This following are my comments on the 389 line version of the Draft Executive Summary for the December 2014 Pathways to Prevention (P2P) Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.

Lines 2-4: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic, complex, multi-faceted condition characterized by extreme fatigue and other symptoms that are not improved by rest.

There are two areas of concern here; the use of an unsupported and made up name for a condition, a name that is NOT and cannot be medically categorized, and the incorrect presentation that the disease which ought to be in focus (ME), is characterized by extreme fatigue.

First, had the ARHQ report utilized its original question of whether or not ME and CFS are the same or different entities the use of this hybridized name (ME/CFS) would not have a place in this report or in any jargon used by agencies with a focus on ME and/or CFS. Using a name that attempts to combine ME and CFS into one condition assumes that the two occur on a spectrum, and ignores the scientifically substantiated fact that the two names, corresponding case definitions, and conditions represent two different patient populations.

It has been established that "PEM is a signature symptom of ME". [1] PEM, as defined by the CCC is as follows: "Post exertional malaise is defined as "an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. There is a pathologically slow recovery period–usually 24 hours or longer."[1] PEM and this definition should present in the report, not fatigue, as the signature symptom.

When applying a diagnostic criteria which require the symptoms of PEM, neurological, and autonomic symptoms a more impaired patient population is identified than when applying a broad diagnostic criteria. This could be evidence that those patients exhibiting PEM, neurological and autonomic symptoms have the disease ME, while the larger population identified by the broad definition actually has medically unexplained fatigue, or CFS, but please consider that these are two distinct entities.

This name clumping would not be done with the disease Multiple Sclerosis and CFS; i.e. we would not expect the HHS to suddenly combine Multiple Sclerosis with CFS creating the hybridized term MS/CFS, and thus creating the allusion that the two now somehow reflect a spectrum disorder. CFS describes patients with medically unexplained fatigue. In patients with Multiple Sclerosis who exhibit fatigue that fatigue is NOT medically unexplained. It is explained by the disease Multiple Sclerosis. Likewise, in patients with Myalgic Encephalomyelitis who exhibit fatigue in the form of PEM that PEM is NOT medially unexplained. It is explained by the disease Myalgic Encephalomyelitis. The use of this hybridized name (ME/CFS) in this report will likely create further confusion unless the panel recognizes this in the report and recommends that the classifications outlined below are properly understood.

ME has been classified by the World Health Organization's International Classification of Diseases (ICD) since 1969 and is NOT characterized by extreme fatigue. The diagnostic term "chronic fatigue syndrome", created by the CDC is listed as 780.71 under "Symptoms, Signs, and Ill-Defined Conditions. ME/CFS has never been included in the WHO ICD while ME has.

Second, the neurological disease Myalgic Encephalomyelitis (ME) is NOT characterized by extreme fatigue. Unexplained fatigue is the characteristic feature of chronic fatigue syndrome (CFS), not Myalgic Encephalomyelitis (ME). This distinction is imperative. It has been established that PEM is a signature symptom of ME, and thus it should be required in the case definition, and belongs in this reports introduction.

Lines 6 and 7 The estimated economic burden of ME/CFS to be greater than $1 billion.

This is grossly underestimated. A more accurate description would be: "The economic burden of ME/CFS in the U.S., including annual health care costs, is estimated to be between $1.9 billion and $7.2 billion. With indirect costs to society as a whole, the annual estimate jumps to between $18.7 and $23 billion in the US alone." [2]

Lines 27-30 We critically reviewed the scientific literature and opinions presented by a group of experts and the ME/CFS community during the public meeting, weighed the evidence, and developed a set of conclusions. This report presents our findings and recommendations.

Clearly the limitations imposed on the AHRQ regarding literature selection has affected the scope of this report and introduced bias into the sample. A large segment of literature on ME and CFS has been published in two non-indexed

journals: Journal of Chronic Fatigue, a quarterly published from 1995 to 2007, and Fatigue: Biomedicine, Health & Behavior, a quarterly just launched in 2013 by the International Association for CFS/ME.

