Dear NIH P2P Panel members,

I want to express my appreciation for the time and energy you put into reviewing the AHRQ materials, attending the Workshop, and writing this draft. There are parts of it I think are on target; however, there are other important components that the Panel, understandably, missed due to its lack of experience with ME/CFS and the limited evidence that was presented in the AHRQ Systematic Review as well during the presentations given in December. I hope the Panel hones its recommendations to include specific, measurable, achievable, results-focused, and time-bound elements and assign them to a designated individual/ party. What is most needed in ME/CFS research is increased funding commensurate to the prevalence, burden, and economic costs of the illness. ME/CFS was one of the least funded diseases in 2013 (actual figures) - $5 million total was spent, putting it at #227/237 conditions. (NIH funding since 2010: http://report.nih.gov/categorical_spending.aspx) Some prominent researchers have suggested funding 5 Centers of Excellence at $25 million each for a period of 5 years to jumpstart research. Another problem are recommendations without a timeline; there is no sense of urgency to achieve goals. Perhaps the Panel is not aware that NIH and the federally-appointed CFS Advisory Committee (CFSAC) had suggested a research case definition be agreed upon back in 2011 yet here again we are left with yet the same recommendation but no real advancement. Part of the fault lies with NIH, who changed the tasks of this Panel in early 2014. I know we can do better. I hope that you will consider my comments in improving the report. Thanks,

A Patient with ME/CFS

What I liked:

1) Retirement of Oxford criteria: This has long been a concern of mine and I am glad that the Panel has recommended discarding its use in research. Using only one symptom, fatigue, to qualify subjects for a study makes for both poor sensitivity and specificity. In the former situation, those patients who have reduced their activity to low levels might have less fatigue and be erroneously excluded while in the latter situation, subjects with other medical diagnoses that could result in fatigue would be erroneously included.

2) Endorsement of a Biobank/ registry/ clinical trials – Lines 233-236; Lines 245-247: The Panel may not be aware that the US CFS Advisory Committee (CFSAC) has and continues to suggest establishment of such entities, most recently in Spring of 2014. However, those ideas were rejected in June 2014 by Dr. Francis Collins at NIH, with the rationale being that there were a lack of scientists and that funding for such measures would take away money from other ME/CFS research projects. The rationale given is irrational: it's because of the poor funding situation that the field has a difficult time attracting/ retaining scientists and has it ever occurred to Dr. Collins that the amount given to ME/CFS could be increased? We will never solve ME/CFS spending at most $6 per patient per year on research. ($6 million/ 1 million patients)

CFSAC Recommendation: http://www.hhs.gov/advcomcfs/recommendations/06142014.html

Dr. Collin's response: http://www.hhs.gov/advcomcfs/recommendations/hhs-cfsac-recommendations-response.pdf

NIH did give $1.5 million US to Dr. Luis Nacul at the London School of Hygiene and Tropical Medicine to establish a ME/CFS biobank there. While I'm all for international collaboration in the sciences, shouldn't

that investment be made for US patients as well? It is unclear to me whether the London Biobank includes any US patients at all; shouldn't we take care of own citizens before those of other countries?

http://blogs.lshtm.ac.uk/news/2013/06/28/uk-mecfs-biobank-project-awarded-1-million-grant/

3) Emphasis on inclusion of patient perspective in research: I agree with this heartily and will note that Heywood's review of patient-reported outcomes related to ME/CFS noted that practically none of the instruments they examined had included ME/CFS patient input during their design or implementation. While there is lack of literature on what symptoms or aspects of disease matter to ME/CFS patients, I would disagree that there is none (Line 166). The AHRQ review and the presentations did not include published abstracts and qualitative studies which address this topic. An example is given below. Futhermore, the Panel asked for a FDA Workshop on ME/CFS (Line 365); in fact, the FDA already held such a Workshop in April of 2013 and published an excellent report detailing which symptoms patients felt were important and which treatments they had tried/ were trying. One major reason pharmaceutical companies were reluctant to invest in ME/CFS was the lack of a good research case definition and lack of knowledge about the basic pathophysiology of the illness.

