From: "Bierman, Arlene (AHRQ)"
To: [redacted]
Cc: "Perry, Wendy (AHRQ)"
Sent: Thursday, December 24, 2015 9:33 AM
Subject: Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Dear Ms. Dimmock,

Thank you for your letter and sharing your concerns about the PACE trial and, by extension, the 2014 AHRQ evidence review on the "Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome" (ME/CFS). I am responding on behalf of Dr. Richard Kronick. We take the concerns expressed by Dr. Tuller in the Columbia University blog regarding the PACE trial seriously.
Determining the quality of the evidence used in this review and all AHRQ evidence reviews is an important step in the evidence review process.

The investigators performing the AHRQ evidence review on ME/CFS adhered to the highest standards in evaluating individual research studies and synthesizing individual studies within the context of a body of evidence. The review followed the Evidence-based Practice Center (EPC) Program's Methods Guide for Effectiveness and Comparative Effectiveness Reviews (http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318). The Methods Guide describes the process for grading the strength of evidence and applicability of evidence. Individual studies have different strengths and weaknesses and are assessed along multiple domains. As with all Evidence Reports, the findings and conclusions in the review are those of the authors who have scientific independence and are responsible for its contents.

We appreciate your letter calling our attention to flaws in the PACE study that have become more evident since its initial publication. Many of these concerns (such as the change in entry criteria) were already highlighted and explicitly considered in the AHRQ report. Despite potential concerns raised related to posting of the newsletter with testimonials and the lack of conflict-of-interest disclosure to participants, the authors do not feel that this additional information would change the overall conclusions of the report since the report is based on all of the literature available at the time.

Below is point-by-point response to the six concerns individually addressed in your letter. I hope you find these comments helpful.

Thank you again for sharing your concerns about the PACE trial and its effect on the AHRQ evidence review. I hope that we can work together to further the evidence-base on how best to treat ME/CFS.

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Below is additional information in response to the concerns raised in your letter:

1. Oxford criteria – one of the tasks of the AHRQ evidence review was to report on the diagnostic criteria for ME/CFS. The Oxford criteria do meet the inclusion criteria set forth at the beginning of the review and as such the PACE trial was appropriately included as were other studies using the Oxford criteria. The review did, however, highlight the distinct differences between the various case

definitions and raised concerns that the populations being studied could be quite variable. The evidence review played an important role in the NIH's recommendation to discard the Oxford criteria. We are glad that we have helped to move the field of study forward.

2. Changes made by the PACE investigators during the course of the trial were highlighted in the AHRQ report. We agree that a sensitivity analysis of the effect of these changes would be beneficial in fully understanding how they may or may not have changed the results. This does not however translate into discarding all of the results but rather is an important consideration when grading the overall strength of the evidence.
3. As per #2 above.
4. In determining treatment effectiveness, the investigators considered all of the studies rather than just the PACE trial. We agree that recovery claims by the PACE trial were not adequate. The AHRQ report gave an insufficient grade to outcomes on recovery
5. The posting of a newsletter with testimonials is highly irregular behavior that ideally would be regulated by an internal review board. We agree that this could have potentially introduced bias.
6. It is unfortunate that PACE trial participants did not receive disclosure of the financial conflicts of interest of some of the study investigators. This information was not part of the review data but would not change the overall conclusions.