Events underlying the publication of Eastell et al., JBMR 2003
Documents supplied by Aubrey Blumsohn

Background and thoughts

1. The purpose of this document is to discuss a public scandal[1] surrounding a pharmaceutical scientific manuscript published in the Journal of Bone and Mineral Research in 2003[2]. This manuscript[2] will be referred to as "manuscript A". The Journal of Bone and Mineral Research (JBMR) is the leading scientific journal of skeletal and osteoporosis related medicine[3].
2. The timing of this document is related to a pending "fitness to practice" hearing involving the lead scientific "author" and corresponding "author" of manuscript A, Professor Richard Eastell. These hearings are to be held by the General Medical Council (GMC), the UK regulator of doctors, in November 2009 following a complaint made more than four years ago in October 2005.
3. The problems relating to manuscript A were only revealed because there was an attempt to implicate me (the complainant) in two further false manuscripts on a similar theme and based on overlapping data. Those data were produced at Sheffield University under contract to a commercial sponsor (Procter and Gamble Pharmaceuticals) and involved the mode of response to a drug (Actonel). The interpretation of those data was prevented by the sponsor, because the sponsor refused to provide randomization codes and relevant event codes to the investigators. As was the case for manuscript A, publication of these other manuscripts (manuscripts B and C)[4] was attempted based on the expectation that authors would blindly trust statistical reports, graphs and computer demonstrations by the research sponsor, and that the academic investigators would be expected to misrepresent their roles as "authors". Key reported findings in these two draft manuscripts were later also found to be untrue.
4. Abuse of trust in science has serious moral implications. Scientific fakery and ghosted science has led to an unfortunate loss of public trust in medicine, and has also resulted in the deaths of hundreds of thousands of patients over the past decade. Regulators have turned a blind eye to abuse of the safeguards of science. The key mechanism that has allowed scientific fakery involving drugs such as Vioxx, Seroxat, Celebrex, Baycol and many others is the flagrant disregard a few important academic authors have had for the scientific

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[1] Details of this public scandal will not be addressed here given the focus on documents: Useful background is provided in :
-many articles in Times Higher Education
-a particularly well written and evidenced piece by Jennifer Washburn in Slate http://www.slate.com/id/2133061/
-collated media reports at: http://www.thejabberwock.org/wiki/index.php?title=Actonel_Case_Media_Reports
-Descriptions authored by myself:

Blumsohn, Aubrey (2006-10). Authorship, ghost-science, access to data and control of the pharmaceutical scientific literature - Who stands behind the word? Volume XIX (3) Summer 2006. American Association for the Advancement of Science (Professional Ethics Report). [http://www.aaas.org/spp/sfrl/per/per46.pdf]

Blumsohn, Aubrey. (2009). "Science, academic integrity and the General Medical Council". CAFAS Update 64: 1-5. http://www.thejabberwock.org/blog/pdf/cafaspreprint.pdf

[2] *Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. J Bone Miner Res. 2003 Jun;18(6):1051-6.*

This publication remains online at [http://www.jbmronline.org/doi/pdf/10.1359/jbmr.2003.18.6.1051]
accompanied by a "Statement of concern" [http://www.jbmronline.org/doi/suppl/10.1359/jbmr.2003.18.6.1051]
but without reference to truthfulness of reported findings and declarations.
Manuscript has been cited extensively [http://tinyurl.com/yfpmhy7] despite incorrect "findings"and incorrect findings continue to be cited.
Remains indexed on Pubmed [http://www.ncbi.nlm.nih.gov/pubmed/12817758] without note of retraction or concern.

[3] http://www.jbmronline.org/ (impact factor 6.44)

[4] Published in *abstract* form in my name in 2003. Ghostwritten manuscripts and statistical reports written by Procter and Gamble were never progressed to full publication because the sponsor refused to release the data. The truthful versions of these abstracts and draft manuscripts have still not been published. The sponsor has refused to reveal the wording of patient consent forms, has refused to allow raw data to be passed to a journal editor with a manuscript submission, and has refused to allow raw data to be placed into the public domain. Abstracts are:

Blumsohn A, Barton IP, Chines A, Eastell R. Relative Contributions Of The Early Changes In Bone Resorption And Later Changes In Hip Bone Mineral Density To The Reduction In Vertebral Fracture Risk With Risedronate. J Bone Miner Res 2003;18(S2):S157

Blumsohn A, Barton IP, Chines A, Eastell R. Relationship Of Early Changes In Bone Turnover To The Reduction In Vertebral Fracture Risk With Risedronate - The HIP Study. J Bone Miner Res 2003;18(S2):S89

process. These implicated authors have almost all been medical doctors. These "authors" provided credibility to falsified representations of data to which they themselves did not have access. In some instances "authors" might have had access to data, but did not trouble themselves to check even the most rudimentary aspects of the representation of data presented in their names by commercial benefactors. These actions have led to deaths and have brought the profession of medicine into disrepute. It is difficult to regard these authors as scientists given any reasonable understanding of that term.

5. The current contemplations at the GMC have only tangential relevance to the actual complaint made to the GMC in 2004 about the conduct of Professor Eastell. This narrative relates only to those aspects that will be "heard". The GMC will focus on a single aspect of research impropriety involving a single publication (A). In accordance with this, this narrative will focus only on that one aspect and on material facts surrounding the timing of that one aspect.

6. The following aspects will therefore not be discussed here in any detail if at all.

   6.1. The GMC (as regulator of a scientific profession) states that it regards scientific misrepresentation as outside of its remit. The details of the misrepresented science and the attempted cover-up of those aspects will not be discussed.

   6.2. The unusual handing of the complaint by the General Medical Council itself will not be discussed. Suffice to say that this does not inspire confidence in the competence or integrity of this agency when powerful doctors are involved. The complaint was made in 2005. In December 2005 Eastell himself conveyed documents to the GMC that any reasonable scientist would find shocking. This was followed by two years of regulatory inaction. I withdrew from communication with the GMC in 2007 but indicated that I would be delighted to resume such communication in the unlikely event that the case examiners ever screened the case to FTP based on the materials Eastell himself had provided. Professor Eastell admitted in public in 2007 that he did not have access to data underlying his publication, and that the statement in manuscript A to this effect was false, as were many of the reported scientific findings. The GMC then waited almost two years before proceeding. The GMC "prosecutors" failed to seek advice or input from the complainant. It is hard to conclude that the GMC are carrying out their obligation as prosecutors to safeguard medicine on behalf of the public with any great enthusiasm. Professor Eastell of course has his lawyers, and has powerful friends in the GMC.

   6.3. The roles of the journal (JBMR) and the University of Sheffield will not be discussed.

   6.4. Given the most convenient exclusion of myself from the process, I have restricted the documents discussed here to those which Professor Eastell will have. These documents speak for themselves. They are legal correspondences, signed letters from himself, or correspondences written or received by himself as well as computer diskettes obtained under the Data Protection Act. E-mail archives of my own correspondences with Professor Eastell were also provided with the kind assistance of Sheffield University Computing Services in 2003 and 2004. Since Professor Eastell will have all of the documents discussed here, any failure by him to provide these documents to the pending hearing would be noteworthy.

7. The reasons provided by the GMC for restriction of the "charges" to only one aspect are extremely troubling, and are worthy of considerable public debate beyond this case.

   7.1. The GMC have now deemed that it is perfectly proper and permissible for doctors to author scientific manuscripts reporting upon data to which they do not have unfettered access (or to which they do not have any access at all)[5]. The GMC also apparently deem it as acceptable that legitimate authorship of scientific reports could take place where access to data has been actively denied by a commercial sponsor. They do not state what sort of science or authorship that would be. This is the most extreme

[5] They do not state whether this is permissible for all scientists or for all doctors, or whether this only to medicine. Not is it clear whether this applies to all medical research or only to research involving pharmaceuticals.

manifestation of ghost authorship (the authors themselves are scientific ghosts), and is far more important than the use of undeclared technical writers to assist with the mere textual aspect of a manuscript.

7.2. This convenient view by the GMC is contrary to reams of guidance for conduct of science over many decades. It is contrary to the rules of every legitimate journal in every field of science. The GMC do not indicate where they think such "science" should or could be published.

7.3. The GMC provide as reasoning that "a company owns the data". It is not clear whether the GMC have simply lost touch with science, whether they regard medicine as being unrelated to science, or whether this view is based on expediency. It is also not clear what this says about the standard to which these academics within the GMC hold their own research. Nevertheless, even the GMC cannot overturn the most basic principle of science. This is that scientific authors should be distinguishable from clowns. If you do not have the data, you do not have a basis for discussing those data as a legitimate scientific author.

7.4. Following from this line of logic, the GMC have deemed while it is perfectly appropriate to be an illegitimate scientific author, it is not appropriate to lie that one is a legitimate author when one is not. In other words, it is inappropriate to state that authors had proper access to data when they did not. Simply not declaring that one did not have access to data would appear to be satisfactory according to the GMC[6]. Since the GMC evidently regards lies as very important, the case revolves not around scientific integrity, but around an acknowledged untruth, and who told it.