Heywood: http://www.ncbi.nlm.nih.gov/pubmed/21590511

"Expressed Needs" of patients: http://www.biomedcentral.com/1471-2458/9/458

FDA Voice of the Patient Report:
http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM368806.pdf

What could be improved:

1) Exclude trials that used Oxford criteria primarily when examining treatment effects: It does not make sense for the Panel to recommend that the Oxford criteria be retired because it is so non-specific yet make conclusions about ME/CFS treatment using meta-analyses that include trials employing Oxford. Either exclude trials that use Oxford or at the very least, conduct sensitivity analyses under two situations - all trials vs. trials that do not employ Oxford – and compare the results. Inclusion of Oxford-related trials overestimates the benefits and underestimates the harms of cognitive behavioral and graded exercise therapy. It also swayed the Committee to oddly suggest that "Studies of homeopathy……are needed" (lines 281-282), based on one "fair" quality (as assessed by AHRQ) Oxford-employing trial, and despite the NIH's own National Center for Complementary and Alternative Medicine concluding homeopathy has not been shown to work for any medical condition and is "inconsistent with fundamental concepts of chemistry and physics". (http://nccam.nih.gov/health/homeopathy)

(Note that the UK PACE trial Fukuda subgroup is not a genuine Fukuda group as the PACE authors themselves noted in their follow-up "recovery" paper that they only required minor Fukuda symptoms to be present for a week under their version of Fukuda, not the 6 months that the official criteria requires.)

PACE Recovery Paper: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3776285/

2) Request that any research case definition constructed be based not only on the scientific literature/ clinical experience/ patient perspective but also be tested/ validated. The problem with the research case definition is not that many different versions exist -- in fact Fukuda is employed in 70% of studies per AHRQ – but rather that Fukuda is a poor case definition to begin with and that there was no nationally supported effort, outside of that of ME/CFS specialists via the ME-ICC and CCC, to validate/ refine/ update it as new research occurred over the last 2 decades. This is an egregious situation that is not seen with case definitions of other illnesses.

3) Ask NIH to consider the clinical case definition that the Institute of Medicine (IOM) will be coming out with as a candidate/ starting-off point for a research case definition. The IOM was tasked at approximately the same time to come up with a clinical case definition that clinicians can use. That report should be coming out shortly. Since much money and resources were already put into that effort and it makes no sense to have a research case definition that is wholly different from the clinical case definition, the Panel should consider asking NIH to consider it as a candidate research case definition. This would also encourage testing/ validation of the newly created clinical case definition.

4) I agree that other symptoms need to be explored besides fatigue but autonomic symptoms, especially orthostatic intolerance, should be added to Lines 58-59 and Lines 106-107. This is in agreement with the AHRQ Systematic Review (p. ES-9, ES-10) where PEM, neurocognitive difficulties, and autonomic symptoms were noted to distinguish a more severe group of patients and could be used for subgrouping.

5) The Panel needs to incorporate the AHRQ's Systematic Review findings and recommendations concerning research on treatment into their final report. Specifically, AHRQ noted that:

a) Their findings may not apply to more severely affected patients, especially those fitting ME criteria

"Treatment effectiveness may not be generalizable to all patients because no study used a case definition that selected for more disabled patients (i.e., case definition for ME)." (p. ES-6, ES-7)

b) Trials of graded exercise therapy often did not report harms well but when they did, higher rates of harm or withdrawal were detected.

"Although harms were not well reported across trials, GET was associated with a higher rate of harm and withdrawals in some trials. (p. ES-9)

Although these conclusions are not recommendations, they are extremely important to patients and clinicians since many healthcare providers and the public, influenced by the trials AHRQ reviewed but without AHRQ's careful examination, believe if ME/CFS patients could just increase their activity/ exercise, they would be cured. This is contrary to the experience of not only clinicians and patients -- 50% of whom report deterioration with GET in multiple surveys over the past decade - but also many studies showing that ME/CFS patients' bodies react detrimentally to incautious exercise/ increased activity.

(For a review, see: http://www.ncbi.nlm.nih.gov/pubmed/19855350. Chu and Jason's survey of 600+ US patients in 2013 showed 65.3% reported worsening with formal exercise programs prescribed by a healthcareprovider:
http://www.iacfsme.org/LinkClick.aspx?fileticket=E8i8MVWh%2bX0%3d&tabid=119)

As recently as this week, the following article, related to the PACE studies came out touting the benefits of exercise: http://www.telegraph.co.uk/news/science/science-news/11343258/ME-fear-of-exercise-exacerbates-chronic-fatigue-syndrome-say-researchers.html

Thus, AHRQ suggested that "[Future] Studies also need to report harms more completely to help identify patients negatively affected by certain treatments." (ES-10). By reinforcing AHRQ's statements in their Final report, the Panel may help prevent ME/CFS patients from receiving harmful treatments.