If it has not already been done, it is respectfully recommended that the panel augment the information already considered by familiarizing itself with 1) The Voice of the Patient series of reports published in September 2013 following the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative for Chronic Fatigue Syndrome and Myalgic Encephalomyelitis, and 2) The 2011 Report from the National Institutes of Health (NIH) State of Knowledge Workshop during which researchers and stakeholders reached consensus on a number of key issues, one being that PEM is a signature symptom of ME/CFS. [3, 1]

Lines 32 and 33 of the draft report state that, "Despite the absence of a clear definition, an estimated million people have ME/CFS, and it overlaps with many other diseases (e.g., fibromyalgia, major depressive disorder, and chronic pain)"

There is no evidence of an overlap with major depressive disorder, and if it is the goal of the panel to list co-morbidities then perhaps a list such as that from the 2003 Canadian Consensus Criteria would be more appropriate to avoid the pitfall of continued somatization of this disease. That list is as follows: Fibromyalgia Syndrome, Myofascial Pain Syndrome, Temporomandibular Joint Syndrome, Irritable Bowel Syndrome, Interstitial Cystitis, Irritable Bladder Syndrome, Raynaud's Phenomenon, Prolapsed Mitral Valve, Depression, Migraine, Allergies, Multiple Chemical Sensitivities, Hashimoto's thyroiditis, and Sicca Syndrome.

Lines 121-122 *Patients experience stigma from the diagnosis of ME/CFS, including social isolation and judgment*

Since 1988 when the CDC created the name CFS this name has trivialized the actual debility caused by ME. This is magnified by the lack of awareness within the medical community about the severe physiological disability caused by ME, and absence of diagnostics and treatments. If there is any stigma experienced by this patient population it is due in most part to this CFS designation and its continued use, and now to the use of the hybridization ME/CFS. A name change to Myalgic Encephalomyelitis, classified by the World Health Organization as a neurological disease with proper ICD-9 reimbursement codes, could help alleviate this stigma. Additionally, proper education of healthcare professionals about the disease ME, use of the CCC in diagnosis, and proper treatment for ME (using the ICC or ICP Primer) will also correct this. [4]

Lines 146-148 Furthermore, a variety of symptoms are often "lumped" into ME/CFS. Carefully defining comorbid conditions is necessary to define ME/CFS subgroups and to move the field forward.

Co-morbid conditions have been carefully defined in the 2003 Canadian Consensus Criteria and are listed above under lines 32-33.

Additionally, on the P2P workshop day 2 at 3:04:29 Nancy Klimas spoke of the many biomarkers identified in patients which are already used to subgroup or create tightly defined groups to pursue pathogenesis and prevention research, (e.g. pathogen discovery, genetic susceptibility and to create a subgroup defined for targeted treatment.

Lines 151-156 Individual ME/CFS studies are too small to have power for subgroup analyses; rarely meet the criteria for good quality evidence; frequently do not address early disease or ME/CFS in children; fail to adequately address harms or who dropped out and why; and include only a short follow-up. In addition, participant variability at different study centers may, in part, be responsible for conflicting results.

Given the meager research budget of $5 million per year from the NIH there is little opportunity for dedicated researchers to do the necessary large and/or validation studies. Most of the research on ME and CFS have been privately funded due to this inadequate government funding, and given the disabled nature of most patients and the subsequent financial strain faced by many of us, we have been the ones to foot the bill. Given this, and that the general public is unaware of the scope of this disease and its disabling nature, it is illogical for our government to expect or recommend that research on this disease be funded by the private sector. This disease should receive NIH funding equal to that of diseases with similar disability like M.S., which according to the NIH website is slated to receive $115 million in 2015, and has a reported prevalence only one third the prevalence of CFS. [5]

During an interview for a Medscape article conducted at the P2P workshop Dr Friedman said, "The government should be embarrassed that the private sector has had to take over because of their lack of funding." [6] As was explained by Dr. Shirley during the same interview, if funding spent on specific areas of research are driven by the number of researchers in a specific research field, their experience in competing for NIH funding, and the number of submissions to NIH for funding, and if, as you report in the P2P summary that this disease affects many bodily systems and should involve various medical specialties,

then experts in those fields should be given the opportunity to compete for and apply for large amounts of funding for studies on ME and CFS. The NIH should first provide the funding and qualified individuals will apply.

