Response to BMJ – May 22nd

BMJ's concerns about coding go to the heart of what this paper is about - for me – authorship. What is laid out below will be of interest to any of you interested in the authorship issues but it also holds completely true if you have no interest in authorship and are just trying to get the best possible version of a research study in the public domain.

Throughout BMJ refer to this as a research paper, which it is. The surprising thing however is given Peter's involvement in all this and his conception of RIAT as an exercise in authorship that BMJ are not availing of the options that a focus on authorship would offer them.

The text below covers Coding, the Coding Process, Legal Conflicts and a Legal Review that seem to have come into the frame.

Coding

BMJ ask that we specify what was done to make the coding reliable, unbiased and reproducible by providing references and other information. There is not a single other article about a clinical trial in the published literature that specifies these steps. They are not specified in the Consort-Harms document.

This state of affairs arises for two reasons. First medicine and journals have been unaware of the issue. Second coding is inherently open to revision – it is never going to and should never produce 100% replication. It is part of clinical history taking – if you get a scrap more information about this patient you should be prepared to review the code.

BMJ profess to be unsettled by the example of our ambiguous coding incident. As Jon outlines we provided them with the most ambiguous we could find. This is as it should be, and their discomfort is exactly the hoped for response but their response to their discomfort is where they are falling down and where if we go along with what they propose we risk selling everyone out.

BMJ have a primary concern - shielding the journal from a legal action (see below).

Along with this concern, their repeated insistence on adhering to items of the protocol (while at the same time blithely introducing imputation which has no place in the protocol) demonstrate the real trap we face, journals face and the field faces in the absence of access to the data.

By conceding on imputation we have perhaps made a mistake. It's one of those Janus things – two faces – good to be seen to co-operate, bad to have given them the impression that if they push we will buckle.

GSK along with Ian Chalmers and the Cochrane Group in general believe that a rigid adherence to analysis per protocol is the answer to all of life's problems – that this will produce definitive outcomes. This is exactly what Andrew Witty's and industry's proposals for Data Access hope for – this is where Data Access on the wrong terms would leave us all in a worse bind than now.

This is a trap which will allow companies to design protocols in such a manner that the evidence from the trial can never come to light as BMJ are demonstrating here. If BMJ/GSK can insist on this position given that the Keller paper is, as it were, beyond libelling, think of what they can do in the case of other trials where it will be insisted upon that researchers have to assume a company's *bona fides* regardless of who the trial was conceived by, paid for by and executed by.

The only way to resolve these issues is through data access. We have attempted to make clear that making the data fully available allows others to interpret it and to claim that we are biased. We the North Wales cell are happy to admit bias – we know the rest of you don't have a shred of bias between you.

BMJ seem to think that in the case of a trial there can be some mechanical procedure for which 'blinding' is a code that will mean that bias is eliminated. In due course when clinical trials happen among androids this may be the case but it will never be the case when human trials are conducted on humans and by humans and for humans.

The solution while we are human is not conflict of interest declarations or not having the work undertaken by people who are expert witnesses but is to make the data available with those doing so fully aware that the process will leave their judgement calls open to scrutiny in a manner that may reveal their bias. This is done because a commitment to the data and its possible meanings is primary even though this means that bias is revealed and may be dissected in the process.

This is as we have said the way to move forward. It will result in an article that is open to revision.

In contrast BMJ operate in a profoundly different world. They want scientific articles to be definitive because of adherence to some mechanical tick-box process that apparently will ensure objectivity. This is not definitive because the scientific process is being followed but rather artificially definitive and in part efforts in this regard may stem from attempts to overcome the perversion of science that is caused by the lack of access to data.

The United States Supreme Court in a 2011 judgement against Matrixx Pharmaceuticals has made a very firm ruling that supports us.

The Matrixx shareholders took an action against the company for withholding adverse event data on their nasal spray Zircam. Zircam causes anosmia. When this became clear the share price of the company dropped. The shareholders argued that they should have been provided with the adverse event data. The company argued that none of the adverse event data regarding anosmia was statistically significant and that on the basis that nothing had been proven there was no need to inform the shareholders. The shareholders' argued that it was not for the company to decide what the adverse event data meant; they had a right to access the data and make their own mind up as to whether their money was well invested or not.

The Supreme Court sided with the shareholders.

Coding and the overall interpretation of adverse event data cannot be something that is left to a company and cannot be sorted out definitively in the manner a journal like BMJ might

want. Different investors (including patients and doctors) faced with the adverse event profile of a drug might choose different options to those GSK or BMJ choose.

Where the data has been thoroughly exposed as in our 329 case, there is a better chance that it can be moved to a point where a majority of investors will take the same view as to what it means but there will never be unanimity on these things and it may well turn out to be that the minority view is correct. Science is all about someone's hunch leading them to overturn a consensus.