8. I do not believe that these matters can be discussed in secret. Science is by its very nature an open activity. Scientists need to have a clear understanding of what is permissible and what is not. Scientists and the public also need to understand which investigators, companies, journals and products can be trusted. The limits of permissible scientific misconduct as allowed by regulatory authorities need to be compared with the view of scientists in general and with ethical guidelines.

9. The linguistic aspects of science are of interest. In the scenario described here, a commercial sponsor of research refused to supply relevant raw data to "authors". The language of such refusals, and the nature of the various excuses and redefinitions is in my view fascinating. The "trust test" is sometimes used by ethicists to test whether behaviour or a conflict of interest is important. This boils down to asking the question: "Would you be willing to have these arrangements generally known"? or "Would a fellow scientist (or a research subject or a patient) trust this researcher's judgment or this company's judgment if they knew the researchers had done this?"

10. I have avoided any discussion of the "gory" aspect of this affair in this narrative. Henry Kissinger is usually credited with the quip :

    "University politics are vicious precisely because the stakes are so small"

    The stakes are not small in pharmaceutical research.

[6] Any reasonable scientist would accept that if an authoring scientist is denied access to data about which he is "writing", then this would need to be made explicit within the manuscript. Such a manuscript would be unlikely to be published in a legitimate scientific forum.

Science in a nutshell

11. The science in question involved three publications and associated "ghost" statistical reports prepared by Procter and Gamble. In each of those three manuscripts it had been stated that in patients taking the osteoporosis drug risedronate (Actonel), the effect of the drug showed a threshold or plateau at a change of around 35% for a key variable NTX.
12. Graphs showing the separate responses of the placebo and treated arms of the studies seemed clear. What was less clear was how those graphs had been constructed. It was suspected that the graphs in all three manuscripts might have been scaled so as to omit large parts of the data.
13. Further it was suspected that "smoothing factors" in these graphs could have been chosen so as to yield almost any shape of graph desired. Without the actual data it was impossible to be sure of any of this.
14. In retrospect we now know that these reported findings (of a threshold in the percentage change of NTX) were false in all three manuscripts, and that graphs had indeed been judiciously "cropped" to omit about 40% of the data. With the data in hand, it is perfectly possible to make the cropped graphs take on almost any shape by choosing a "smoothing factor".
15. More than four years after concerns were raised, Eastell admitted in public that he had indeed not had access to data in the first of the three publications when it was published. He admitted that the key scientific finding regarding the NTX change plateau in that publication had been false. There was indeed no threshold change in NTX in patients taking risedronate in publication A (just as there is no such effect in publications B or C). As I had suspected, graphs had in fact been cropped so as to omit around 40% of the data. By combining the placebo and treated arms of the study together in a completely erroneous analysis, the *mea culpa* came up with a curious compromise. Through this interesting analysis it was concluded that despite the fact that the results as previously presented were wrong, the previous "conclusions" were somehow correct. Fortunately readers of the mea culpa were not so easily baffled[7,8]. The other two manuscripts were not addressed.

Events surrounding manuscript A

16. The research was carried out under contract with Procter and Gamble Pharmaceuticals (P&GP) and involved a widely used drug (Actonel, or risedronate).
17. The first "author" and "corresponding author" of manuscript A was Professor Richard Eastell of the Academic Unit of Bone Metabolism at the University of Sheffield (UK).
18. Professor Eastell was at the time also the Research Dean of Sheffield Medical School and the Research Director of Sheffield Teaching Hospitals. In those roles he would have had overarching responsibility for clinical research governance at Sheffield University and the associated adult teaching hospitals. I believe that such a role carries particular responsibilities, and irregular conduct by a person in such a role should be viewed more seriously, rather than less seriously.
19. Professor Eastell was also Chair of the UK scientific advisory board of P&G Pharmaceuticals. He was recipient of substantial amounts of research income and staff salary funding from P&G. During the years spanning this incident, several members of staff within this academic unit received 100% salary funding via P&G. It is unknown to me whether Professor Eastell received any personal remuneration from P&G for his chairmanship and other activities as Key Opinion Leader for the company.

7 http://tinyurl.com/y87j6sr

8 http://tinyurl.com/yec74j7

20. The work was based on measurements performed (in Sheffield) on many thousands of frozen specimens provided by participants during the three key multinational multicenter randomised trails used to gain registration and licensing for Actonel (Vert-NA, Vert-MN, HIP).

21. Manuscripts A, B and C were based on overlapping data. The research and the resulting manuscripts were intended to detail the relationship between bone turnover reduction and subsequent bone fracture in patients taking the drug risedronate (Actonel). The scientific benefits perceived by the company with not be discussed here.

22. In or around March 2002 the first of the three intended P&G manuscripts (A) was submitted to the Lancet in the name of Professor Richard Eastell. Professor Eastell was the first author and also the corresponding author.

23. The GMC response to the second application by Richard Eastell to cancel his hearing (response dated 20 October 2009, GMC author Professor Roger Green) provides a summary of what happened prior to that submission based on the evidence supplied by Professor Eastell himself:

    "A copy of tracked changes on the fourth draft of the paper (out of eleven) which is where the statement about full access to the data was inserted by an in house medical writer at Proctor and Gamble, Lisa Bosch (who, incidentally was not one of the authors who finally appeared in the published paper), to comply with the requirements of the Lancet[9]"

    …..

    "Prof Eastell has apparently accepted that the statement that all authors had full access to the data is incorrect. The changes to the article initiated by Lisa Bosch were specifically drawn to Prof Eastell's attention and he did not seek to amend the statement about full access.

    ….

    "the changes to include the statement were made by someone (sometimes referred to as a Ghost Writer) who did not have a part in the study. Nevertheless the changes were highlighted to the authors. "Tracked changes" prints out the changes in a different colour from the original so that it is easy to see what has been changed. In addition in the covering E-Mail this particular change was noted (along with several others). In this respect Prof Eastell (and other authors) could not easily have overlooked it."

    ….

    "Apparently it was necessary at that time for a statement of this nature to be present before a paper could be accepted by the Lancet. Thus the deception, if such it is, is to gain publication in a prestigious journal."

24. The submission for publication was rejected by the Lancet. The manuscript was then submitted to the Journal of Bone and Mineral Research, again in the name of Professor Richard Eastell (as first author and also as corresponding author).

25. The time-course of manuscript submission is relevant to the various refusals by the company to allow authors to have the relevant randomization and event codes so as to allow the Sheffield laboratory data to be interpreted. The eventually published manuscript reveals the following information in terms of dates:
    October 2001 : Work first presented in public by Professor Eastell at the meeting of the American Society for Bone and Mineral Research.
    [**March 2002**: Submitted to Lancet as above]
    May 1 2002 : First received by Journal of Bone and Mineral Research
    Nov 5 2002: Received by Journal of Bone and Mineral Research in revised form following peer review
    Dec 12 2002: Accepted for publication by Journal of Bone and Mineral Research
    June 2003: Published in Journal of Bone and Mineral Research

[9] The Lancet's instructions to authors require authors to "state that he or she had full access to all the data in the study and had final responsibility for the decision to submit for publication" and "At any time up to 5 years after publication of research in the journal, authors may be asked to provide the raw data."

26. In May 2002, shortly after the manuscript had been submitted to JBMR I was informed that "difficult questions" had been asked of Professor Eastell at the ASBMR and IOF meetings when he had presented the work. Those questions related to "who had analysed the data". Professor Eastell admitted that he had no acquaintance with the raw data whatsoever but had simply trusted the statistical representations of those data as provided to him in a report and in a guided computer display. This was of concern to me because I was about to sign a research contract with P&G to extend this work by measuring further samples from these trials in my laboratory. Professor Eastell wrote to Ian Barton, senior statistician at P&G on **27 May 2002** to say that:

    "I was discussing our work with a US investigator (who will remain anonymous) who was really surprised when I told him that all the analyses for the IOF presentation were done by P&G employees. I told him that I had worked with you and Simon extensively on the risedronate database and that I thought you adhered to the highest principles. However, I think that to avoid criticism in the future it would be good if we could say that we had done the analyses independently."[See original E-mail of 27 May 2002 as footnote][10]

[10]From: "Richard Eastell" <r.eastell@sheffield.ac.uk>
To: barton.ip@pg.com
CC: "Aubrey" <ablumsohn@sheffield.ac.uk>
Subject: RE: NTX/CTX data
Date: Mon, 27 May 2002 09:17:04 +0100
Message-ID: <NAEDLHFPJIKKALPANFLPOEDNDCAA.r.eastell@sheffield.ac.uk>

Dear Ian
Thanks a lot. We have all the samples and are ready to go. Aubrey says we will have the urinary NTX ready by the end of July. The PINP may take a little longer because we may have problems with fibrin clots, as these are being measured is serum. The NTX is the primary endpoint, anyway.

