

PACE Trial Key Dates and Chronology of Complaint

Professor Malcolm Hooper 14th November 2015

Background

24th October 2002: Professor Peter White's initial application to the West Midland Multi-centre Research Ethics Committee (MREC), which was approved subject to clarifications

22nd April 2004: first meeting of the PACE Trial Steering Committee (TSC)

27th September 2004: joint meeting of the TSC and the Data Monitoring and Ethics Committee (DMEC)

March 2005: study opens to recruitment

1st February 2006: unabridged Final Protocol Version 5.0 completed but not published (there were subsequent versions up to 5.2)

9th February 2006: Substantial Amendment 5.1 -- Professor White applies to MREC requesting permission to increase the SF-36 entry threshold from 60 to 65 and the "categorical positive outcome" from 70 to 75 (which he asserted would have the "advantage" of bringing the sibling FINE and PACE trials "into line")

14th July 2006: Substantial Amendment 5.6 – due to recruitment difficulties, Professor White applies to MREC requesting permission "to advertise the trial to GPs". His proposed letter to GPs said: "If you have a patient with definite or probable CFS/ME, whose main complaint is fatigue (or a synonym), whom you think might be interested and suitable for the study, please consider referring them to XXXXXX CFS/ME clinic at XXXXXX (one of the PACE trial centres)" (<http://www.meactionuk.org.uk/White-letter-to-MREC-re-synonym.pdf>).

8th March 2007: abridged trial protocol published online: BMC Neurology 2007:7:6

18th February 2011: selective results of the PACE Trial published by The Lancet online

5th March 2011: selective result of the PACE Trial published in The Lancet.

Chronology of formal complaint to The Lancet by Professor Malcolm Hooper

(For ease of understanding, it is written in the third person).

Professor Hooper was so concerned at what he read that he requested the article be retracted.

21st March 2011: Margaret Williams spoke at length to Dr Stuart Spencer, listed on The Lancet Editorial Board as an Executive Editor; it was he who was responsible for publishing the PACE Trial article. He confirmed to her that Professor White had insisted the article be fast-tracked. He was informed that a formal complaint was being submitted by Professor Malcolm Hooper.

28th March 2011: Professor Hooper's formal complaint and accompanying letter were sent to Dr Stuart Spencer at The Lancet. Both the letter and the formal complaint asked for the PACE article to be retracted pending further review (<http://www.margaretwilliams.me/2011/complaint-to-Lancet-re-pace.pdf> and <http://www.margaretwilliams.me/2011/lancet-complaint-letter.pdf>).

The two documents provided illustrations that by publishing selective results of the PACE Trial, The Lancet was in apparent breach not only of its own Elsevier publication policy but was also in breach of the WAME publication policy (World Association of Medical Editors), of which The Lancet is a member.

The Elsevier Ethical Guidance policy is unambiguous: *“Authors of reports of original research should present an accurate account of the work performed as well as an objective discussion of its significance. **Underlying data should be presented accurately in the paper. Fraudulent or knowingly inaccurate statements constitute unethical behaviour and are unacceptable.** Review and professional publication articles should also be accurate and objective”*.

The Elsevier Publishing Ethics Resource Kit (PERK) is also unambiguous; **Research Error and Fraud (PERK 5)** stipulates: *“**Fraud is publishing data or conclusions that were not generated by experiments or observations, but by data manipulation or invention. Changing the data measurements to conveniently fit the desired end result is fraud, but excluding inconvenient results is deliberate research error, which, in effect, is the same result – fraud**”*.

WAME is equally clear: *“**Falsification of data ranges from fabrication to deceptive selective reporting of findings and omission of conflicting data, or wilful suppression and/or distortion of data.... Journals have an obligation to readers and patients to ensure that their published research is both accurate and adheres to the highest ethical standard....If a published paper is subsequently found to have errors or major flaws, the Editor should take responsibility for promptly correcting the written record in the journal**”* (<http://www.wame.org/about/recommendations-on-publication-ethics-policie>).

In addition, all Elsevier journals are members of the Committee on Publication Ethics (COPE) which provides resources to support the investigation of and response to possible breaches in research and publication ethics.

29th March 2011: Margaret Williams spoke again to Dr Stuart Spencer; this time Spencer was very angry. Margaret Williams was (verbatim quote) “warned” and was threatened (verbatim quote): “*You’d better be damned sure that you’re right or The Lancet’s lawyers will be on to you if it (the formal complaint) goes into the public domain*”. Having regained his temper, Spencer then confirmed that it was very likely that the PACE article would go for re-review; he also confirmed that he had passed on the complaint to Richard Horton, The Lancet’s Editor-in-Chief. He then repeated that it would be (verbatim quote) “not wise” to put the complaint in the public domain. He further said (verbatim quote): “*We have to take it (ie. what Professor White said) on trust. We don’t get statisticians to go round and check every calculation that’s been done*”. He also confirmed that Richard Horton had instructed him to notify Professor White about the complaint and that he (Spencer) had sent White an email advising him that a complaint was coming. Spencer then confirmed to Margaret Williams that Professor White had replied to him by email saying he was not surprised and that (quote) “*We’ll deal with it*”.

