October 20, 2014

The Solve ME/CFS Initiative and our Research Advisory Council thank the Evidence-Based Practice Center and AHRQ for preparing this report and for the attention to detail in the comprehensive review of the literature. Below we have provided specific areas of comment and correction in the suggested format for the authors to consider as they finalize this document.

Structured Abstract
On page vi of the conclusions in the structured abstract, either list all interventions that showed benefit or state simply that there are several interventions that showed benefit. The conclusions should not list only CBT and GET as beneficial.

Introduction
On page 2, last sentence of 1st paragraph, "*Economic impact is considerable with most adult patients never returning to work.*[9,21]" the original economic impact papers (there are 3) should be cited rather than these review articles.

On page 1, 3rd paragraph of the Introduction, it indicates that few if any risk factors have been identified. However, there are several published epidemiology, birth cohort, twin and primary care studies that have identified risk markers including being female, recent viral infection, genetic vulnerability and family history. All of these provide important and potential diagnostic clues for ME/CFS and while excluded from the review, should at least be noted in the Introduction.

On page 1 of the Introduction it is stated, "*This review is not intended to address the question of etiology nor underlying factors that lead to the onset or perpetuation of ME/CFS but rather to focus on the diagnosis and treatment of this syndrome.*"

- It would be helpful to clarify how diagnosis is possible without understanding the cause or perpetuating factors of ME/CFS. We believe what is intended here is to help the reader understand that the review will focus on evidence using symptoms for diagnosis versus objective markers (since none have been validated) or possible causes (since no causal factors have been confirmed).

The last sentence of the Introduction on page 2, "*This report is not intended to be used or likely to be useful to develop criteria for disability or insurance"* somewhat contradicts what is stated on page ii, *"The final report (not draft) may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies"* and should be clarified/corrected.

Methods

In the Literature Search Strategy on page 4 it is noted that "*scientific information packets were requested from drug and device manufacturer who potentially had data on the use of medications or devices for ME or CFS, who had the opportunity to submit data using the portal for submitting scientific information packets on the Effective Health Care Program Web site. Seventeen submissions were received*". However, it is not clear where these 17 submissions are listed, how they were analyzed, included or excluded and whether they provided evidence-based information.

Results

Incorrect citation for the study at the bottom of page 19, "*Specifically, 21 patients had been given a psychiatric diagnosis when one did not exist, and 13 patients who had never been given a psychiatric diagnosis actually had a treatable psychiatric condition in addition to CFS.[52]"* Please note we do not know what the correct citation is, only that citation 52 is not correct.

On page 22 under Medications, even though rintatolimod is not FDA approved, at one time it was approved (and it still may be approved) for compassionate use. If this is true, this should be added to this section.

Discussion

The authors should add a paragraph describing the strengths and limitations of comparative effectiveness systematic reviews for medically unexplained disorders like ME/CFS where little to no comparative effectiveness has been conducted.

General Comment

Even though the review points out the lack of coherence in the field and the absence of high quality clinical trial data, this systematic review would be greatly improved and the field would benefit from an acknowledgement and citation of the substantial body of etiology and biomarker research that can in fact provide clues to diagnostic criteria and potential identification of ME/CFS subtypes. For example, all of the studies that attempted to objectively assess the autonomic nervous system and sleep disturbances (using polysomnography for example) were excluded from this review and not used to address Key Question 1. The same is true for the many important endocrine, neurology and immune studies that have been conducted in an attempt to identify subtypes as well as understand pathophysiology. While these studies may not meet comparative effectiveness review criteria, they are important steps and do provide important clues that could be used to model ME/CFS and inform further fruitful areas of study – including the identification of diagnostic criteria. This seems to be the "Catch 22" for ME/CFS; little funding resulting in small studies of heterogeneous populations. Even still, biological signals do appear to be

emerging from some of the clinical trials that were directed at possible etiology (e.g., rintatolimod) and biomarkers such as heart rate variability.