There is another issue I wanted to raise with you. I was discussing our work with a US investigator (who will remain anonymous) who was really surprised when I told him that all the analyses for the IOF presentation were done by P&G employees. I told him that I had worked with you and Simon extensively on the risedronate database and that I thought you adhered to the highest principles. However, I think that to avoid criticism in the future it would be good if we could say that we had done the analyses independently. I couldn't possible do these, but I think that Aubrey Blumsohn could, if he was shown how to use the method of Li et al. Could I suggest that Aubrey works with you to see how you did the analysis for the VERT trial and then when we have the HIP data we could have the analyses run by you and by Aubrey so that we can say that we got the same result with independent analyses? The person who raised this is the sort of person who is likely to come to the microphone at meetings and ask lots of questions, so I would like to be prepared!
Best wishes,
Richard
Professor Richard Eastell, MD, FRCP (UK, Edinburgh, Ireland), FRCPath,FMedSci
Research Dean for the School of Medicine and Biomedical Science
<address truncated>

27. Barton replied on **14 June 2002** refusing access to data by authors. He wrote:
"No, we do not intend for someone else to the analysis.….I just feel that we're being very clear in what we are doing and don't need to ask an independent person to analyse the data just to make a few people happy[11]*."*[See E-mail as footnote][12]

28. On **2 July 2002** I signed (with Professor Eastell) a research contract with P&G to extend this work by performing measurements on samples from remaining registration trial for risedronate in my laboratory. The contract was an appropriate one. It specified that the academics would be able to analyse and interpret the data, and report on the findings without interference by the company[13]. The extended work would eventually include all three registration trials for Risedronate (VERT-MN, Vert-NA and HIP) including as a subset the data already submitted for publication and under journal review.

[11] The "independent persons" referred to being the authors of the intended and already submitted publications!

[12] From: barton.ip@pg.com [mailto:barton.ip@pg.com]
Sent: 14 June 2002 13:37
To: Richard Eastell
Subject: Re: HIP analyses

Hi Richard

Yes I didn get it and am sorry I didn't reply earlier. I'm snowed under with other work.

Anyway, here are answers to your questions:

Adjustment for BMD can be done and I plan to perform this once the HIP samples are available for analysis. Non-vertebral fractures can be divided into meaningful groups and analysed, again I plan to perform this once the HIP samples are available.

No, we do not intend for someone else to the analysis. As far as I'm aware, the Alliance is very transparent in the analyses we perform. We always clearly explain what statistical methods have been undertaken and are happy to share with as many external people as possible. Resource wise it wouldn't make sense for me to spend a lot of time training someone else to perform the analyses. Also, the FDA never perform our primary analyses and write our clinical reports.

Please don't take the last point the wrong way. I just feel that we're being very clear in what we are doing and don't need to ask an independent person to analyse the data just to make a few people happy. Phil Ross does a lot of the MSD analyses and no one raises objections.

What I would say is that I want us to generate a prospective statistical analysis plan. I would like to state that the analyses would look at patients in the HIP trial who have confirmed osteoporosis as well as the ITT. I would also like to mention that we include the VERT trials in a pooled-analysis with the HIP trial. We can also include adjustment for BMD and dividing the osteo-non vert fx data by skeletal-site subgroups.

Kind regards,
Ian

[13] For text of the contract see http://tinyurl.com/yh6dou9

29. On **8 July 2002** Dr Mike Manhart (Director of Clinical Development, P&G, USA) wrote with astonishing clarity, again refusing access to raw data by "authors":
"On the plus side it does add an extra layer of external "credibility". With this however, Industry looses the opportunity to demonstrate its ability to be a true partner in scientific endeavours. …. Finally, transferring databases which the Compnay [sic] has invested hundreds of millions of dollars to obtain is not something to be taken lightly. That's not to say it can't be done, but the reasons must be sufficiently important to justify it.[14]" [See original E-mail as footnote][15]

30. On **24 July 2002** a "statistical analysis plan" was conveyed by P&G. It was stated in this and in prior communications that this would avoid having to reveal the codes to authors because *"this way, Richard can proactively state that these analyses were prospectively planned prior the receipt of the analysed samples"*. The "statistical analysis plan" contained little in the way of statistics. In fact from a statistical point of view it was almost meaningless. It mentioned instead the "*business purpose*" a "*brand tactic*" and that this tactic was to induce an "*osteoporosis paradigm shift*".

31. Despite these denials of data, the record shows that on **Nov 5 2002** manuscript A was revised following peer review and was transmitted again to the Journal of Bone and Mineral Research. On **12 December 2002** the manuscript was accepted for publication by JBMR. Professor Eastell could easily have withdrawn the manuscript from the peer review process prior to this point, and in my view was negligent even at that stage in not doing so.

32. In **December 2002**, final raw data required for overlapping publications B and C were transmitted from my laboratory to P&G. Randomization codes were not provided in turn since P&G were insisting that they had to perform the analyses themselves according to their business plan.

33. During **April 2003** we received a variety of graphs and tabulated summaries from P&G showing their representation of our data. The cover E-mails were ebullient "*This is the one that the medical community have being asking for*", "*I truly believe that these data are so important. ..... this fits nicely with our hypothesis..*", "*... this way the oral/poster could show our previous work from both the VERT and HIP trials looking at the "threshold" of both changes in BMD and BTM*"

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[14] In reality, all that would have required transferring would have been the randomisation codes, event codes, bone mineral density results, and potential confounding variables. The rest of the data was supplied to P&G by academics at Sheffield University.

[15] From: manhart.md@pg.com [mailto:manhart.md@pg.com]
Sent: 08 July 2002 15:02
To: Richard Eastell
Subject: Re: HIP data analysis

Richard
I think we should look carefully at the pros and cons of Dr. Blumshon conducting the analysis you refer to. One the plus side it does add an extra layer of external "credibility". With this however, Industry looses the opportunity to demonstrate its ability to be a true partner in scientific endeavours. Beyond this, the practical issues to training up a new statistician and the corresponding delay in "time to result" may make the option difficult.

Finally, transferring databases which the Compnay has invested hundreds of millions of dollars to obtain is not something to be taken lightly. That's not to say it can't be done, but the reasons must be sufficiently important to justify it.

Might there be some alternative approaches to the potential ciritcism? For example, Ian this morning spoke of wanting to do a formal analysis plan prior to any data in hand adn having this agreed by yourself and others as needed. In hte manuscript reporting the reuslts it would be made clear a formal analysis plan was developed and agreed by all investigators and the statistician conducted the analyses according to plan.

I'd be happy to discuss this further if you wish. I'm in the Staines office today and Tuesday morning, busy all day Wednesday, but then in the Geneva office on Thursday from about mid-morning. IF there is a time you can talk, let me know and I'l arrange the proper phone numbers be set up so we can talk.

34. On 1 April 2003 Richard Eastell received a private E-mail from Ian Barton at P&G. It was said that meeting abstracts for ASBMR must somehow be produced within 2 days for "internal review" by P&G based on the outputs they had sent. It also said that
"when we start writing up the manuscript (you proposed JCEM) we will provide a medical writer to help (Mary Royer, she's fantastic)". [See E-mail in footer][16]

35. Two meeting abstracts[4] were submitted to the ASBMR meeting. The submissions were made by an unknown P&G employee directly to the meeting organisers. These were written in my name (as first author) by unknown parties, possibly by Richard Eastell on the basis of the "reports" Procter and Gamble had produced for us. I did not object, but was bewildered. Professor Eastell (who was the senior author) was apparently unperturbed.

36. On **16 Apr 2003** I attended the Procter and Gamble Sheffield Centre Grant Meeting. The minutes of the meeting show that I (AB) was to write publication drafts based on the reports produced by P&G over the previous weeks. Professor Eastell stated that he felt the data could be published "*as it stands*" and should be sent to the Journal of Clinical Endocrinology and Metabolism.

[16] From: barton.ip@pg.com [mailto:barton.ip@pg.com]
Sent: Tuesday, April 01, 2003 3:40 PM
To: r.eastell@sheffield.ac.uk
Cc: kasibhatla.c@pg.com
Subject: ASBMR Abstract Deadline

Hi Richard

I know I only sent you the updated group 1 tables this morning, but I've just got off the phone with Chandu (who is leading the ASBMR abstract effort) and he said that if you could send him your vert fx vs. changes in BTMs abstract by tomorrow or very latest this Thursday he will have enough time to send it for internal review. We need 6 signature approvals!!!

Also, when we start writing up the manuscript (you proposed JCEM) we will provide a medical writer to help (Mary Royer, she's fantastic).

No pressure!
Ian

37. Things were moving very fast. A few days later on **24 Apr 2003** Ian Barton wrote introducing a different ghost writer (Mary Royer) and her function in a candid manner. It was said that P&G wished the publication drafted by mid June. [See Email in footer][17]

"She is very familiar with ... our key messages".
"we should all know the key messages/data etc".
"Lisa Bosch (our internal medical writer) helped us finalised the JBMR manuscript, if you remember."

38. The draft publication (B) then produced by P&G stated those "key messages":
"Consistent with findings from the VERT trial, a non-linear function was more appropriate than a linear function for modeling the relationship between early changes in NTX and vertebral fracture risk over 3-years (5mg Risedronate, p=0.008)".
"There was little further improvement in fracture benefit below a decrease of 30 to 35% for NTX."
"In conclusion, ...there may be a level of bone resorption reduction below which there is no further fracture benefit."
"Key Message: The relationship between early changes in NTX and longer term fracture risk for 5mg Risedronate is non-linear (p=0.008), consistent with findings from the VERT trial."