Lines 231-234 Biologic samples

As previously recommended by the CFSAC in their Spring 2014 recommendations to the Secretary of Health and Human Services, the NIH should adapt the architecture of the National Autism Research Database (NDAR) to setup and provide ongoing support for a data and bio-bank sharing platform for ME/CFS research. This platform should allow for both phenotype and biologic data.

The National Autism Research Database (NDAR) is an NIH-funded research data repository that aims to accelerate progress in autism spectrum disorders (ASD) research through data sharing, data harmonization, and the reporting of research results. NDAR also serves as a scientific community platform and portal to multiple other research repositories, allowing for aggregation and secondary analysis of data. NDAR is an extensible, scalable informatics platform for ASD relevant data at all levels of biological and behavioral organization (molecules, genes, neural tissue, behavioral, social and environmental interactions) and for all data types (text, numeric, image, time series, etc.). NDAR was developed to "share data" across the entire ASD field and to facilitate collaboration across laboratories, as well as interconnectivity with other informatics platforms. A similar database is needed to advance ME/CFS research.

Lines 275-276 Studies addressing biopsychosocial parameters (including the mind-body connection), function, and QOL should be encouraged.

The inclusion of the word "biopsychosocial" has understandably caused much recoil from the patient and expert community for the simple reason that one of the greatest struggles for all involved in this disease has been to change the focus from psychosomatic to biological. If it your intent to suggest the inclusion of endpoints such as mind-body connection, function, and QOL in biological studies then perhaps this "hot" word could be removed so that no further money is spent on future studies with a psychosomatic focus.

Lines 315-316 Patients—in addition to the medical therapies they are receiving, patients must become active participants in their overall treatment.

Since the outset ME and CFS patients have been left to manage their own disease. Speaking personally I saw 23 specialists and underwent many tests before finally receiving a diagnosis of CFS and Fibromyalgia by a rheumatologist, who then told me it was not necessary to return to her because I was the first patient she had diagnosed as such who was in "recovery". Ten years later I am still on full disability and operate at about 50-60% of my pre-disease level and that is only because I no longer work and minimize other activities through pacing. That very compassionate doctor had nothing further to offer me, and a decade later this has not changed. I am fortunate in that I am highly educated with a science and medical background, and having worked in the medical field I am skilled at navigating through that community and setting. Patients with ME and CFS not only do not have access to specialists in our disease, we don't even have access to healthcare professionals who are the slightest bit educated in our disease. ME and CFS patients are already mostly self-managed.

Line 350 Future treatment studies should evaluate multimodal therapies.

The use of the term multimodal therapies requires further detail. If this is meant to suggest that future treatment studies should evaluate various therapies, then perhaps those should be listed. If multimodal is used here to indicate a form of psychotherapy, this statement should be qualified to include that this should only be utilized after the disease has been effectively treated and only for those patients who suffer from psychological co-morbidities.

Lines 359-362 Patients and their advocates may benefit from education on how to effectively communicate their symptoms and concerns to clinicians, while health care providers could benefit from enhanced active listening skills and increased education. We note that education alone cannot fix this problem, but will facilitate a partnership in medical decision-making, thereby optimizing care.

As stated above, patients have been forced to learn to effectively communicate their symptoms and concerns to clinicians. A serious gap occurs though when undiagnosed or newly diagnosed patients try to convey their loss of functionality and exhaustion with activity and doctors interpret this as fatigue rather than PEM. New ME and CFS patients are unaware of the existence of PEM, and so cannot describe it properly and leave the clinic without learning about it. The absence of this clarification added to the fact that US clinicians do not utilize the Canadian Consensus Criteria, leaves new patients to continue to be misdiagnosed using Fukuda as having CFS rather than ME further confounding the subject pool for future research.