The Coding Process

As mentioned Loder asks us to provide references or other information that will convince BMJ that our process of coding is reliable, unbiased and reproducible.

Coding is an issue not covered in any other paper anywhere. This should bring home to Loder and others the novelty and utility of what we are doing. Our paper will provide the basis for future researchers to specify what the processes Loder is now asking us to reference should be.

Our paper should make it impossible for BMJ to feel comfortable publishing any clinical trial ever again without access to the trials data. This uncomfortable prospect may be shaping BMJ's response.

BMJ are concerned that the coding process could not have been blind because if anyone looks at Appendix D the name of the drug sits beside the list of verbatim terms and if anyone wished to be unblinded while coding from these printed pages it would be easy to be so.

This is absolutely true.

But in fact, we engaged with this study months before we had access to the electronic database. As a result, we had little option but to extract all of the information in Appendix D into Excel sheets of our own creation. These are the sheets that we are offering to lodge in BMJ's data repositories and on the Restoring Study 329 website and anywhere else that will have them. They probably can be reconstructed to show the sequence in which things were entered.

The first thing moved over into these sheets were the verbatim terms and the ADECs coding terms. These were moved over without any of the extra columns about date of onset, date of offset or name of drug. The additional columns were added later.

This work was undertaken by Carys Hogan who took no part in the actual coding although she herself is MedDRA trained. There was a huge amount of work involved in undertaking this and maintaining blinds. It broke Carys, who left soon afterwards, costing us a research post in the process.

All coding was done before the drug names were added in. It was blind. Even though I personally think blinding is irrelevant here, and even counter-productive, it was clear that the process should be blind.

One of the problems we have run into is that soon after this happened, Peter Doshi raised the question of blinded coding. Rather than tell him straight up that it was all blind, I put it to him that blinding is irrelevant and might be counter-productive. He didn't accept this. I later told him that the coding had in fact been done blind but who knows whether he believes this.

In the coding process one of the striking features looking at the data without access to the drug names was for instance that there were a large number of sore throats which GSK had in almost all instances coded as pharyngitis. BMJ asked for a specification of process that would allow others to reproduce what was done. Well, this is an instance where GSK almost certainly could not specify a process that would allow others to reproduce what was done.

At the time Study 329 was collecting patients and long before anything was coded there were a number of publications showing that SSRIs can cause sore throats, but that these are dystonic in origin for the most part. GSK have leapt to a diagnosis here rather than stuck with the verbatim term.

When doing the coding we could have leapt to a diagnosis – dystonia. Doing so blind, there is every chance that we would have been confounded by the process, as when we later had the drugs names it became clear that a greater number of dystonias in the SSRI group simply didn't materialise.

We were saved from this outcome by sticking strictly to the process which was to stay as close to the verbatim terms as possible. In this we were assisted by MedDRA that sticks with verbatim terms more than any other coding system.

There are a few other points to note about coding.

BMJ have asked us to revert to ADECS. As a matter of fact, no one appears to be able to access ADECS.

Second the original protocol did not specify ADECs. It makes no specification as regards coding dictionary.

Third MedDRA is now the industry standard – endorsed by FDA and GSK. If we had used a coding dictionary other than MedDRA, BMJ could legitimately ask what we are up to – and is what we are doing shaped by our bias or conflicts of interest.

Fourth BMJ have most recently asked us to report both ADECs and MedDRA codes. We do this in so far as Keller is reported in ADECs and the Keller adverse event data is reported in our paper allowing a comparison between the two systems.

This is another key point about coding that risks making BMJ look ridiculous.

All this talk about reproducible processes conceals the fact that the greater part of what is involved has not been any process whereby some committee came to a view with a third and fourth committee acting as data safety monitoring board but rather a simple transcription over from CRFs to CSRs that GSK didn't do and should have done.

GSK failed to transcribe over from their own CRFs a startlingly large number of adverse events. When they did transcribe into Appendix D, they then coded so the verbatimness was lost.

We have used a coding dictionary that clove to verbatimness. We have also simply transcribed.

We have used the word audit about this because this is the term that may have been what got beneath GSK's radar and let them allow us access to the CRFs. "We're used to audits; FDA does them the whole time and they never amount to anything".

This was not an audit. There is no need for the record to be complete. For BMJ to suggest taking the CRF effects out of the paper means to remove from the paper adverse events that GSK have recorded – not us. This is not an option.

If they understood what was going on BMJ should be horrified and should be publishing and calling on GSK to complete the dataset in a completely transparent fashion.

In the original Appendix D there were instances where GSK had lumped three side effects together under the one verbatim term.

This is terrible practice. These had to be broken out into three side effects. But again there is no mystery about this. No exercise of some mysterious judgement process that might have been corrupted by bias.

Part of the reason we can be so confident in our position is that there was in fact very little room in all this for an exercise of individual judgement.