6) Contrary to the Panel's belief that "there is no agreement from the research community about what needs to be studied" (Line 34), there have been publications related to this topic that were were not presented to the Panel. Alas, the AHRQ Systematic Review's narrow parameters would not have allowed them to be included. For example, the NIH State of the Knowledge Conference report, CFSAC's Research Working Group suggestions, and, more indirectly, the International Association for Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis 2014 Conference Abstracts provide direction and ideas.

NIH Report:

http://www.meassociation.org.uk/wp-content/uploads/2011/08/SoK-Workshop-Report-508-compliant-8-5-11.pdf

CFSAC Research Working Group Spring 2014 recommendations:

http://www.hhs.gov/advcomcfs/recommendations/06142014.html

IACFS/ME 2014 Abstracts:

http://www.iacfsme.org/DesktopModules/DigitalDownload/2014Syllabus25.pdf

7) Lines 87 and 373, about the need for patient education, stand out as condescending statements towards patients in an otherwise sympathetic document. These lines seem to imply that patients' problems stem from a lack of communication from their end and less the unwillingness of clinicians to listen open-mindedly. The problem of patients not being educated to fit their symptoms/ concerns/ medications, etc. in a 5-minute narrative bullet to fit 10-minute clinical appointment slots is not unique to ME/CFS and is a general problem for many chronic, and even acute, illnesses. Would the Panel have put the same statement in a report about multiple sclerosis, coronary artery disease, or diabetes? I do not feel it is appropriate to single this out as a main or even relevant reason for the problems associated with ME/CFS diagnosis or treatment.

8) Contrary to Lines 130 and 360, many patients have been "self-managing" for years; it's just that no one has seriously listen to or studied how they self-manage through balancing activity with rest, called pacing. In numerous surveys within and without the US over the years, patients have cited "pacing" as the most or one of the most effective way to manage their symptoms. In fact, Dr. Bruce Campbell, a psychologist, with the help of an occupational therapist, has run an online course teaching pacing to thousands of patients for over a decade at www.cfidsselfhelp.og.

2012 review of pacing: http://informahealthcare.com/doi/abs/10.3109/09638288.2011.635746

9) I believe patients would be happy with even getting "incremental improvement" (Line 78) as that is not mutually exclusive with "meaningful recovery" but what patients do NOT want is to have supportive

treatments like CBT or GET or palliative treatments like sleep medications confused with disease-modifying treatments.

10) Contrary to Lines 143-144, some studies offer clues to the "inciting event" for many cases of ME/CFS. Again the AHRQ Review parameters excluded such papers from their review. In fact, many patients recall an infection prior their illness and in some studies, these have been identified even as Epstein-Barr virus, parvovirus B19, girardia enteritis, influenza, Ross River virus, Coxiella. Two such examples are below:

http://www.ncbi.nlm.nih.gov/pubmed/23263024

http://www.ncbi.nlm.nih.gov/pubmed/16950834

11) Contrary to Line 54, which states that "there are no data to confirm whether minorities have a higher or lower risk," there have been several studies that suggest African-American, Latino, and Native Americans may have a higher prevalence of ME/CFS compared to Caucasians. In addition, they may also experience more severe symptoms and be even more underdiagnosed. Here are some examples:

http://iacfsme.org/Portals/0/pdf/Jason%20vol17%20n3.pdf

http://ije.oxfordjournals.org/content/38/6/1554.full

file:///C:/Users/User/Downloads/09e415092d1f1936e6000000.pdf

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3902687/

The Panel could also make suggestions about how to include more ethnic minorities in studies. I have a personal interest in this as I and several of my friends affected by ME/CFS are non-Caucasian. For example, community-based studies in clinics with diverse populations can screen all patients endorsing ME/CFS symptoms with a clinical examination/ basic laboratory testing. This situation is more likely to attract minorities than studies recruiting based on an existing physician diagnosis. Minorities often have difficulty accessing care due to financial/ logistical reasons and both they and their healthcare providers may not view ME/CFS as an illness affecting non-Caucasians. Funding and assistance could also be sought from the DHHS' Office of Minority Health.

Vague spots:

1) Be more specific about the economic costs of ME/CFS, $18-$54 billion a year, rather than underestimating it at "greater than $1 billion." The figures below are a sum of both direct (e.g medical care) and indirect (e.g. lost productivity) costs.

$18-$24 billion by Jason: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2324078/

$54 billion by CDC in "Conclusions" : http://www.resource-allocation.com/content/9/1/1

2) Line 50 – I think you mean to put not "163 symptoms" here but rather "163 *combinations* of symptoms." This can be verified by going back to Dr. Nacul's talk.

3) Line 52 – I think you mean that research has focused on "women", not "men" as written.