Given the provision of data by P&G on April 2006, and some information obtained earlier in 2004 and 2005, these statements are now known to be untrue. Indeed, they could not have been more untrue. Several variants on the same draft publication were produced, all containing these same scientific statements and conclusions. We also now know that graphs in these drafts were scaled (as for publication A) to exclude about 40% of risedronate treated patients.

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[17] Subject: Ideas For Writing Publications For The Two Recently Submitted ASBMR Abstracts
To: r.eastell@sheffield.ac.uk, ablumsohn@sheffield.ac.uk
CC: mroyer@twcny.rr.com, chines.aa@pg.com, pack.s@pg.com, david.cahall@aventis.com
From: barton.ip@pg.com
Date: Thu, 24 Apr 2003 14:36:41 +0100

Dear Richard and Aubrey

I wanted to introduce you to one of The Alliance's external medical writers, Mary Royer. I've had the great privilege to have worked closely with Mary on a number of manuscripts which The Alliance have recently published. Mary is based in New York and is very familiar with both the risedronate data and our key messages, in addition to being well clued up on competitor and general osteoporosis publications.

Chandu has agreed that Mary will be the external medical writer for your two planned BTM vs Fx manuscripts. Lisa Bosch (our internal medical writer) helped us finalised the JBMR manuscript, if you remember.

I told Mary that last week you agreed to put together publication briefs for the two manuscripts, and once these were written we should all know the key messages/data etc. Richard and Aubrey, how do you want to proceed? Richard, I know you allocate "publication writing days", so are you thinking of drafting the publications first and then let Mary take over or would you like Mary to write from the beginning? I'm very flexible. Mary and I have just finished writing a publication with Steven Boonen (Richard you will be contacted as you're a co-author!) and Mary was involved at the very beginning and wrote from scratch.

If you could let both Mary and I know how you envisage us all working together that would be extremely helpful. I'm hoping that we can get the publication briefs written in the next couple of weeks and get the publications drafted by mid-June. What do you reckon?!

Take care and hope to hear from you soon, Ian

39. On 9 June 2003 I wrote again to Ian Barton asking for the randomization and event codes. Professor Eastell was party to all E-mails. [See E-mail at footer][18]

[18] From: Aubrey Private <aubreyprivate@btinternet.com> on 09/06/2003 22:28
To: Ian Barton-IP/PGI
Cc: Richard Eastell <r.eastell@sheffield.ac.uk>, Rosemary Hannon <R.A.Hannon@sheffield.ac.uk>
Date: 09/06/2003 23:28
Subject: Re:HIP Trial: BTM vs Fx

Dear Ian,

Hope you are fine. I have a major crunch of things on my to-do list. However, I have been going through all the various documents and results we have relating to the Hip data. Before I go ahead with the big writing push, I think I would want to get a better feel for what the data is telling us. In particular, I would quite like to have a bit of a play with a variety of different intuitive presentations (particularly graphical ones showing individual data points, and also focussing on the treated group and placebo groups separately). In the longer run, I think we might be able to incorporate the data into some sort of a clinical decision model.

I wonder if you have any thoughts about the ideal way to look at the data in this sort of detail. The best from our point of view would be to merge the randomisation codes (and fracture data) into our marker database, and we can have a bit of a fiddle with plots of various sorts. Another option is for you to do some different plots. This has the downside of us having to counter the Black/Bauer et al arguments that we don't know our own data. I doubt any of this would alter the main presentation, but would inspire us with confidence that the arguments are sound.

We also need to have a discussion about the absolute values for NTX in the different studies. Rosemary and I have been looking at this. I don't think a simple conversion factor is ideal (the association between old and new results may be non-linear), but this may be a reasonable first approximation to the truth. I think another issue (if we are comparing prediction by DXA and markers) is to take account of the relative imprecision of these measurements. It may not be possible to do this easily.

Let me know what you think.

Kind regards

Aubrey

40. My colleague Rosemary Hannon (an author on the soon to be published manuscript A) admitted that she had never seen any raw data, and wrote to compliment me on my diplomacy. [See E-mail at Footer][19]

41. More than diplomacy was required. The following day (**10 June 2003**) Ian Barton replied to the effect that
    a) such access/analysis of data by authors would be a “distraction”
    b) that the priority was to get the "publication briefs" written
    c) That the data was "interesting and unique" and that "I don't want us to be delayed/distracted" and that "our competitors [would] pip us to the post".
    d) He would draft the "publication briefs" himself if necessary.
    As before, Professor Eastell and Rosemary Hannon were included in the correspondence.
    [See E-mail at footer][20]

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[19] From: "R.A.Hannon" <R.A.Hannon@sheffield.ac.uk>
To: ablumsohn@sheffield.ac.uk
Date: Tue, 10 Jun 2003 09:20:17 +0100
Subject: Hip data

Dear Aubrey,
Thanks fro copying me in on the HIP data email to Ian. May I say it was the height of diplomacy! Well done. I hope you get the desired response.

Rosemary
Rosemary A Hannon, PhD
Bone Metabolism Group
Section of Medicine
Division of Clinical Sciences (North)
University of Sheffield

[20] Subject: Re:HIP Trial: BTM vs Fx
To: Aubrey Private <aubreyprivate@btinternet.com>
CC: Richard Eastell <r.eastell@sheffield.ac.uk>, Rosemary Hannon <R.A.Hannon@sheffield.ac.uk>, <pack.s@pg.com>
From: barton.ip@pg.com
Date: Tue, 10 Jun 2003 15:33:39 +0100
Message-ID: <OFDCDC54BF.D8D005B2-ON80256D41.004EECA6@na.pg.com>

Hi Aubrey
Thanks for the email.

I personally would like us all to solely concentrate on getting publication briefs for the two manuscripts written by end of June. These briefs would have to go through internal review and will result in additional questions/analyses. Therefore, in terms of writing the actual manuscripts this will not happen until July. I think we should concentrate on each manuscript separately.

I agree with you that we should explore the data more. I would be interested in receiving detail on your thoughts in terms of trying to understand the data more. I'm happy to perform additional analyses etc. However, this shouldn't delay writing the publication briefs. We do have all data available in one dataset (i.e. treatment group, fracture data, BTM data, BMD data, baseline data, ...).

In terms of NTX conversion factor, this should only relate to publication 3 (i.e. does baseline NTX predict fracture incidence and treatment effects). With regard to publication 2 (i.e. BMD and BTM data) the analyses do take into account the variability of the measurements and I don't think we need to worry about the conversion factor as the Z.Li model looks at the treatment effect (i.e. mean difference between treatments for both NTX and BMD).

If you would find it easier to talk via phone, please let me know your availability. As you can tell, I really want to get these manuscripts written and submitted before a) we move onto other projects, b) our competitors pip us to the post and c) ASBMR. We have really interesting and unique data and I don't want us to be delayed/distracted.

Hopefully talk to you soon, Ian
PS. I'm more than happy to draft the two publication briefs if timings etc are difficult for you to meet.

42. On **12 June 2003** P&G conveyed the draft of a third publication (relating to the other meeting abstract in my name). Key conclusion of this manuscript was again that:
"5mg Risedronate showed an apparent "threshold" (i.e. fracture incidence is not continually decreased)."

    This conclusion is now known to be false. Patients taking risedronate with the largest change also show the largest fracture reduction. All of these patients (40% of the total) "fell off" the end of the P&G graphs. But that was impossible for the intended "authors" to know this at the time.

43. On **13 June 2003** I approached Professor Eastell to say that I felt we would both be accused of scientific fraud.

44. In response to that conversation, we both received an E-mail (**19 June 2003**) from Ian Barton again refusing data. It stated:

    "I've just spoken to Richard about you wanting to gain more of an insight into the data prior to writing a pub brief. I explained that the Alliance has received a couple of requests from external parties to obtain the BTM/FX data and we have declined. Therefore, as we have set a precedent we would be unable to share the d/base with Sheffield." [See E-mail here][21]

45. A few days later (**in June 2003**) the first publication (manuscript A in Professor Eastell's name as first author and as corresponding author) appeared in press in JBMR. It stated as primary conclusion that there was a threshold for percentage change in NTx at 30-40% in patients taking 5mg of risedronate. This is now known to be false. It stated that "all authors had full access to the data and analyses". This was false. Graphical display of the data showed a clear apparent threshold for NTX in the risedronate study arm. This was a serious misrepresentation. Furthermore, the graphical display of data is now known to have omitted at least 40% of the data for these patients. As first and corresponding author, Professor Eastell would have been expected to review and to approve the publication proofs, and took responsibility for the manuscript. He was however apparently disabled from taking such responsibility.

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[21] Subject: Re:HIP Trial: BTM vs Fx
To: Aubrey Blumsohn <ablumsohn@sheffield.ac.uk>
CC: Richard Eastell <r.eastell@sheffield.ac.uk>
From: barton.ip@pg.com
Date: Thu, 19 Jun 2003 09:31:42 +0100

Dear Aubrey

Hope all is well. I've just spoken to Richard about you wanting to gain more of an insight into the data prior to writing a pub brief. I explained that The Alliance has received a couple of requests from external parties to obtain the BTM/FX data and we have declined. Therefore, as we have set a precedent we would be unable to share the d/base with Sheffield. However, I don't want to be seen as hiding any of the data so we agreed that you should come down for 2-3 days to our R&D site where you and I can a) look at the data in more detail, b) perform the analyses you require and c) write up the publication briefs.

