House of Commons

Science and technology Committee

Clinical trials

Written evidence

6 March 2013

Available online at:

http://www.parliament.uk/documents/commons-committees/science-technology/Clinical%20trials%20combined.pdf

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

Introduction

1. We are the Global Alliance of Publication Professionals (www.gappteam.org). We are a global organisation set up to highlight the work of professional medical writers. As such, the question of publication of clinical trials falls firmly within our area of interest and expertise.

2. We note that the scope of the inquiry is wider than just publication of clinical trials, and also refers to the conduct of clinical trials, which is less within our core area of interest. We will therefore not be submitting evidence in relation to questions 1 and 2 of the committee's terms of reference, but will concentrate instead on questions 3–5.

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

3. Turning first to the question of the evidence that pharmaceutical companies withhold clinical trial data, we are concerned about how the debate is framed by use of the word "withhold". This implies an active process of trying to hide data. In reality, data may remain unpublished for a variety of reasons, such as lack of the resources needed to ensure that data are written up for publication and submitted to journals, or rejection of papers by journals.

4. We are not aware of any evidence at all that pharmaceutical companies specifically "withhold" data (as distinct from not publishing data for other reasons), and in the absence of such evidence it would be wrong to claim that data are withheld.

5. In contrast, there is considerable evidence about the extent to which clinical trials remain unpublished, albeit that that evidence seldom if ever examines the reasons for non-publication. However, much of that evidence is severely limited by being out of date.

6. The relevance of the date of research on non-publication of clinical trial results should not be underestimated. In recent years, publication practices have changed dramatically within the pharmaceutical industry. Data on publication rates from 10 years ago are likely to have little relevance to today's situation.

7. Guidelines on Good Publication Practice (GPP) for Pharmaceutical Companies were first published in 2003 [1]. These guidelines recommended that pharmaceutical companies should publish the results of all their clinical trials. To our knowledge, this was the first serious attempt within the pharmaceutical industry to ensure completeness of publication. Public backing by pharmaceutical companies was initially slow. However, an updated version of the guidelines (known as GPP2) was published in 2009 [2], which gave the guidelines new impetus.

8. During the same period of time, the FDA Amendments Act (FDAAA) of 2007 came into force in the USA. This required pharmaceutical companies to make the results of their clinical trials publicly available on the clinicaltrials.gov website, which further increased the impetus for transparency of clinical trials results.

9. In light of these moves towards greater openness, many pharmaceutical companies now have policies which commit to publishing the results of all their clinical trials, irrespective of outcome. An example of such a policy is the one by GlaxoSmithKline [3]. Such policies were rare 10 years ago. The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) published a position statement in 2010 encouraging pharmaceutical sponsors to publish all their clinical trial results in the peer-reviewed literature [4].

10. It is therefore important that data on completeness of publication be up-to-date. One widely quoted statistic is that 50% of clinical trial data remain unpublished. This comes from a systematic review which was published in 2010 [5], but which included results of older studies, many of which dated from the 1990s. It is therefore unlikely to be relevant.

11. We are not aware of any systematic reviews looking only at recent data. However, we are aware of two reasonably recent good quality studies looking at completeness of publication of clinical trial data.

12. Bourgeois et al investigated publication of drug trials registered on clinicaltrials.gov and reported their results in 2010 [6]. They found that overall, 362/546 studies (66%) were published in peer-reviewed journals and a further 75 had results disclosed on a website, giving a total of 437 studies (80%) with disclosed results.

13. Ross et al also examined clinical trials registered on clinicaltrials.gov, although limited their research to studies funded by the US National Institutes of Health. They published their results in 2012 [7]. Their results were remarkably similar to those of Bourgeois et al, finding that 432/635 trials (68%) were published in peer-reviewed journals. They did not report whether any studies were made available on websites.

14. Both studies found that publication was often slow, taking longer than 2 years after study completion in many cases. This is not entirely surprising, as writing up results for publication can be a time-consuming process, and it may be many months from completion of a paper to publication, as many journals have long lead times. If a paper is rejected from one journal and has to be submitted elsewhere, then delays will increase. It is therefore possible that final disclosure rates would have been higher in both studies, had follow up been longer.

15. Contrary to the popular myth that non-publication of data is a problem mainly of the pharmaceutical industry, Bourgeois et al found that total rate of disclosure of clinical trial results (ie publications in peer reviewed journals plus postings of results on websites) was higher in industry-sponsored studies than in independent studies. 305/346 industry sponsored studies (88%) had disclosed results, compared with 41/74 government sponsored studies (55%) and 50/65 non-profit studies (77%). This seems to be consistent with other evidence: a systematic review published in 2010 found 5 studies that compared industry-sponsored studies with independent studies, 3 of which found a higher probability of publication in the industry studies, one of which found no difference, and only one of which found higher publication rates in non-industry studies [8].

16. Bourgeois et al also found that, despite the higher eventual publication rate of industry sponsored studies, they were initially slower to be published than independent studies. However, industry-sponsored studies were larger and more often multicentre studies, and it is reasonable to hypothesise that the greater delay before publication was a consequence of the greater complexity of the studies.