31st March 2011: Margaret Williams spoke to Dr David McNamee, an Executive Editor at The Lancet, who contradicted what his colleague Dr Stuart Spencer had said: David McNamee was adamant that all studies go for statistical review before publication by The Lancet, saying that this requirement had been set up by him in 1990. He asked if the allegation was one of scientific misconduct, saying that there was a formal procedure for dealing with such an allegation. Margaret Williams informed Dr McNamee that a copy of the formal complaint and accompanying letter had been sent to Erik Engstrom (Chief Executive Officer, Reed Elsevier). For the avoidance of doubt, no acknowledgement or response was ever received from Erik Engstrom, despite a chasing telephone call on 14th April 2011 to Patrick Kerr (Deputy Director, Corporate Communications, Reed Elsevier Group), who dismissively said of Engstrom’s failure to reply that (verbatim quote) “*He’s got a £6 billion company to run*”.

Also on **31st March 2011** Margaret Williams received an email from Dr Stuart Spencer: “*We have asked Professor White to respond to the criticisms made by Professor Hooper. In view of the length of the document we have asked for a response within 2 weeks. I hope we shall then be in a position to decide on our next steps*”.

1st April 2011: Margaret Williams received an email from Dr David McNamee in which he said that The Lancet’s Editorial meeting that morning “*did not go further*”.

than to say we need now to wait until we hear back from the authors of the PACE paper”.

On **13th April 2011** Dr Stuart Spencer sent Margaret Williams an email saying they were still awaiting a written response from Professor White.

On **18th April 2011** Stuart Spencer sent Margaret Williams an email in which he said: *“The (sic) will be a further delay to the response to Professor Hooper. This is because we have now forwarded other letters to the authors and we will want to deal with just one response to all the comments. It would not be right to favour one correspondent over others”.*

Also on **18th April 2011** Richard Horton spoke on Australian ABC radio about the PACE trial; interviewed by Dr Norman Swan, Horton was openly contemptuous about Professor Hooper’s complaint: *“the paper went through peer review very successfully, it’s been through endless rounds of peer review and ethical review so it was a very easy paper for us to publish. It was only at the point of publication and just after that we have had this extraordinary negative reaction....We have been deluged with dozens of letters raising serious objections to the conduct and interpretation of the study. Most recently a 43 page diatribe (Professor Hooper’s formal complaint) calling for the paper to be retracted based upon the fact that it is entirely invalid and unethical....Pretty much every aspect of the study you can think of has been impugned....I think the criticisms about this study are a mirage, they obscure the fact that what the investigators did scrupulously was to look at chronic fatigue syndrome from an utterly impartial perspective....The accusations that are being made about (the investigators) is that they have behaved unethically, breached international standards of ethics.... One sees a fairly small, but highly organised, very vocal and very damaging group of individuals who have I would say actually hijacked this agenda and distorted the debate so that it actually harms the overwhelming majority of patients”*

(<http://www.abc.net.au/rn/healthreport/stories/2011/3192571.htm>).

On **17th May 2011** Zoe Mullan (listed on The Lancet Editorial Board as a Senior Editor) sent an email to Professor Hooper and Margaret Williams in which she said: *“We asked the authors of the PACE trial to respond to your concerns, which they have duly done. Your complaint and their response were discussed at the highest management level and this group of executive editors was fully satisfied that there were no grounds whatsoever on which to take further action. We attach the response provided to us here. From an editorial perspective, the case is now closed. If you believe the editors have acted inappropriately, you could approach our independent ombudsman”.* For clarification, The Lancet’s “independent” ombudsman was Professor Charles Warlow who in 2005 had co-authored the Scottish Neurological Symptoms study (that was dismissive of the neurological

manifestations of ME) with Professor Michael Sharpe, one of the PACE Trial's Principal Investigators, so he was already conflicted.

In his **undated letter** to Richard Horton sent to Margaret Williams on **17th May 2011**, Professor White stated something remarkable: *"The PACE trial paper refers to chronic fatigue syndrome (CFS) which is operationally defined; it does not purport to be studying CFS/ME but CFS defined simply as a principal complaint of fatigue...(Oxford criteria)"*

(http://www.margaretwilliams.me/2011/white-response-to-lancet-complaint_17may2011.pdf).