It would be good if this could happen as soon as possible, definitely within the next 4-5 weeks. Below I've listed dates which I am available.

30JUN-04JUL
14, 16-18JUL
21-24JUL
28-31JUL

Obviously P&G would pay for all expenses (travel, food and hotel).

Hope to here from you soon,
Ian

46. On **28 July 2003** I met with Ian Barton who had agreed to show me some analyses on a computer screen at P&G facilities. Some of these graphical analyses were also copied into a document which I took away with me. It immediately became apparent to me that the data analyses as represented by P&G could not possibly have been correct. No complex statistical analysis was required. Even the most rudimentary graphical inspection of plotted data was wholly discordant with the conclusions produced by P&G in both sets of draft publications and abstracts in my name. I required the raw data so that truthful publications could be produced.

47. All authors as well as P&G were in serious difficulties at that point, and I complained to Professor Eastell that something had to be done. He should in my view have alerted JBMR to a likely problem in manuscript A, and should also have demanded all of the raw data relating to the three manuscripts. However he did not do so.

48. I was due to present the data at three scientific meetings over the next 12 weeks based on the submissions by P&G to those meetings. By now, we knew that the analyses were not correct, but were unable to write our own publications, or to establish quite how incorrect they were.

49. An urgent compromise was reached which I now regret. I met again with Ian Barton, and all mention of a threshold effect was removed from the intended meeting presentations. A graphic was produced that showed quite clearly that there was no advertised threshold in the risedronate treated arm of the combined HIP/VERT studies. I went ahead with these presentations thinking that the company would surely then be forced to supply the full data so that two full correct publications could be produced, and that the likely problems with the published manuscript A could be addressed.

50. Because these data included (as a subset) the very data that formed part of Professor Eastell's just published manuscript in JBMR, he must have realized that there were urgent questions to address about that manuscript. Even though P&G were forced to alter their presentations for manuscripts B and C, he failed to address those questions, or to ask for the data for analysis and checking.

51. When I returned from these meetings, there was an interchange with P&G in which I tried to be cooperative, thinking that the data would surely be supplied eventually. However, I was then informed by Professor Eastell that to avert the problem P&G were going to try to alter the "aim" of the study somehow in retrospect (alter the study hypothesis) and would try to complicate matters in order to avoid having to show the results altogether. An entirely new draft manuscript was produced by P&G which addressed a different question. A new author would also be introduced by P&G (Pierre Delmas).

52. On **29 February 2004** I wrote to Eastell to say that this was inappropriate. Our quality control data would not allow alterations to the hypothesis in any event. The most urgent need was to get the data, and to "*correct the misconceptions in print as soon as it is possible to do this*" and to publish the truthful results based on the existing intended analyses. I did not believe there was any threshold in patients taking risedronate. [See E-mail in footer][22]

53. Professor Eastell "replied" on **1 March 2004** to the effect that he wanted to progress this different publication, and that "I have no doubt that Pierre and David wish you to continue to take a lead role on writing the papers". [See E-mail in footer][23]. Right then, there was nothing to write without data.

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[22] Date: Sun, 29 Feb 2004 19:21:54 +0000
From: Aubrey Blumsohn <aubreyprivate@btinternet.com>
To: "R Eastell" <r.eastell@sheffield.ac.uk>
CC: Rosemary Hannon <R.A.Hannon@sheffield.ac.uk>, corrin45901@yahoo.com, ablumsohn@sheffield.ac.uk
Subject: Re:normality of NTX/Cr

Dear Richard,

Still significantly non-normal when restricted to age 30-40, but less obviously so (attached).

I don't think any simple conversion factor from Hip to Vert (or visa versa) is possible. Firstly the comparison was not using the same sets of reagents or at the same time. Furthermore, although there was a 21% mean difference in the samples run a) the 95% confidence intervals of the Deming slope is from 0.72 to 1.04, b) it is not clear that this is a simple proportionate bias (see attached). We could apply a correction factor, but I think this would not be legitimate.

I am quite confused about who is writing these papers. The most urgent thing seems to be to write the two papers based on the two abstracts submitted in my name. We already have a draft version of the first paper, and I have heard nothing more about this. Although several aspects of these abstracts are correct, we need to correct the misconceptions in print as soon as it is possible to do this (for the first paper along the lines of the already written draft, for the second to state that PINP was not in fact a significant predictor of fracture in those treated in the Hip study). Who is writing this and why am I not involved in this process?

Correcting the results to generate t-scores does not seem to me to be of primary importance until these problems are addressed.
Aubrey

[23] From: "R Eastell" <r.eastell@sheffield.ac.uk>
To: "'Aubrey Blumsohn'" <aubreyprivate@btinternet.com>
CC: "'Rosemary Hannon'" <R.A.Hannon@sheffield.ac.uk>, corrin45901@yahoo.com, ablumsohn@sheffield.ac.uk
Subject: RE: normality of NTX/Cr
Date: Mon, 1 Mar 2004 09:18:14 -0000

Thanks, Aubrey
I am meeting with David Cahall and Pierre Delmas on Friday in Malta. The data on normality will be really helpful for the discussion over = T-score. It is useful that I understand about the repeat measurement of the VERT samples, as I had thought that they had been measured using the same reagents. I agree that we can't make a correction factor.

I met you after the meeting at Heathrow Airport with Pierre Delmas, David and Ian Barton and fed back to you Pierre's comments on our analysis. I would be happy to meet you and go through this in more detail this week. I am also prepared to ask David Cahall for you to join us in Malta on Friday, but I don't think we will spend much time on these analyses as Ian Barton won't be there. I raised the issue of your participation in these analyses and I have no doubt that Pierre and David wish you to continue to take a lead role on writing the papers. It would seem to me that the best approach is that when we next meet with Ian, David and Pierre that you attend the meeting so that we can firm up our publication plan. As you know, we have this plan in writing, so that is a good place to start.

Richard

54. On **30 March 2004** I again wrote to Ian Barton asking for the data, copying the request to Richard Eastell and blind copying the request to my Union representative who was by that stage keeping an archive of correspondences. My request was entirely ignored. [See E-mail with headers here][24]

55. On **24 May 2004** and **26 May 2004** I wrote formally to Professor Eastell by E-mail and by identical letter. The letter/E-mail were also sent to the Dean of the medical school and to others [that letter is reproduced in full over the following two pages]

[24] Date: Tue, 30 Mar 2004 16:44:28 +0100
From: Aubrey Blumsohn <ablumsohn@sheffield.ac.uk>
To: Ian Barton <barton.ip@pg.com>, Richard Eastell <r.eastell@sheffield.ac.uk>
BCC: Fairbrother <P.M.Fairbrother@sheffield.ac.uk>
Subject: Re:Risedronate D/base: BTM vs BMD vs FX [Summaries For Review]

Thanks Ian

Hope you are well

There are several different issues to discuss. I agree that it is important to get both papers submitted soon,
but we have to be happy that the results are correct.

Two issues to start.

1) I think we have to look in much greater detail at the difference between the EV and ITT populations, and in particular at the non group that falls out of the ITT.
We discussed this before and you did some helpful plots. I think the current plots relate to the ITT population.

As the first step, what is the

a) fracture rate in the in the i) ITT population (already done) ii) the EV population iii) ITT population that doesn't make EV
For both placebo and treated arms

b) Mean and distribution of change and mean and distribution of final value for NTX, Bone AP and BMD in each of the above groups.
They could be categorised by the same histogram thresholds specified for ITT population.

This would be really helpful. I think this would be quicker and easier if I could look at the appropriate data fields myself. There is also the data for PINP for the Hip study alone (second abstract), and again I could make a start at looking at this.

Secondly, I don't understand the analysis relating to either T scores or the absolute NTX value on treatment. We had previously decided it was not possible to combine the data from the two studies as anything other than percentage change. This is because there is a fairly large bias between the absolute values in the two studies, and the fracture rates in the two studies differ different. This would explain why the graphs are apparently a little steeper when looking at the absolute data. Please clarify.

Speak to you soon

Aubrey

Bone Metabolism Group
Clinical Sciences Centre
Northern General Hospital
Herries Road, Sheffield
S5 7AU, UK
Tel: (0114) 271-4705
Fax: (0114) 261-8775
E✉: ablumsohn@sheffield.ac.uk

26th May 2004

Professor Richard Eastell
Research Dean
University of Sheffield
Clinical Sciences Centre
Herries Road
Sheffield S5 7AU

Dear Richard

I have had several E-mails relating to a planned meeting about the HIP/vert data at the ECTS meeting. My previous and often-stated concerns relating to the probity of this data analysis have been largely ignored. Another meeting to pressurise me to acquiesce with this process would not be feasible.

To summarise our previous and extensive conversations:

1) No self-respecting scientist could ever be expected to publish findings based on data to which they do not have free and full access.