17. We are not aware of any direct evidence that non-publication of clinical trial data harms public health. However, it seems reasonable to assume that it would have this potential. Public health is continually improved by the application of new research findings, and if trial results remain unpublished, then they cannot benefit public health. Further, non-publication of clinical trial data breaks the "ethical contract" researchers make with clinical trial participants to share clinical trial data to advance medical knowledge and potentially benefit others.

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

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

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

19. We would like to stress the importance of ensuring that specific resources are available for publication of research results. Publications do not write themselves. It is likely that many studies remain unpublished simply because the researchers simply lack the resources to write up their results for publication.

20. Although lack of resources is less often a problem in the pharmaceutical industry, we suspect it is a very common problem in non-industry research, and may contribute to the lower publication results seen in research that is not sponsored by the pharmaceutical industry, as we noted in paragraph 15 above. We suggest that when grants are awarded for clinical research, it should become standard practice to ring-fence an element of the grant for publication, as we have argued in more detail in a recent published article [9]. This is a no-cost solution that could be readily implemented

21. We believe that non-publication of clinical trial results is an ethical issue, and so should be a legitimate concern of research ethics committees. There is a good argument for a commitment to publication of results being a condition of ethical approval to conduct trials. We understand that the National Research Ethics Service is sympathetic to this point of view, but currently lacks any robust means of following up such commitments to ensure that they are met. One of us (AJ) is a member of an NHS Research Ethics Committee and has written about some of the challenges of this in more detail [10].

22. Ensuring that research ethics committees monitor completeness of publication would be a highly achievable and practicable step. Although there are some barriers to doing this, we believe that those problems are solvable, and we urge Parliament to give whatever support it can to the National Research Ethics Service to help it to implement a suitable system.

23. Grant giving bodies, such as the MRC, could also play a useful role in this context. It should be a condition of any grant for clinical research that the results of the research be published. Again, enforcement mechanisms would need to be in place if this were to be meaningful.

24. Much clinical research in the UK takes place within the NHS and/or academic institutions: these are organisations over which the government has at least some influence. It should be possible to ensure via researchers' contracts of employment that they are obliged to ensure that any clinical trials in which they are involved are published.

25. Considering the pharmaceutical industry, the industry itself has already taken great strides to improve the completeness of publication in recent years. However, we believe that further steps could and should be taken, and one possible such step would be for regulatory bodies such as the MHRA and the EMA to adopt a more open culture. Currently, clinical study reports submitted to those bodies remain confidential. There could be greater on-line disclosure of CSR content.

26. We understand that there might be commercial implications to full CSR disclosure; however, this might be mitigated if all sponsor companies are required to provide the same degree of disclosure.

27. It is worth noting that making clinical study reports available would do considerably more for transparency than any attempt to increase rates of publication in peer-reviewed journals. The level of detail available in clinical study reports submitted for regulatory purposes far exceeds that in publications in journals.

28. Nonetheless, concerns have been expressed that making reports widely available could lead to inappropriate secondary analyses by those with an axe to grind, and if picked up by the press could potentially do harm.

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

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

30. Turning to your final question about what evidence can be learned from other countries, the USA has passed laws that mandate the disclosure of clinical trial results for licensed drugs. The FDA Amendments Act of 2007 (FDAAA) requires, among other things, that results of clinical trials be posted on the clinicaltrials.gov website within 1 year of study completion.

31. In addition to the benefits of posting results, posting details of the design of studies on the clinicaltrials.gov website helps eliminate redundancy and inefficiency in the design of clinical trials. This allows competitive Pharma/independent researchers to follow a sanctioned lead in design of their trials. This is particularly useful in the establishment of acceptable trial design, such as choice of comparators, sample size, treatment and sample collection schedules, and outcome measures.

32. Although there was apprehension from industry about the FDAAA requirements, extensive efforts and resources have been made to develop and implement results disclosure policies (eg, entire departments have been created within industry to cope with results disclosure requirements). Recent evidence indicates that industry compliance with FDAAA is significantly higher than non-industry compliance [11]. Notably, the time required for results disclosure was greatly under-estimated by the US government and updated estimates had to be issued [9]. Researchers and sponsors should be provided with realistic estimates if governments expect compliance with their legislative initiatives.

Conclusions

33. We must stress the importance of ensuring that sufficient resources are available for publication of results. Publications do not write themselves. Good researchers are not always efficient writers of scientific papers, and it is important that assistance from professional medical writers be made available to those who need it.

34. It is important to realise that non-publication of clinical trial results is not primarily a problem of the pharmaceutical industry: recent evidence shows that, although non-publication remains a problem in all sectors, it is closer to being solved in the pharmaceutical industry than elsewhere.

35. While much public discourse has focussed on demonising the pharmaceutical industry, this is not only unsupported by evidence, but is also unhelpful. There are those who make money by selling ineffective “alternative therapies” who use public distrust of the pharmaceutical industry as one of their main marketing strategies. Painting the pharmaceutical industry as being evil helps these quacks and charlatans considerably when they employ that strategy, which can result in real harm to patients.

36. We would therefore urge the committee to focus on practical solutions to the problem of inadequate disclosure of clinical trials rather than on apportioning blame. We believe that the three most effective practical solutions would be to ensure that researchers are properly funded to disclose their results, embedding monitoring of results disclosure firmly within the National Research Ethics Service, and evaluating the possibility of opening up data submitted to drug regulators to public scrutiny.

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

Conflict of interest statement

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

January 2013

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