THE LANCET

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Press Complaints Commission
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February 12th 2013

Dear Ms Cobbe

Thank you very much for your email of Feb 5. We are disappointed that the PCC has chosen to continue to investigate the Countess of Mar's complaint despite the fact that she has breached the PCC's guidance by publishing excerpts of my response without my consent, and while the complaint remains under investigation. We ask the PCC to reject the complaint on this basis, or, at the very least, to take this breach of its guidance into account in its decision making.

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We stand by our confidence in the accuracy of Drs Bleijenberg & Knoop's Comment, as do the authors themselves, and are happy to provide further information and clarification.

We are very concerned, however, that the situation is being oversimplified. Clinical research is complex in execution and interpretation, and we urge the PCC to consider all aspects of the case. The complaint focuses narrowly on alleged discrepancies between the PACE article in *The Lancet* and Bleijenberg & Knoop's Comment; in fact the trial protocol and a recent publication from PACE need to be taken into account to achieve a full understanding of the case. We note that the complaint is about the Comment, yet confuses the matter by also criticising the *Lancet* paper written by Prof White and co-workers.

PACE was a clinical trial carried out several years ago. As is customary, planning of the trial involved preparation of a very detailed protocol setting out details of the patients to be included in the trial and the treatments that they would receive, as well as the assessments that would be made of the patients' health; this document was published in 2007 in *BMC Neurology*.[1] Clinical trials must follow the protocol on which they are based, which the PACE trial did, with the exception of changes incorporated into the detailed statistical analysis plan that were justified scientifically. Clinical trials submitted to *The Lancet* must be submitted with their protocols, as stated in our Information for Authors. The PACE protocol, which links to *The Lancet* 2011 paper on *The Lancet*'s website via the Methods section (so the protocol is directly accessible via www.thelancet.com and should be considered to be part of the *Lancet* paper), contains the following definition of recovery:

"Under Secondary Outcome Measures: 4. "Recovery" will be defined by meeting all four of the following criteria: (i) a Chalder Fatigue Questionnaire score of 3 or less [27], (ii) SF-36 physical function score of 85 or above [47,48], (iii) a CGI score of 1 [45], and (iv) the participant no longer meets Oxford criteria for CFS [2], CDC

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criteria for CFS [1] or the London criteria for ME [40]." (The reference numbers refer to those cited in the full protocol document.)

Clearly, defining "recovery" is complex, and the PACE research article in *The Lancet* reported the main participant-rated primary outcomes from the trial (the Chalder fatigue questionnaire and the SF-36 physical function score).[2] These two primary outcome measures are valid and reliable and have been used in previous trials. On page 831 in the Results section of the PACE research article in *The Lancet*, the authors report "25 (16%) of 153 participants in the APT [adaptive pacing therapy] group were within normal ranges for both primary outcomes at 52 weeks, compared with 44 (30%) of 148 participants for CBT [cognitive behaviour therapy], 43 (28%) of 154 participants for GET [graded exercise therapy], and 22 (15%) of 152 participants for SMC [specialist medical care]". The PACE article was accompanied by a Comment piece by Bleijenberg & Knoop.[3] The Comment authors state, on page 787, that "PACE used a strict definition for recovery: a score on both fatigue and physical function within the range of the mean plus (or minus) one standard deviation of a healthy person's score. In accordance with this criterion, the recovery rate of cognitive behavioural and graded exercise therapy was about 30%—although not very high, the rate is significantly higher than that with both other interventions".

Bleijenberg & Knoop have told *The Lancet* that "one way of defining recovery is to say that a patient is no longer fatigued and disabled, two key elements of the CDC definition of CFS. One could further operationalise recovery as scoring within normal range on questionnaires assessing both aspects. Using this criterion, the recovery rate of CBT and GET in the PACE trial was about 30%. We think that this indicates that recovery following behavioural interventions of CFS is possible".

It is also worth pointing out that the PACE team have now reported their full data on recovery in a peer-reviewed paper, and it seems that these data appeared in the public domain after the Countess of Mar's complaint.[4] It is important to note that there is nothing suspicious or unusual in this process. Reporting on the findings of clinical trials often results in several papers being published in different journals over a period of several years—not only does detailed statistical analysis of the data take time but also peer review and publication can proceed slowly.

With this background, we believe that definitive answers can now be obtained to the issues raised in the complaint:

Did PACE use a strict criterion for recovery? Yes, it did; as detailed above this definition is included in the published trial protocol, and results based on this criterion have now been published in the *Lancet* paper[2] and in the 2013 PACE article.[4]

Was the criterion [for recovery] a score on both fatigue and physical function within the range of the mean plus (or minus) one standard deviation of a healthy person's score? Yes, as detailed above. The *Lancet* article[2] contains the following definition (under "statistical analysis"): "we compared the proportions of participants who had scores of both primary outcomes within the normal range at 52 weeks. This range was defined as less than the mean plus 1 SD scores of adult attendees to UK general practice of 14·2 (+4·6) for fatigue (score of 18 or less) and

equal to or above the mean minus 1 SD scores of the UK working age population of 84 (−24) for physical function (score of 60 or more),[32,33]"

Was the recovery rate in patients treated with cognitive behavioural therapy or graded exercise therapy about 30%? These are reasonable estimates, as described above.

Does the PACE trial show that recovery from chronic fatigue syndrome is possible? As noted by Bleijenberg & Knoop and others, this depends on the definition of "recovery" used. But based on the results presented in the 2011 *Lancet* paper and the 2013 PACE article, we can conclude that a proportion of patients do recover. We should bear in mind, of course, that the mechanistic basis of chronic fatigue syndrome is poorly understood, and we cannot expect the high rates of recovery achieved with drugs such as antibiotics where pathogenic mechanisms are well characterised.

In sum, we have provided complete answers to the complaint from the Countess of Mar.

We ask the Commission to dismiss the complaint.

As far as the wider context of research on chronic fatigue syndrome is concerned, there has been a recent debate on PACE in the House of Lords which the Commission may find interesting.[5] Other than the Countess of Mar, who tabled the debate, the consensus appears to have been strongly supportive of the PACE trial, which Lord Winston is quoted as having described as "an example of really excellent research".

Please note that this letter is not intended for publication, and we trust that the complaint will be judged invalid if this letter, or any part of it, should appear in the public domain.

Yours sincerely

Astrid James
Deputy Editor
The Lancet

1 White PD, Sharpe MC, Chalder T, DeCesare JC, Walwyn R, and the PACE trial group. Protocol for the PACE trial: a randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy. *BMC Neurology* 2007; **7:** 6.

2 White PD, Goldsmith KA, Johnson AL, et al, on behalf of the PACE trial management group. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* 2011; **377:** 823–36.

3 Bleijenberg G, Knoop H. Chronic fatigue syndrome: where to PACE from here? *Lancet* 2011; **377:** 786–88.

4 White PD, Goldsmith K, Johnson AL, Chalder T, Sharpe M, and PACE Trial Management Group. Recovery from chronic fatigue syndrome after treatments given in the PACE trial. *Psychol Med* 2013; 1–9. DOI:10.1017/S0033291713000020.

5 http://www.publications.parliament.uk/pa/ld201213/ldhansrd/text/130206-gc0001.htm#130206114000195 (accessed Feb 12, 2013).