On **18th May 2011** Professor Hooper provided his initial response to Professor White's letter to Richard Horton

(http://www.margaretwilliams.me/2011/hooper-initial-response-to-lancet_18may2011.pdf).

On **28th May 2011** Professor Hooper provided his detailed response to Professor White's letter to Richard Horton

(http://www.margaretwilliams.me/2011/hooper-detailed-response-to-lancet_28may2011.pdf).

On **1st June 2011** a University of Edinburgh zoology graduate, James Campbell, wrote to Zoe Mullan: *"I am writing concerning the PACE Trial article...and The Lancet's astonishingly inadequate response to the valid concerns which have been raised by many people. I would like to draw your attention to Professor Hooper's response to Professor White's letter to Dr Horton. As you can see, Professor Hooper has drawn attention to the fact that Professor White failed to address many of the valid concerns raised by himself and numerous other researchers. In addition, Professor White's response contains many factual inaccuracies, errors and inconsistencies. For example, Professor White now claims that the PACE trial did 'not purport to be studying CFS/ME', an astonishing claim with serious implications. It is surely incumbent on The Lancet, under its own guidelines, to take this matter further and require the authors of the PACE trial to fully address the very significant problems with their response"*.

On **3rd June 2011** Zoe Mullan replied: *"We were perfectly satisfied with Prof White and colleagues' response to Prof Hooper's complaint. If Prof Hooper has any further concerns we would welcome his contacting us about it"*.

On **5th June 2011** James Campbell replied to Zoe Mullan: *"Speaking frankly, I cannot understand how any science journal could say they 'were perfectly satisfied with Prof*

White and colleagues' response to Prof Hooper's complaint'. Anyone with any background in science can see that there are serious questions to be answered about the PACE paper and that Prof White did not fully address these concerns. This whole business reflects very badly on The Lancet".

On **6th June 2011** Margaret Williams sent the following email to Zoe Mullan:

"Dear Ms Mullan

An email which you sent to Mr James Campbell on 3rd June 2011 has been forwarded to Professor Hooper (and hence to me). Professor Hooper has asked me to contact you on his behalf.

In that email you say you are perfectly satisfied with Professor White and colleagues' response to Professor Hooper's complaint (as indeed you said to us in your email of 17th May 2011), but you also say that if Professor Hooper has any further concerns, you would welcome his contacting you about them.

He does have further concerns, but believed that as you advised him that from an editorial perspective the case was closed, there was no point in sending you a copy of his response.

It is not clear if you have read it, so for convenience a Word copy is attached.

In the light of your email to Mr Campbell, Professor Hooper asks you to accept his response as being a due part of the Elsevier formal complaints procedure.

As requested, he will let you have his further concerns as soon as possible.

I hope you will accept that Professor Hooper bears no personal animosity towards Professors White, Sharpe and Chalder, nor indeed towards Professor Wessely or other members of the Wessely School, but he does have the greatest condemnation of what is internationally accepted to be their cavalier and idiosyncratic attitude towards people with ME/CFS, their dismissal of patients' intense physical suffering as aberrant beliefs and their unshakable assertion that it is a somatoform disorder (SD) amenable to CBT and GET, when chemokine, cytokine and genetic profiling, as well as proteomics, have identified critical features which make it incontrovertible that it is not an SD and cannot be managed as such.

Professor Hooper's overriding concern is for the welfare of – and justice for – very sick people who are suffering not from an aberrant illness belief and deconditioning (the premise upon which the PACE Trial was predicated) but from a chronic, complex, multi-system neuroimmune vascular inflammatory disorder in which incremental aerobic exercise is contra-indicated and has been shown by various ME charities to be at best unhelpful and at worst actively damaging in 50% to 95% of patients.

In the light of this, Professor Hooper has asked me to attach another Word document containing extracts from Witness Statements provided by international experts in the disorder for the Judicial Review of the NICE Clinical Guideline on CFS/ME (CG53), electronically available at <http://www.margaretwilliams.me/2009/statements-of-concern-for-high-court.pdf> from which you will see how firmly these experts reject the notion that CBT and GET are the management options of choice for people with classic ME/CFS as distinct from those who suffer from chronic fatigue. Busy though you undoubtedly are, I would ask you to read it with attention. Perhaps I should explain that for reasons of professional misconduct by the Claimants' own lawyers, these Witness Statements were not put before the Court.

In the meantime, there is a major problem with the Comment by Bleijenberg and Knoop which The Lancet editorial team has so far failed to address, namely their claim of a 30% recovery rate with CBT and GET for PACE participants.

It cannot be argued that this is merely a matter of semantics (Bleijenberg & Knoop state: "The answer depends on one's definition of recovery"): those authors have unequivocally misrepresented the findings of the published paper.

