To: Dr. Thomas Frieden and Dr. Richard Kronick
CC: Dr. Ermias Belay, Dr. Beth Unger, Dr. Suchitra Iyer, Dr. Nancy Lee, Dr. Susan Levine, Dr. Walter Koroshetz
Subject: PACE Trial for Chronic Fatigue Syndrome
Date: November 2, 2015

On October 21-23, David Tuller, DrPH, published a three-part article on Columbia University Dr. Vincent Racaniello's Virology Blog[1] outlining fundamental flaws in the conduct and results of the U.K. £5 million PACE trial for chronic fatigue syndrome. The multiple flaws in this study call into question the validity of the 2014 AHRQ ME/CFS Evidence Review and CDC's clinical guidelines for ME/CFS, both of which rely upon PACE in recommendations for cognitive behavioral therapy (CBT) and graded exercise therapy (GET). We ask that the validity of the PACE trial be investigated and appropriate steps taken to protect patients.

Echoing the analyses done by advocates and reiterated by other writers since, Mr. Tuller's article identified numerous problems with the design, conduct and analysis of the PACE trial and subsequent publications, including:

1. PACE subjects were selected using the Oxford definition of CFS,[2] which requires only six months of fatigue. The NIH's 2015 Pathways to Prevention Panel on ME/CFS recommended that the Oxford definition be discarded because it is overbroad and includes patients who do not have the disease.
2. Entry criteria, improvement/recovery criteria, and data analysis methods were all changed after the trial began. This is especially problematic as the trial was completely unblinded, and no analysis of the effect of these changes has been published.
3. The change in recovery criteria meant that patients could worsen from their entry baseline and still be counted as recovered. Thirteen percent of the PACE subjects met recovery criteria when they entered the trial.
4. Almost every objective measure set forth in the study protocol was discarded, and these data have never been published.
5. Some trial participants received a newsletter during the trial that included positive testimonials from other patients, and government endorsement of the therapies under investigation. This is, at best, highly irregular in an unblinded trial that is at serious risk of participant bias.
6. PACE trial participants did not receive disclosure of the financial conflicts of interest of some of the study investigators, despite those investigators having previously agreed to disclose the conflicts.

Many prominent US-based ME/CFS researchers have already voiced their strong concern about the PACE study quality, content and methodology. Numerous patient surveys have reported physical harm from these therapies. Dr. Arthur Reingold, University of California, Berkeley told

---

[1] David Tuller. "TRIAL BY ERROR: The Troubling Case of the PACE Chronic Fatigue Syndrome Study." Virology Blog. October 21-23, 2015.
First installment: http://www.virology.ws/2015/10/21/trial-by-error-i/
Second installment: http://www.virology.ws/2015/10/22/trial-by-error-ii/
Third installment: http://www.virology.ws/2015/10/23/trial-by-error-iii/

[2] PACE selected patients by Oxford first, then subgrouped by modified ME and CDC CFS criteria. One PACE publication noted that CDC CFS criteria modifications could result in inaccurate patient characterizations but did not discuss impact of ME criteria modifications.

Mr. Tuller, “Under the circumstances, an independent review of the trial conducted by experts not involved in the design or conduct of the study would seem to be very much in order.” We agree.

The multiple and fundamental flaws of the PACE trial would be problematic in any field. However, the PACE trial is the largest study of this treatment approach and is used in the formulation of numerous clinical guidelines and medical provider education efforts for ME/CFS today. There is great potential for harm to patients arising from the broad use of such a questionable and compromised study, particularly when that study includes patients who do not have ME/CFS.

Therefore, we ask that you examine the issues identified in Mr. Tuller’s analysis, along with the subsequent analyses and accompanying evidence. Given the implications for both the PACE study itself and for the AHRQ Evidence Review and for all U.S. clinical guidelines that currently rely upon PACE and/or the AHRQ Evidence Review, we ask that:

- CDC remove all recommendations and risk and prognosis statements based on PACE and other Oxford studies from its current and planned medical education material;
- AHRQ issue a revision of its Evidence Review in light of the concerns with PACE and with the Oxford definition studies as noted by NIH’s Pathways to Prevention report;
- HHS use its leadership position to communicate these concerns to other U.S. mainstream clinical guidelines providers; and,
- HHS call upon the *Lancet* to ensure an independent review is conducted.

We respectfully ask for feedback on the results of HHS’s analysis and what HHS plans to do as a result. Feedback can be sent to Mary Dimmock (medimmock@gmail.com).

Thank you.

Signed

Massachusetts CFIDS/ME & FM Association

MEAdvocacy.Org

Pandora Org

Phoenix Rising

ProHealth

Solve ME/CFS Initiative

Speak Up About ME

Vermont CFIDS Association, Inc.

Wisconsin ME and CFS Association, Inc.