Lines 364-368 "Specifically, continuing to use the Oxford definition may impair progress and cause harm. Thus, for needed progress to occur we recommend (1) that the Oxford definition be retired, (2) that the ME/CFS community agree on a single case definition (even if it is not perfect), and (3) that patients, clinicians, and researchers agree on a definition for meaningful recovery."

Regarding #1 - The patient population is ever so grateful for your recommendation to retire the Oxford definition from use as it incorrectly identifies patients who do NOT have this disease. With the Institute Of Medicine report and its recommendation for a clinical case definition due out in February 2015 it is understandable that you would not make a recommendation for either CCC or ME-ICC, but at the least the draft summary should go the next step to recommend that Fukuda et al 1994 also be retired on the basis that it does NOT require cardinal symptoms of THIS disease (PEM), and it incorrectly identifies patients who do NOT have THIS disease.

Regarding #2 - Clearly the majority of the ME and CFS community, including patients, clinicians and researchers have agreed that the CCC and/or ME-ICC are the best choices. In a letter to the Secretary of Health and Human Services dated September 13, 2013 more than 50 of the world's experts on ME and CFS stated that they support the adoption of the 2003 Canadian Consensus Criteria (CCC) "as the case definition for this disease." Many of the people who signed the letter have been using the CCC for some time. The letter goes on to urge HHS to adopt the CCC as the single case definition for all Department activities, both research and clinical uses. [7]

Additionally, since you have recommended that the Oxford Definition be retired, might you not also recommend that studies which have used the Oxford criteria for subject selection, such as PACE and NICE, no longer be used to endorse treatment strategies for ME/CFS?

The letter was mentioned throughout the workshop by presenters as well as the audience. This is based on the CCC's requirement of the symptom PEM, as well as its sensitivity to identify those with this disease (ME) and the specificity to eliminate those without it. The CCC was endorsed in the Primer for Clinical Practitioners published by the International Association of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFSME). This organization is the major international professional organization concerned with research and patient care in ME and CFS. This report would do more service to this patient population by acknowledging this consensus to recommend the adoption of the Canadian Consensus Criteria.

Perhaps since the HHS has charged the IOM to develop a clinical diagnostic criteria for this disease all stakeholders (patients, advocates, ME and CFS researchers and clinicians should first be in agreement about the results of the recommendation from the IOM published report especially if it does not recommend adoption of the CCC, and from that develop a complementary research case definition to be used by all who conduct research on ME and CFS. Both definitions should be fluid as research develops.

It is my hope that this panel will consider my and all other comments submitted with respect and will find a way to incorporate these changes to make this report a better representation of the opinions held by stakeholders in this disease, namely patients, advocates, and expert clinicians and researchers. This panel and thus the final summary hold the power to affect positive change not only for the 1 million U.S. patients who have been sorely neglected and at times mistreated, but for the 17 million worldwide. I hope you see the value in these and other suggestions.

Thank you,
Claudia Goodell, M.S.

1 Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research April 7–8, 2011 NIH, Bethesda, Maryland Workshop Report http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH_SKW_Report.pdf
2 Jason LA, Benton MC, Valentine L, Johnson A, Torres-Harding S. The economic impact of ME/CFS: individual and societal costs. Dyn Med. 2008 Apr 8;7:6. PMID: 18397528
3 The Voice of the Patient A series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative Chronic Fatigue Syndrome and Myalgic Encephalomyelitis Public Meeting: April 25, 2013 Report Date: September 2013 http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM368806.pdf
4 Carruthers BM, van de Sande MI et al. Myalgic Encephalomyelitis – Adult & Paediatric: International Consensus Primer for Medical Practitioners. Published online October 2012. http://www.name-us.org/DefintionsPages/DefinitionsArticles/2012_ICC%20primer.pdf
5 http://report.nih.gov/categorical_spending.aspx
6 http://www.medscape.com/viewarticle/833428#vp_4
7 https://dl.dropboxusercontent.com/u/89158245/Case%20Definition%20Letter%20Sept%2023%202013.pdf