2) This is particularly so when
a) there is a preconceived desirable result which is dictating statistical analysis, b) the results are likely to benefit a pharmaceutical company patron,
c) results are likely to have a direct impact on patient care,
d) results are likely to influence our scientific understanding of drug action, and
e) where the experiment is unlikely to be repeated or refuted by subsequent work.

2) It is inappropriate for a head of a University Department to pressurise a colleague (let alone a senior one) to get involved in such activities based on data generated by that colleague, to accept blindly the findings of company statisticians or the use of particular statistical techniques, or to accept other misleading aspects of the treatment of
56. data.

3) Based on my limited view of this data I have every reason to believe that the proposed and previous presentation of the data is misleading in several respects. I have already discussed these concerns with you on several occasions over many months and do not plan to reiterate them.

4) I also have reason to believe that several aspects of the existing three abstract presentations relating to this data and published in my name are incorrect and misleading. This contamination of the scientific record has to be corrected as soon as possible.

5) I do not believe that attempts to alter the unit of analysis (t-score approach), to ignore analyses already done, to repeat/add assays (to allow different statistical analysis) or to add authors will solve the fundamental problem we have.

6) I have severe ethical concerns about the way in which this process has worked, irrespective of the way in which this might have altered the perception of the data. I cannot reconcile this with my personal values or statutory responsibilities as a clinician, pathologist or responsible scientist.

This obfuscating process has been going on for a year now, and the misleading analyses have been in the public domain for 7 months. Given the persistent attempts to a) prevent full and proper examination and presentation of these data, and b) to prevent correction of the scientific record, I can only assume that you have not conveyed my views to the company. If you feel that you have not properly represented my concerns in your private meetings with the company about a) the data generated by me in my laboratory or b) the data analysis, please do let me know.

Yours Sincerely

Dr Aubrey Blumsohn MBBCh, BSc(hons), MSc, PhD, MRCPath
Senior Lecturer in Metabolic Bone Disease
Honorary Consultant in Metabolic Bone Disease
University of Sheffield and Sheffield Teaching Hospitals

57.

58. On **2 June 2004** Professor Eastell "replied", completely ignoring every part of my concerns. He stated that *"There were other issues raised in your e-mail, particularly the need to have your own copy of the data. These issues are best discussed face to face."*
[See E-mail in footer][25]

[25] From: "Richard Eastell" <r.eastell@sheffield.ac.uk>
To: "Aubrey Blumsohn (current) (Aubrey)" <ablumsohn@sheffield.ac.uk>
Subject: HIP BTM study
Date: Wed, 2 Jun 2004 12:17:39 +0100

Dear Aubrey

Thanks for your message about the meeting in Nice this coming Sunday. It would seem that there are two main issues that you would raise were you to attend such a meeting.

1.The first is the issue of the display of the results. Should we display the results as percentiles, and if so how can we make these figures comprehensible? The alternatives are to show the data as T-scores or as percentage change. If we take the T-score approach we will need to measure all samples in the same analytical batch as the premenopausal controls.

2. The second is whether to use the entire population that we measured ('intent to treat') or a subset with good compliance (e.g. 'the evaluable group, EV').

We discussed these issues at the Alliance visit and so I think that David will be familiar with your arguments. If you would like me to represent your views then it would help me for you to make an argument for each that I can repeat when I attend the meeting on Sunday. Please e-mail me with this argument in the next couple of days so that I can prepare myself. If I am unclear about any issues, then I can discuss it with you when we meet in Nice on Saturday.

There were other issues raised in your e-mail, particularly the need to have your own copy of the data. These issues are best discussed face to face. I understand from Tony Weetman that he has now spoken to us both about holding regular meetings. This issue could be discussed at such meetings, as well as other issues that are pressing such as our work with Unipath.

Best wishes,
Richard
Richard Eastell, MD, FRCP, FRCPath, FMedSci

59. It is hard to imagine a more inappropriate reply, particularly given Eastell's position as Research Dean at Sheffield University, and as R&D director of Sheffield Teaching Hospitals. I replied angrily on the same day (**2 June 2004**): [See E-mail in footer][26]

60. On **18 October 2004** I received a letter signed by Ian Barton of P&G, Richard Eastell and Pierre Delmas suggesting that they were planning to go ahead and write an entirely different publication without me if I did not cooperate. The issue of the hidden data was not mentioned. The letter asserted that they had "discussed in some depth the issues I had raised". It was a good example of the fallacy of *ignoratio elenchi* (asserting a number of peripheral problems, quite different from "the issues I had raised" and then addressing those instead).

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[26] Date: Thu, 3 Jun 2004 18:39:48 +0100

From: Aubrey Blumsohn <aubreyprivate@btinternet.com>

To: Richard Eastell <r.eastell@sheffield.ac.uk>

CC: Tony Weetman <a.p.weetman@sheffield.ac.uk>

BCC: "Pat M. Fairbrother" <P.M.Fairbrother@sheffield.ac.uk>, Annie Cooper <annie.cooper@sth.nhs.uk>, Brian Morris <brian.morris@sth.nhs.uk>, Godfrey Gillett <Godfrey.Gillett@sth.nhs.uk>, Hilary Powers <h.j.powers@sheffield.ac.uk>, Margo Barker <M.E.Barker@sheffield.ac.uk>, Sheila Macneil <S.Macneil@sheffield.ac.uk>, Simon Heller <S.Heller@sheffield.ac.uk>

Subject: Re:HIP BTM study

Dear Richard,

I have attached for the record the two emails about which you are replying. I think that they are perfectly clear, as were prior communications about these issues. Your reply is certainly friendly, but bears no evident relation to them.

Supposed non-comprehension has proved useful as a temporary strategy [redacted] but such management tricks may have a limited shelf-life. I am simply not prepared to accept [redacted] and inappropriate scientific activity any longer.

I am going to propose to Tony that detailed external psychiatric/psychological assessment of our Unit would be in order. I do not think that "regular meetings" to resolve difficulties would be at all appropriate or feasible prior to [redacted]. Roger Arkell (University of Nottingham) comes highly recommended, and I have approached him to enquire about charges.

I will not otherwise reply to your email, and will instead refer you to previous correspondence about this.

Aubrey

RE> Dear Aubrey

RE> Thanks for your message about the meeting in Nice this coming Sunday. It would seem that there
RE> are two main issues that you would raise were you to attend such a meeting.

61. I replied accordingly on 8 November 2004.

The University of Sheffield

Bone metabolism Group

Bone metabolism Group
Clinical Sciences Centre
Northern General Hospital
Herries Road, Sheffield
S5 7AU, UK
Tel: (0114) 271-4705
Fax: (0114) 261-8775
E✉ :
ablumsohn@sheffield.ac.uk

8 November 2004

Professor Richard Eastell
Professor of Bone Metabolism
Research Dean and R&D Director for STHT
University of Sheffield
Clinical Sciences Centre (North)
Herries Road
Sheffield, S5 7AU

Dear Richard

Thank you for the letter from yourself, Ian Barton and Pierre Delmas (letter dated 29/6/04; received originally as an unsigned photocopy in August 2004 and more recently in hard copy). Pierre Delmas seems to be the primary author of the letter. The reason for his involvement in this process is not clear to me. I am therefore replying only to you.

You will be fully aware that the letter has only peripheral relevance to the fundamental issues I have raised about the probity of this work and our relationship with this pharmaceutical company. My requests have been clear, and there is no reason to think that another "meeting" will help to resolve the difficulty.

Although not directly pertinent, I should point out that the questions addressed in the letter have already been discussed, and I disagree with the approach. I believe that these issues are highly relevant but have no means of verifying whether this is the case.

Retrospective changes to the question being asked, addition of authors and elimination of primary investigators will not help to resolve the problem. From a scientific point of view, I would clearly be expected to wish to maintain authorship of this work (particularly since I spent more than a year its execution). I am more concerned about my general scientific and clinical obligations, the integrity of the scientific literature and my own integrity. This is particularly so since this work has considerable implications for patient management, and is unlikely to be repeated.

[redacted]

Yours Sincerely

Dr Aubrey Blumsohn
Senior Lecturer and Honorary Consultant in Metabolic Bone Disease

62. Regardless of all concerns raised, over the next several months, the concept of a threshold for % change in NTX on risedronate was widely promoted in educational material and several other publications produced by or for Procter and Gamble. These productions were produced in anticipation of and in response to Merck's FACT trial which suggested that alendronate was a more potent drug than risedronate. At least two of these publications were authored by or fronted by Professor Richard Eastell. The findings had already been reported in a multitude of press releases and other educational material by P&G.

    62.1. Educational material ostensibly by Richard Eastell suggested that suppressing bone turnover by more than 40% or so provided no additional benefit. This statement is not true.

    62.2. The same concept was repeated in the brochure and in educational material produced by the manufacturer of the diagnostic technology NTX in which it was stated "A decrease of 40% in uNTX is associated with maximal response in fracture risk reduction for patients taking risedronate". The brochure referenced the Eastell JBMR publication of 2003. This statement is false and is not supported by the data now provided to Eastell and to myself. The company manufacturing this diagnostic technology was later purchased by P&G for approximately $500 million.