An extreme case arose in a serious adverse event narrative where literally the coding term at the very top of the page in bold and large font is **DRUG WITHDRAWAL SYNDROME. A**nd yet this was not carried over into Appendix D.

As regards the coding terms used by GSK they are stuffed full of diagnoses such as pneumonia. GSK have repeatedly done what BMJ are questioning us about doing – something we haven't done.

Pretty well the only instance we think there has been something that might be categorised this way is the ambiguous case in the coding box that we have outlined in the course of the paper that has made Loder and her colleagues feel so uncomfortable. There is no way around this discomfort.

While it would be a mistake to jump from sore throat to dystonia or pharyngitis without extra material to warrant this leap, in this instance there is a large amount of material in the record that clamours for coding. We have made it clear that there is a judgement call that not all will agree with. But this was the exception. Close to the only case where judgement was called for.

It should be borne in mind in this context that companies in the course of clinical trials have been happy to have people on their drug pour petrol over themselves and set themselves alight and when they survived the process but died from their burns five days later to code this as death from burns rather than suicide.

BMJ and other journals are publishing articles like this every week. They have become very blasé. We at least are attempting to show that coding events like this need constant and repeated scrutiny.

The book should never be closed on any of these events. But it gets closed when the data is sequestered.

Legal cases

When this paper was submitted first to the BMJ at the start of September 2014, with the BMJ website stating that on average papers take eight weeks from submission to publication, Jon J. completed the conflict of interest statements for all of us. I am not sure what exactly was submitted. At the time I was involved in no legal cases involving GSK.

There was a notional case. In 2011, Wendy Dolin had approached Baum Hedlund about a legal action following the suicide of her husband, ironically a lawyer working for a company that defended pharmaceutical companies in drug induced adverse event cases. I happened to be in Los Angeles and was asked by Michael Baum passing in the corridor whether I would be willing to prepare a general causation case should this case go ahead. In the corridor I indicated that I probably would.

Mr Dolin was on generic paroxetine. The case if there was one would be against Mylan.

I heard nothing more about the Dolin case for three years until March 2014 when an extremely interesting judgement by a judge in Chicago hit the news. He decided that although Mr Dolin was on generic paroxetine that the branded company still had some responsibility for his death. This came as a big shock to GSK.

This verdict was only of passing interest to me. My original assumption in 2011 was that as with 99.9% of cases that this case would have resolved without any involvement from me, but that it would be unlikely to go ahead to resolution as the Supreme Court had made clear that generic companies bore no responsibility for a drug's label and this is critical to Failure to Warn cases.

Now that the lawyers had surmounted this hurdle, I thought it was even more likely the case would settle. There was nothing in it for GSK to let this go forward. Nobody approached me to do anything. This was the situation facing us in September 2014. The possibility of an involvement in a case involving GSK was remote enough for me in good conscience to tell Jon I was involved in cases but nothing involved GSK.

On January 15th 2015 I had an email from Baum Hedlund asking me whether I would be prepared to submit a general causation report in Dolin. At that stage our article had been reviewed, we had responded and we were at a point where the very slow response to our revision (Dec 8th - 6 weeks at that point) was in its own right becoming surprising.

The report I submitted on February 15th lifted a 127 page report that I had prepared in a GSK case (Thompson) in 2009. It changed Thompson for Dolin. It updated the list of cases I had been involved in. It added a brief summary of 329's history at the end of the report indicating that I was involved in this rewrite and would make the article available if published or in pre-publication form when any deposition might go forward. Aside from minor changes the rest of the report was identical.

A deposition in the Dolin case happened on April 3rd – after our paper had been provisionally accepted by the BMJ. In a spirit of full transparency I gave the lawyers for GSK, not their ordinary lawyers but in fact corporate crime lawyers from Phillips Lytle, a copy of the paper we had returned to BMJ.

These lawyers had the opportunity in a deposition lasting 10 hours to question me about Study 329 and the exchanges with the BMJ and possible implications of Study 329 or any other aspect of what we were doing for the Dolin case but they chose not to ask a single question about anything to do with the study. It was ignored.

Legal Review

Jon and Leemon have had an experience with BMJ that has a lot of similarities to our current experience. It would be good if Jon could add a brief section into this document which hopefully will form part of a response to Loder and BMJ after they clarify their intentions re publication – whether or not they opt to publish.

I have had two experiences that relate to Jon's.

In 2005 I submitted an article to BMJ looking at the issue of company use of washout suicides and suicidal acts and coding these under the heading of placebo. This was illegal. The regulators were fully aware companies were doing this. It can only have been done on purpose. There is no scientific justification for what was done. My article outlined the fact that these things were done. It was very temperate. It didn't blame companies or say anything awful about them. It simply showed how different the data looks if you undo this.

