers themselves and external sources with appropriate expertise. Be wary of scientists and press releases over-claiming for studies.
- Distinguish between findings and interpretation or extrapolation; don't suggest health advice if none has been offered.
- Remember patients: don't call something a "cure" that is not a cure.
- Headlines should not mislead the reader about a story's contents and quotation marks should not be used to dress up overstatement.

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