    62.3. In direct response to the Merck FACT trial, Professors Eastell and Delmas responded in a scientific letter published in the JBMR on February 28 2005 to say that "there may be no further fracture benefit from further suppression of NTx/Cr < 40%". This statement is incorrect, and refers again to the Eastell 2003 JBMR publication.

63. The intention of P&G was made very clear in separate publications by Ian Barton in which he suggested that there was a threshold in the treated arm for bone turnover.

64. Although about a bone density threshold, the commercial strategy of P&G was laid out lucidly in another P&G coauthored and supported paper (Watts et al., J. Clin. Densitometry, 7: 255-61, 2004; Medical Writer Mary Royer). This claimed that in patients given Risedronate there is a plateau in the relationship between BMD change and fracture risk on therapy.

64.1. The title byline and "Key Message" in this manuscript was:
"Greater increases in bone mineral density do not relate to greater decreases in fracture risk".

64.2. The conclusion of the paper neatly summarizes the company strategy
"Clinical trials designed to make "head-to-head" comparisons of the effects of osteoporosis treatments on BMD are currently underway.....The results of our analyses, as well as observations from the published literature, indicate that the magnitude of change in BMD associated with antiresorptive treatment does not predict the size of the effect of treatment on fracture risk (i.e., an increase in BMD reflects lower fracture incidence, but larger increases in BMD do not necessarily result in greater reductions in fracture incidence). These findings indicate that the relative effects of osteoporosis treatments on fracture rates cannot he predicted on the basis of comparisons of their effects on BMD."

64.3."Although physicians treating patients with osteoporosis have been advised to "choose agents that provide the greatest increases in BMD relative to placebo to reduce their patient's risk of fractures" we believe that this advice is incorrect. First, there Is Increasing evidence based on individual patient data, within a drug's clinical program, that not only do greater increases in BMD not provide greater decreases in fracture risk but also that the observed BMD changes account for a relatively small proportion of the antifracture treatment effect. Second, meta-regression analyses based on study-level summary statistics do not model the underlying association between an outcome and a potential surrogate or the variability at the patient level. Clinicians treating patients with osteoporosis should prescribe drugs on the basis of their antifracture efficacy, not on the basis of the magnitude of changes in BMD."

64.4. They cited previous work in the names of Sheffield academics : *"Eastell recently reported that changes in bone resorption markers accounted for a large proportion of the effect of Risedronate in reducing the risk of vertebral fractures in patients treated for 3 yr (18).*

65. On **13 December 2004** I received a reply to my letter to Richard Eastell of 8 November 2004. Of all the communication received as part of this saga, this was the most damning. It suggested that if I wished to maintain a status as author on my own first-author manuscripts I had to be prepared to accept that I would not be able to have any access to the underlying data, and that I would have to sign journal declarations asserting that I was in full agreement with the work. This would have been a false declaration. The declaration about access to data would also have been false. It was stated that should be no access to the data (to authors) because this was in accordance with PhRMA guidelines. PhRMA is the American Pharmaceutical Company lobby organization, and even their "guidelines" do not state this. Even if such lobby group guidelines had any relevance, they would contradict every guideline known to science, as well as the rules of every respectable journal in any branch of science [See letter below]

THE UNIVERSITY OF SHEFFIELD

Division of Clinical Sciences (North)
Academic Unit of Bone Metabolism

R Eastell. Professor of Bone Metabolism
Research Dean, School of Medicine & Biomedical Sciences

Northern General Ho
Herries
Sheffield S5
Tel: (0114) 271
Fax: (0114) 261
Email: r.eastell@sheffield
Web: www.shef.ac.ul

RE/GKH

13th December 20(

Dr Aubrey Blumsohn
Senior Lecturer in Metabolic Bone Disease
Clinical Sciences Centre
Northern General Hospital
Sheffield S5 7AU

Dear Aubrey

Re: letter of 8th November 2004

Thank you for your letter about the manuscript I have been preparing with Professor Pierre Delmas and Dr Ian Barton. I note from your letter that you would like to be a co-author of this work. I also note that you disagree with the approach we have taken to data analysis. You will realise that when we submit the manuscript to a journal that you will need to sign an authorship agreement form stating that you are in full agreement with the work. If you wish to be a coauthor then you need to work towards a resolution of the issues we described in our letter. We have listened carefully to your concerns, and we feel that we have addressed all of these. We have now prepared several drafts of the manuscript and would like to submit this shortly. Please reassure us that you are prepared to work with us constructively on this manuscript in a timely way. We would like you to respond to this letter within the next month and if you still wish to be a coauthor then we will send you the manuscript for your comments. We would appreciate you giving us your comments in a clear and constructive fashion within a month of us sending you the manuscript.

You mention the issue of probity and from your previous e-mails I understand that your major concern is that you have not had access to the original data. I have checked with Aventis and with other pharmaceutical companies in the field of osteoporosis for their guidelines to publication. They state that they take the approach described in the PhRMA guidelines and that in these guidelines there is not access to the data (other than those from your centre) for investigators. I think that the approach we have taken for this manuscript of working closely with the statisticians to identify the best approach to analyse the data is an example of best practice, particularly the visit that Ian Barton paid you to go through the data analysis in detail and actually conduct the data analysis during the visit.

Please let us know whether you still wish to be co-author on this manuscript,

Yours sincerely

R Eastell

Richard Eastell
Professor of Bone Metabolism

66. On **25 May 2005** my legal representative at McKay LAW also wrote to Professor Eastell demanding that he provide the raw data underlying the two abstract presentations and draft publications written in my name, and also the raw data underlying Eastell's JBMR paper of 2003 based on a subset of the data.

Professor Richard Eastell
Clinical Sciences Centre (North)
Northern General Hospital
Herries Road,
SHEFFIELD
S5 7AU

Our ref: SM/DO
Your ref:
Date: 25th May 2005

Dear Professor Eastell,

We are instructed by Dr Aubrey Blumsohn.

You will be aware that our client has serious concerns and questions relating to studies carried out in Sheffield regarding pharmaceutical clinical trials involving the drug Risedronate. He has instructed us to request that you to send all raw data relating to three scientific abstracts published in his name relating to this drug. Two of these abstracts are:

1. Relative Contributions Of The Early Changes In Bone Resorption And Later Changes In Hip Bone Mineral Density To The Reduction In Vertebral Fracture Risk With Risedronate. A. Blumsohn, IP Barton, A Chines, R Eastell. American Society for Bone and Mineral Research, 2003

2. Relationship Of Early Changes In Bone Turnover To The Reduction In Vertebral Fracture Risk With Risedronate - The HIP Study. A. Blumsohn, IP Barton, A Chines, R Eastell. American Society for Bone and Mineral Research, 2003

The third abstract contains identical information. Further my client requests that you make available to him all raw data relating to the following published scientific paper relating to the drug Risedronate:

> Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. J Bone Miner Res. 2003;18(6):1051-1056

You will be aware that the data underlying the information presented in this paper forms a subset of the data underlying the two abstract presentations published in our client's name. Our client wishes to compare data obtained with other information and data in his possession. He believes that the scientific process leading to these publications was improper. Further, he believes that the presentation of information in all these publications was false.

67. The response from Eastell's legal representative on 9 June 2005 confirmed that "this is not information to which Professor Eastell has access" and that he does not have access to it. The reply stated that Eastell had indeed asked for the data himself (and that it was presumably not supplied). He again supplied a copy of his letter saying that there should not be access to data by authors because this was dictated by PhRMA guidelines.

6-7 Park Place
Leeds
LS1 2RU
www.rlb-law.com
Direct Dial +44 (0)113 261 5515

Tel +44 (0)113 234 1220
Fax +44 (0)113 234 1573
DX 14086 Leeds Park Square
info@rlb-law.com
kate.williams@rlb-law.com

RadcliffesLeBrasseur

Messrs McKay Law
Solicitors
41 St Paul's Street
LEEDS
LS1 2JG

9 June 2005

Our Ref: CJW2/MD/900100.8703

Your Ref: SM DO

L 250363 v1

Dear Sirs

Re: Our Clients - Professor R Eastell

We act for the Medical Protection Society on behalf of its member Professor Eastell. We have been passed a copy of your letter to Professor Eastell dated 25th May, asking for certain raw data underlying certain abstracts, which you identify.

As you say, your client has asked for this information before. But it is not information to which Professor Eastell has access. It belongs to the pharmaceutical companies. As your client knows, Professor Eastell has already requested the data from the Pharmaceutical companies. (Profesor Eastell explained this in a letter to your client dated 13th December 2004, a copy of which is enclosed). Therefore Professor Eastell regrets that he is unable to help.

Yours faithfully,

RadcliffesLeBrasseur

68. On 25 May 2005 my legal representative at McKay LAW also wrote to Dr Larry Games, Vice President Research and Development, Procter and Gamble, Cincinnati and to Barbara Slatt, Manager R&D, P&G Cincinnati to ask for the raw data underlying abstracts submitted and the previous publication.

