Dr. Richard Horton

The Lancet
125 London Wall
London, EC2Y 5AS, UK

Dear Dr. Horton:

In February, 2011, *The Lancet* published an article called "Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomized trial." The article reported that two "rehabilitative" approaches, cognitive behavior therapy and graded exercise therapy, were effective in treating chronic fatigue syndrome, also known as myalgic encephalomyelitis, ME/CFS and CFS/ME. The study received international attention and has had widespread influence on research, treatment options and public attitudes.

The PACE study was an unblinded clinical trial with subjective primary outcomes, a design that requires strict vigilance in order to prevent the possibility of bias. Yet the study suffered from major flaws that have raised serious concerns about the validity, reliability and integrity of the findings. The patient and advocacy communities have known this for years, but a recent in-depth report on this site, which included statements from five of us, has brought the extent of the problems to the attention of a broader public. The PACE investigators have replied to many of the criticisms, but their responses have not addressed or answered key concerns.

The major flaws documented at length in the recent report include, but are not limited to, the following:

*The *Lancet* paper included an analysis in which the outcome thresholds for being "within the normal range" on the two primary measures of fatigue and physical function demonstrated worse health than the criteria for entry, which already indicated serious disability. In fact, 13 percent of the study participants were already "within the normal range" on one or both outcome measures at baseline, but the investigators did not disclose this salient fact in the *Lancet* paper. In an accompanying *Lancet* commentary, colleagues of the PACE team defined participants who met these expansive "normal ranges" as having achieved a "strict criterion for recovery." The PACE authors reviewed this commentary before publication.

*During the trial, the authors published a newsletter for participants that included positive testimonials from earlier participants about the benefits of the "therapy" and "treatment." The same newsletter included an article that cited the two rehabilitative interventions pioneered by the researchers and being tested in the PACE trial as having been recommended by a U.K. clinical guidelines committee "based on the best available evidence." The newsletter did not mention that a key PACE investigator also served on the clinical guidelines committee. At the time of the newsletter, two hundred or more participants—about a third of the total sample– were still undergoing assessments.

*Mid-trial, the PACE investigators changed their protocol methods of assessing their primary outcome measures of fatigue and physical function. This is of particular concern in an unblinded trial like PACE, in which outcome trends are often apparent long before outcome data are seen. The investigators provided no sensitivity analyses to assess the impact of the

changes and have refused requests to provide the results per the methods outlined in their protocol.

*The PACE investigators based their claims of treatment success solely on their subjective outcomes. In the *Lancet* paper, the results of a six-minute walking test—described in the protocol as "an objective measure of physical capacity"–did not support such claims, notwithstanding the minimal gains in one arm. In subsequent comments in another journal, the investigators dismissed the walking-test results as irrelevant, non-objective and fraught with limitations. All the other objective measures in PACE, presented in other journals, also failed. The results of one objective measure, the fitness step-test, were provided in a 2015 paper in *The Lancet Psychiatry*, but only in the form of a tiny graph. A request for the step-test data used to create the graph was rejected as "vexatious."

*The investigators violated their promise in the PACE protocol to adhere to the Declaration of Helsinki, which mandates that prospective participants be "adequately informed" about researchers' "possible conflicts of interest." The main investigators have had financial and consulting relationships with disability insurance companies, advising them that rehabilitative therapies like those tested in PACE could help ME/CFS claimants get off benefits and back to work. They disclosed these insurance industry links in *The Lancet* but did not inform trial participants, contrary to their protocol commitment. This serious ethical breach raises concerns about whether the consent obtained from the 641 trial participants is legitimate.

Such flaws have no place in published research. This is of particular concern in the case of the PACE trial because of its significant impact on government policy, public health practice, clinical care, and decisions about disability insurance and other social benefits. Under the circumstances, it is incumbent upon *The Lancet* to address this matter as soon as possible.

We therefore urge *The Lancet* to seek an independent re-analysis of the individual-level PACE trial data, with appropriate sensitivity analyses, from highly respected reviewers with extensive expertise in statistics and study design. The reviewers should be from outside the U.K. and outside the domains of psychiatry and psychological medicine. They should also be completely independent of, and have no conflicts of interests involving, the PACE investigators and the funders of the trial.

Thank you very much for your quick attention to this matter.