The PIs do not report the number of participants who recovered, only those who fell within their own much criticised definition of "normal range" for fatigue and physical function.

It cannot be acceptable for The Lancet to allow Bleijenberg and Knoop to claim that 30% of participants recovered after CBT or GET when the definition of "recovered" on which they rely has been set artificially low by White et al – so low in fact that a participant described by them as recovered could still be sufficiently disabled to meet the trial's entry criteria.

This surely represents a significant failure of both the peer review process and editorial oversight.

Anyone reading Bleijenberg and Knoop's Comment will be left with a grossly incorrect understanding of the results of the PACE Trial.

*As mentioned in his response to Peter White, Professor Hooper quoted medical statistician Professor Martin Bland: "**Potentially incorrect conclusions, based on faulty analysis, should not be allowed to remain in the literature to be cited uncritically by others**" (BMJ: 19th February 2000:320:515-516).*

In view of this, Professor Hooper once again formally requests that The Lancet either retracts or corrects the Bleijenberg & Knoop Comment and he would appreciate being informed of your editorial decision about this important issue.

If you require further information or clarification, please do not hesitate to contact me and, as mentioned, Professor Hooper will let you have his further comments as soon as possible".

On **8th June 2011** Zoe Mullan replied to Margaret Williams: *“Thank you for your email and the attachments, which I will read. In the meantime, yes I do think we should correct the Bleijenberg and Knoop Comment, since White et al explicitly state that recovery will be reported in a separate report. I will let you know when we have done this”*.

On **9th June 2011** Professor Hooper provided an update on the PACE Trial results (http://www.margaretwilliams.me/2011/pace-trial-results-update_9jun2011.pdf).

On **24th June 2011** Professor Hooper provided his further concerns about the PACE results published in The Lancet which were sent to Zoe Mullan on **25th June 2011** (http://www.margaretwilliams.me/2011/further-concerns-pace-lancet_hooper_24jun2011.pdf).

On **29th June 2011** Zoe Mullan acknowledged its receipt.

On **12th July 2011** Margaret Williams sent an email to Zoe Mullan asking when to expect the promised correction of the Bleijenberg and Knoop Comment.

On **15th July 2011** Zoe Mullan replied to Margaret Williams: *“We are awaiting the outcome of some investigations before making a final decision about publishing a correction to the Bleijenberg and Knoop Comment. I will keep you posted”*.

Despite chaser emails sent on **24th July 2011** and on **11th August 2011**, nothing further was heard from Zoe Mullan.

On **10th December 2012** the Countess of Mar submitted a formal complaint to the Press Complaints Commission about The Lancet’s failure to correct the Bleijenberg and Knoop Comment.

On **26th February 2013** in her correspondence with the PCC, Dr Astrid James, Deputy Editor of The Lancet, wrote: *“I can confirm that our editor of our Correspondence section, Zoe Mullan, did offer her personal opinion at the time, in which she said that she thought we should correct the comment. Zoe made a mistake in not discussing this approach with a more senior member of our editorial team. Now, however, we have discussed this case at length with all members of The Lancet’s senior editorial*

team, and with Zoe, and we do not agree that there is a need to publish a correction”.

It was not until **13th November 2015** that, following a series of articles by David Tuller exposing the fundamental flaws and inadequacies of the PACE Trial (<http://www.virology.ws/2015/10/21/trial-by-error-i/>) that six renowned scientists (Ronald W. Davis PhD, Professor of Biochemistry and Genetics, Stanford University; Jonathan C.W. Edwards MD, Emeritus Professor of Medicine, University College London; Leonard A. Jason PhD, Professor of Psychology, DePaul University; Bruce Levin PhD, Professor of Biostatistics, Columbia University; Vincent R. Racaniello PhD, Professor of Microbiology and Immunology, Columbia University and Arthur L. Reingold MD Professor of Epidemiology, University of California, Berkeley) wrote an open letter to Richard Horton and The Lancet. They called for a truly independent examination and re-analysis of the raw data from the PACE Trial, with the appropriate sensitivity analyses by highly respected reviewers with extensive expertise in statistics and study design. The reviewers should be from outside the UK and outside the domains of psychiatry and psychological medicine; they should also be completely independent of, and have no conflicts of interest with, the PACE investigators and the funders of the trial (<http://www.virology.ws/2015/11/13/an-open-letter-to-dr-richard-horton-and-the-lancet/>).

The refusal by The Lancet to even countenance the call for retraction by Professor Hooper clearly shows the unwillingness of The Lancet’s editors to recognise the many significant flaws that were brought to their attention and raises the question of the integrity of all publications in The Lancet.

The renewed call for retraction of the PACE paper by such eminent signatories leaves the Lancet editors open to charges of ideological bias if they refuse to comply.