Dear Professor Watt,

Robert Saunders asked me to comment on your letter of 9th July to his MP, Jeremy Quin, regarding funding for ME/CFS research and concerns about the PACE trial. As it happens I was about to contact you anyway with regard to the MRC position on PACE. I had originally drafted something to Colin Blakemore (copied in, together with Stephen Holgate), because I know him and he was at MRC around the time of PACE planning, but then thought it better to approach you directly. I was also at the Ribaroff dinner you mention, which was a useful introduction to problems with ME/CFS research, but perhaps not the full picture.

I think that collectively we have to face up to just how big an error setting up PACE was, because it continues to have severe adverse effects on both clinical care and research that will go on until we do.

In your letter to Mr Quin you say of PACE 'I do believe that the trial was designed, conducted and overseen in accordance with expected standards at the time...' I am hoping that you are not fully familiar with the design of the trial and its problems and wonder if you have been poorly briefed. You mention the problems of trials where it is impossible to anonymise either the patient or the clinician involved. The actual problem is 'anonymising', or blinding, treatments – i.e. not labelling them as 'the good new treatment' or 'the usual old nothing much'. Not only did the PACE authors not try to conceal which was which, but they emphasised it in quite unusual ways – including both information sheets and a newsletter during the trial.

This problem has nothing to do with 'expected standards at that time'. It has to do with something we as scientists had drummed into us as students. If your assessment of results, whether in a clinical trial or (in my case) scoring cells in a tissue section, is open to subjective bias, then you have to blind yourself to whether you are scoring 'test' or 'control'. If you cannot blind yourself to that then you have to *make use of objective measurements*. Otherwise your data are valueless.

It might be argued that a basic truth about how human nature colours scientific observation was not known to clinical triallists in 2004, but it was. At the time PACE was being planned I was publishing my proof of concept trial for rituximab in rheumatoid arthritis in NEJM and had been involved in trials for over a decade. That trial included cyclophosphamide, which cannot be blinded. Everyone involved was aware of the problem and the potential solutions – solutions that the PACE team made no attempt to make use of. With a trial the size of PACE you only need slight systematic bias to get statistically significant differences. Multicentre trials are a big problem for bias because peripheral centre staff think they are 'helping' by feeding in 'positive' results. These basic realities were all too familiar to those of us doing trials.

On this basis alone my expectation is that if you asked anyone else heavily involved in trials around that time, such as Ravinder Maini or Bob Souhami, they would agree that PACE was nowhere near expected standards for 2004, or even 1984, in terms of being capable of producing usable positive evidence of efficacy. No drug trial using this format would have been publishable in a quality journal – so why a trial of therapist-delivered treatment, where bias problems were known to be worse? Perhaps psychiatrists were ignorant of trial standards, but surely, ignorance of established rules of practice is no defence. The argument that if you do not know how to get interpretable results you get uninterpretable results and treat them as interpretable clearly does not wash.

And that is just the first layer of the problem. The second layer is that the PACE trial suffers from the problems of subjective bias in worst-case scenario terms. The two treatments that purportedly came out better involved *training the patient to take on a mindset of being better*. The primary outcome measure was a questionnaire and it is hardly surprising that patients in those two groups said they were better. People do what they are told. In the other 'test' arm patients were trained to accept their condition and cope with it by pacing. The comparator arm was not a meaningful control because it was explicitly 'nothing more than usual'.

In other words, the *subjective biasing* that in most experiments we try to minimise by recognising our tendency to cherry pick was, in PACE, the *intended mechanism of the treatment*. This should have been obvious to psychologists!

I think it is significant that the recent 'SMILE' trial of an alternative therapy, which also trains patients to think they are better, produced a similar result to CBT and GET. We do not know whether any of these treatments have a specific effect. (If PACE shows anything, it is that there is no useful effectl: no return to work, no reduction in benefit claims, no increased activity and not even a subjective difference at two and a half years.) There is nothing like a dose response curve. We are left knowing pretty much nothing, as was predictable.

There are all sorts of other issues about the trial that make it very difficult to maintain that 'the authors made every effort to ensure that research was conducted to a high standard'. For instance, an objective measure of activity could have been built into the primary outcome in the way the American College of Rheumatology measure for arthritis trials combined objective and subjective components using multiple thresholds. But we have minutes from a PACE committee meeting where it was decided to abandon such a measure for PACE because previous studies had not shown a positive change in response to treatment. And so on...

I do not see how we can escape the conclusion that the supervision of PACE was not competent. Some people may have to eat humble pie but too much is at stake for that to be a consideration. The lapse seems surprising but may be explained by too much focus being put on statistical and structural issues and not enough on practical psychological realities.

Part of the reason I did not send my message to Colin was that after the Ribaroff meeting I felt that perhaps PACE should be put to one side. Maybe there was sufficient indication that the trust and respect you mention were emerging, at least between scientists, to wait and see how things developed at this year's CFS/ME Research Collaborative meeting in September. But not everything was on the table at that meeting. There are also longer-term problems that need considering.

As Stephen knows, there are still important research groups who do not feel they can fully trust the MRC, based on what has happened in the past and with no sure indication things will change. This is not about psychology versus biology. It is about substandard research going unchallenged. Stephen has worked very hard to take things forward but I suspect has been in an impossible position much of the time when it comes to finally lancing the boil.

In the longer term, PACE continues to have a disastrous effect on clinical care, equally relevant to research. It seems likely that treatments are being provided that do not work and cause distress. PACE is a major prop for the £1B expansion of so-called evidence-based therapies proposed now not just for ME but for any unexplained symptoms. The more I see the more I suspect none of this 'evidence' means much. Even Simon Wessely, who helped set PACE in train, is looking on, like the Sourcerer's Apprentice, as PACE is used to underpin subcontracting care to providers whose staff are not even formally trained in CBT, let alone have useful knowledge of the illness. Commissioning groups are dispensing with physician contact. Whereas in the past physicians like Stephen and I could gain experience with the clinical picture and ponder possible causes we are faced with a future in which nobody even knows what the problem is that requires scientific input.

NICE are forming a new committee to reassess guidelines for ME/CFS. The outcome of that re-assessment will depend on whether or not *evidence quality is put foremost*. Cochrane are now realising that all has not been well with systematic reviewing for ME/CFS but re-commissioning reviews will take time. Despite the obvious failings of PACE opinions are still heavily influenced by the stance of establishment bodies like Lancet and MRC. PACE was not competent science and I do not think it is ethical to continue to defend it as such.

Above all, we need that trust and respect. Both patients and scientists need to feel that there is some form of quality assurance in the science. And the only way I see it coming is if the **MRC makes a public statement acknowledging that by any reasonable view of scientific standards the sponsoring of PACE was a serious misjudgement that should have been foreseen**. I would like to make a formal, but private, request that such a statement be made. Trust and respect from patients is paramount, but trust and respect within the scientific community is also critically important. It could be achieved very simply.

Yours sincerely,

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