Dr Larry Games
Vice President Research and Development
The Procter & Gamble Company (P&G)
Miami Valley Laboratories
P.O. Box 538707
Cincinnati, OH 45253-8707

Our ref: SM/DO
Your ref:
Date: 25th May 2005

Dear Dr Games,

We are instructed by Dr Aubrey Blumsohn.

We are writing in relation to matters of serious concern which have been raised about proper procedure and data analysis in trials involving Risedronate carried out in Sheffield (United Kingdom). Our client has serious questions about studies involving himself as academic investigator, and we are advising him in this matter.

The studies in question were carried out as part of an agreement with the University of Sheffield dated July 2002 and signed by yourself on behalf of Procter & Gamble Pharmaceuticals.

Our client has raised matters of procedure and scientific honesty which he understands were conveyed to Procter & Gamble Pharmaceuticals by Professor Richard Eastell of Sheffield University. Our client has also discussed the most important aspect of the problem mentioned below with Dr David Cahall, but resolution was refused.

Information has been published in our client's name while denying him access to the raw data upon which such publication was based. Our client will allege that this flouts fundamental principles of science, and of clinical pharmaceutical collaboration in particular. Further our client believes that several aspects of data analysis and or presentation were false.

We write to ask that all of the raw data pertaining to this study is disclosed to our client immediately.

Yours sincerely,

McKAY LAW

69. Procter and Gamble lawyers replied several months later on **9 September 2005** after some contact from journalists. No data was supplied in response to the request. The reply asserted that because I had once been in the same room as the data, and had had some sort of statistical demonstration, somehow constituted access to data. The fact that that this minimal contact with the data and the several plots that I had, had in fact revealed that the public representations of the data and draft publications were wrong seemed irrelevant. It stated bizarrely that Ian Barton had said that I had been supplied with the data on a compact disk. Given all previous discussion it is hard to imagine any circumstances under which this would be true. Even if this were the case, it would have been perfectly simple to supply it again. But P&G clearly did not want me to have the data.[27] No data at all was provided in response to our legal letter in order to allow scientific correction.

P&G

Matthew M. Malloy
Associate General Counsel
Tel: (513) 622-5419
Fax: (513) 622-5327
e-mail: malloy.mm@pg.com

P&G Pharmaceuticals, Inc.
Health Care Research Center
8700 Mason-Montgomery Ro
P.O. Box 8006
Mason, OH 45040-9462
www.pg.com

August 18, 2005

Simon McKay
McKay Law
41 St. Paul's Street
Leeds LS1 2JG

Re: Dr. Aubrey Blumsohn

Dear Mr. McKay:

I am responding to your May 25, 2005 letter to Dr. Larry Games, Vice President of Research and Development at Procter & Gamble Pharmaceuticals ("P&GP"), concerning your client Dr. Aubrey Blumsohn. Your letter requested that P&GP disclose to your client the raw data pertaining to studies performed pursuant to the July 2002 Research Agreement between P&GP and the University of Sheffield (the "Research Agreement").

It is not the standard practice of P&GP to allow unlimited access to raw data from clinical trials to individual investigators, as these data are proprietary and are generated only after the investment of substantial R&D effort and funding by P&GP. In addition, we are unable to determine from your letter the specific nature of Dr. Blumsohn's concern. Since Dr. Blumsohn presented some of the analyses of this clinical data at the annual meeting of the American College of Rheumatology (ACR) in November 2003, we also do not understand the allegation that the analyses were presented in a false manner.

P&GP provided Dr. Blumsohn with the raw clinical trial data relevant to the posters and presentations published or made under his name, and relevant to the studies contemplated by the Research Agreement. These were provided to him on a compact disc by Ian Barton, an employee of P&GP, in July and October of 2003. As is customary with proprietary clinical trial data, after Dr. Blumsohn analyzed the data on his laptop computer, they were returned to P&GP.

I hope this responds to the concerns expressed in your letter. Please feel free to call me directly if you would like to discuss further.

Sincerely,

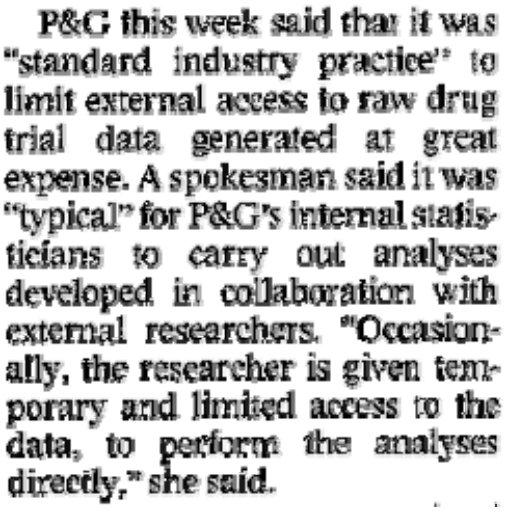
Matthew M. Malloy

[27] I note in GMC briefings that Barton apparently states that "he had data available at several meetings with Prof Eastell and other members, notable Pierre Delmas". "He says that they were free to ask for the data whenever they required it". It is hard to imagine any circumstances under which this could be a truthful statement, given the facts and timescale of events, the failure of Richard Eastell to withdraw the JBMR manuscript given the obvious errors, or the many refusals to supply data. Again it is asserted that mere contact with some manifestation of data (such as a computer demonstration of purported findings) somehow constitutes access to data. What this means effectively is that readers of a scientific publication would effectively have the same reported information as would authors.

70. I note from GMC briefings "As a time line of the course of events, Prof Eastell will give evidence that when concerns were expressed in 2005 about the paper, he requested full access to the data and permission to get an independent statistical analysis. The data were not made available [by P&G] until May 2006 and this accounts for the length of time before the retraction was published."

    It will be obvious from this narrative that concerns were not raised in 2005. They were raised in 2003, 2004 and 2005. Indeed they were raised long before the manuscript appeared in press.

71. Press responses from Procter and Gamble were all on similar theme. It was said that I had been provided access to information deemed "relevant" by P&G.



P&G this week said that it was "standard industry practice" to limit external access to raw drug trial data generated at great expense. A spokesman said it was "typical" for P&G's internal statisticians to carry out analyses developed in collaboration with external researchers. "Occasionally, the researcher is given temporary and limited access to the data, to perform the analyses directly," she said.

72. The eventually published "retraction" of manuscript A stated:

We discussed the need for the independent analysis with Procter & Gamble (P&G), the sponsoring company. We asked for the raw data and proposed that the two authors of the original report used by the company would not be involved in the preparation of this letter. The data were provided to us by P&G in May 2006, together with a report

…

In the original paper,[1] one of the authors, a statistician working for P&G (IB), had full access to all data. P&G (like most pharmaceutical companies we contacted over this issue) used the PhRMA guidelines in relation to publication of clinical trial data, and these restrict the release of original data to investigators (http://www.phrma.org/). He worked closely with all of the authors of the original report on the data analysis by preparing a publication brief and responded to all requests for further analyses. Thus, the authors had full access to the analyses they had requested based on data held by one of the authors but not all had direct access to the raw data.

At the time of writing (2002/03), not all the original authors were given access to the raw data. In 2006, the Ameri-

73. In his initial response to the GMC on 14 December 2005 Eastell confirmed (truthfully) that he did not have access to data. His lawyers wrote:

> Dr Blumsohn does not say in what way the procedure was inappropriate, but appears to refer to the lack of access afforded by Procter and Gamble to the "raw data" of the original samples. (Raw data" is a reference to the database of clinical information about the participants in the original trial).
>
> However, this is normal practice and we refer to the 'PhRMA Guidelines' "Principles on the Conduct of Clinical Trials", which are widely accepted in the research and pharmaceutical world. We refer to paragraph d on page 21 (enclosed), which states

He also sent to the GMC two of his own letters confirming that he did not have access to data. These included the letter in which he had attempted to persuade me to falsely sign journal declarations that I was in agreement with the work, while being denied data.

74. In more recent correspondence with the GMC Eastell asserts that :

74.1. He somehow had telepathic access to data by being in a room when it was also present on a computer.

74.2. He also asserts that he did not in fact lie on journal declarations, but rather that P&G lied on his behalf. With respect, this rather underlies the entire problem.

74.3. He asserts that Procter and gamble would have supplied the data if he had asked for it. The problem is that he and I both did ask – many times – and were not provided with the data requested.

74.4. He seems to imply that asserts that his name on the head of a manuscript is meaningless (as presumably are his examinations of the page proofs of a manuscript written on his name). It is impossible to find a piece of paper asserting that he signed to the effect that he actually had the data. I would have thought that this was rather an implicit part of authorship.

It is little wonder that one GMC assessor wrote in apparent exasperation

> of the authors but not all had direct access to the data". There now seems to be an effort by the defence to say that that statement was not a true reflection of what occurred. It is thus difficult to know what to trust and what is false.

74.5. Some involvement from the complainant, from real scientists, real journal editors, ICMJE, COPE, WEAME and ethicists would no doubt have served to prevent such an attempt to confuse that which is true and that which is false. Indeed it would have helped if the GMC had read the complaint. This would also have helped to preserve the reputation of the GMC in this farce. This applies both to this publication issue, and to an unrelated complaint (not made by me to the GMC) of inappropriate actions in relation to the use of NHS funds for research.