There was an extensive peer review process with some of the reviews longer than the original article. One of the reviewers (Simon Wessely) said that if this had happened it was clearly fraud. All points were answered, the paper was accepted. I was sitting with the galley proofs in my hand when an email came from BMJ saying that their legal department had advised against publication.

The article was ultimately published a year later with only one change – any hint that companies might have done anything wrong was removed. The title of the article instead asked Did Regulators Fail in the case of the SSRIs. BMJ were happy for readers to believe the ball was dropped by the regulators rather than the companies. Regulators don't sue.

In 2010, I had the same experience – an article accepted by BMJ on how companies can Spam academic journals with studies or reviews stating adverse events just don't happen. I sitting with the galleys in hand only to be faced with BMJ saying legal had advised them not to go ahead.

BMJ never published this article. It's content appears on Pharmageddon – with no problems in terms of legal actions.

There is a further precedent here. In 2004 Lancet produced it's so called Award Winning editorial about Depressing Research which outlined the fact that NICE had become aware that most publications regarding clinical trials of antidepressants in children remained unpublished and that the publications in the public domain were at odds with the data.

This led Leemon (and perhaps Jon) to write to the Lancet who refused - as I remember it but Leemon and Jon can correct this – to publish the letters while at the same time publishing a letter by Alistair Benbow of GSK claiming that GSK had done nothing untoward, that everything was totally above board - letters written at a time when GSK were resolving New York State's Fraud case against them, effectively admitting fraud, part of the settlement of which was a commitment to publish the Study 329 CSR on the company website.

There is one further point of note. On February 9th I had an email from BMJ asking me to write an editorial on Serotonin and Depression – from Tony Delamothe whom I had last heard from in Nov 2010 when he had told me legal were nixing publication of my article.

I demurred saying I could not be more conflicted – that too many people would choke on their breakfast cereal if an editorial on this topic from me went ahead. You are all welcome to all emails.

BMJ over-rode my objections but did ask one thing – that I complete a conflict of interest statement and sent me the most comprehensive document I have ever seen. You are all welcome to this also.

Having pushed very hard for me to agree to do the editorial, after I sent this COI statement back, they took close to a month to get back to me and agree to go ahead with the editorial. Tony said when asked that it had to be taken through Fiona Godlee first – who as he put it was taking BMJ on a journey.

One he implied that I and others should applaud. At the moment I would have difficulties saying anything decent about "The" BMJ.

Conflicting Interests

BMJ, and EL and Peter are going to say till the cows come home that they are committed to publication. They will be regretful if legal get in the way. Or if we withdraw. They cannot be seen to reject us. They cannot be seen to be impolite. But the mood music is Do it Our Way or It Ain't Going to Get Done.

They can sit this out for months, confident that at some point we will make a mistake or the group will fracture. This is asymmetric. If they make a mistake in what they say, we don't gain any ground in terms of publication. If we make mistakes we hand them reasons to stonewall.

BMJ are committed to the AllTrials campaign and through this are signed up to GSK's model of clinical trial data access.

This is a model industry promote that emphasizes analysing data per protocol. Once you realize this it should be immediately clear that if this rule is kept a company like GSK can offer data access secure in the knowledge that the investigators will necessarily have to come to pretty well the same conclusions from a study as the company.

BMJ are providing a master-class in how the model will work in practice and it seems pretty important to me to get this entire correspondence with BMJ into the public domain soonish so that others can see exactly what is going on.

Adhering to this model, the RIAT proposal would reduce to offering to do industry's job for them for free. The unpublished studies will get written up without industry even having to pay for a ghostwriter and the final copy will differ little from what Sally Laden would produce.

Challenged on still unpublished studies, industry can simply say "you just can't get decent academics these days – we have all these studies waiting for them to write up".

Maybe even – universities shouldn't be letting their academics waste their time on history or other research – they should have them writing up these data driven studies immediately. What else is an industry-academia partnership for?

I'm sure you can invent your own far-fetched proposals. The way things are going as evidenced by the recent NEJM editorials, however far-fetched the proposal you invent it is likely to be a reality soon.

Second with apologies to Melissa and maybe Jon, the reviewer that was the most tone deaf to what we are saying is linked to the University of Toronto, the institution with perhaps the most to lose if Study 329 is restored. This reviewer like everyone else is no doubt fully committed to having the best possible Study 329 published.

Third we have the Dear James Dear Fiona letters, and we now have EL beating on about involvement in Legal Cases.

Fourth, I am certain we can publish elsewhere. Back in November 2014 I approached a number of different places re publication saying we should know where we stood pretty soon and might need to seek alternate publication.

I cannot start approaching these outlets again without clarity as to where we stand. If somewhere else decides within a week which would be quite possible given the volume of reviews and responses, we are stuck if BMJ then "seem" to say yes. If we turn them down we look bad.

BMJ have to be courteous and decent and give a firm Yes or No.