To: Dr. Carmen Green and the Pathways to Prevention Panel for ME/CFS
From: Mary Dimmock
Subject: Comments on the Draft Executive Summary
National Institutes of Health Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/chronic fatigue syndrome
Date: January 16, 2015

Thank you for this opportunity to comment on the draft Executive Summary of the Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome held on December 9–10, 2014.

The draft Executive Summary (403 line version) outlines a number of the issues that have prevented progress on this disease for the last thirty years and provides a range of recommendations, including many that this community has long called for. You are to be commended for recognizing these issues, particularly given that your exposure to this disease was through an AHRQ Evidence Review and P2P Workshop agenda that both excluded broad swaths of the relevant research on this disease.

But there are a number of critical issues that the draft Executive Summary fails to grapple with that must be if we are to escape the quicksand that has trapped this disease for the last thirty years. These include:.

1) **Lack of clarity on the disease being addressed in the draft Executive Summary.**
The first and most fundamental issue that should have been addressed in the draft Executive Summary is whether ME and CFS are the same disease or not. Put another way, do Fukuda, Empirical and Oxford all encompass the same group of patients as CCC and ME-ICC.

   The draft Executive Summary rejected Oxford for including patients without the disease and noted that PEM is part of a consistent constellation of symptom. But then the draft Executive Summary failed to say that PEM is mandatory or call out that Fukuda encompasses many disparate medically unexplained fatiguing conditions that do not require PEM. And while the draft Executive Summary states that the disease is not psychiatric (line 92, 296), it then calls for further research into multimodal therapy, the biopsychosocial approach, CBT and GET (line 282, 359) to the virtual exclusion of biomedical treatments like antivirals, immune modulators and similar therapies.

   If you truly accept, as patients, disease experts and CFS Advisory Committee do, that PEM is the sine qua non of this disease and that the disease is not psychological,[1] then you must explicitly reject Fukuda and Empirical for the same reasons that you rejected Oxford – both encompass patients who do not have the disease as Drs. Nacul and Jason clearly demonstrated. And you must direct scarce resources to biomedical treatments, not to further investigation of therapies like the biopsychosocial approach that has been primarily studied in Oxford.

   Accepting that Fukuda includes people who do not have the disease or the mandatory PEM while touting psychological approaches is the same kind of definitional confusion that has held ME hostage for thirty years. It must be corrected by clearly stating that PEM is a hallmark, mandatory symptom, explicitly acknowledging that Fukuda and Empirical are also flawed because they include patients who do not have the disease and calling for a definition at least as restrictive the Canadian Consensus Criteria to be adopted.

2) **Failure to acknowledge the impact of NIH institutional barriers and research funding decisions** *(further details in background)*

The draft Executive Summary acknowledges that a lack of funding has impeded research and calls for public-private partnership, including industry, to move research forward. But this draft Executive Summary fails to acknowledge NIH's role in egregiously underfunding this disease for so many years and for failing to address the stigma and NIH institute barriers that have kept researchers at bay.

It is naïve to expect that industry is going to invest when there is such a dearth of basic research or that an impoverished, stigmatized community can make up for NIH's shortfall. NIH is the only group with the resources and power to address the funding problems and the barriers and they have the responsibility to do so given that the issues arose because of a thirty year history of NIH underfunding and mismanagement.

The Executive Summary must explicitly call for NIH to establish funding commensurate with the $19-24B burden of disease – something greater than $120M based on the funding for MS, which has similar burden and half the prevalence. Further, the Executive Summary must call on NIH to aggressively address the barriers results from disease stigma, NIH's institute structure and the lack of researcher interest by issuing a series of well-funded RFAs as called for by CFSAC, IACFS/ME and congressional leaders in 2014, a request that NIH rejected. Finally, the Executive Summary must call on NIH to work *openly and transparently* with the stakeholders to establish a publicly available research strategy, with an aggressively defined timeline and explicit benchmarks monitored to ensure forward progress.

3) **Need for a new model of engagement**

The draft Executive Summary states that the research and medical community has frustrated constituents (line 10). This statement misrepresents the reality. In the U.S., patients are particularly frustrated with HHS, which has underfunded research, miseducated doctors and failed to act openly, transparently and inclusively. HHS has repeatedly ignored the recommendations of its own CFS Advisory Committee, experts and the patient community. HHS has acted unilaterally in direct opposition to those recommendations as demonstrated in its rejection of the call by 50 international experts to adopt the CCC. HHS' actions and its failure to achieve any meaningful outcomes for thirty years are directly responsible for the tremendous frustration, mistrust and hostility that exist today.

You might say that this is the past and everyone should move on. But HHS' non-functional engagement model toward this community still exists today, making it unlikely that the goals of this Executive Summary, particularly those that require openness, transparency, collaboration and direct engagement of patients, will be achieved. For real progress to be made, the Executive Summary must call for a new engagement model to be forged, likely one that requires congressional oversight.

If you want your work to have a meaningful impact in patients' lives, I ask you to carefully consider each of these areas and find ways to explicitly address them in the final version of this Executive Summary. I also ask that you review and address the additional needed points of clarification and correction listed below.

Thank you for the opportunity to provide feedback.

Mary Dimmock

Additional Background

A. Details on Clarifications and Corrections needed in each of the following lines of the draft Executive Summary.

The following specific lines needs to be corrected and/or clarified as indicated below.

- Line 2-5. "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."
  This statement does not begin to reflect the reality of this disease and perpetuates the idea that the only defining feature is fatigue. I support the CFSAC recommendation for modification of these lines and ask that you adopt their revised text for those lines in total.
  Requested modification: incorporate the text approved by CFSAC and submitted to P2P.
  "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic, complex, multi-faceted condition characterized by hallmark symptoms of neurological dysfunction, sleep disturbances, and post exertional malaise with predominant symptoms of immunological and endocrinological dysfunction. 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.

  "The etiology and pathogenesis of ME/CFS remains unknown and there are no known cures. There is no single diagnostic test or standard set of tests being used to diagnose ME/CFS in the clinic at this time. However, a number of common biomarkers are being used by experts in the field to aid diagnosis, to strategize treatment, to define comorbid states and for research. Strong evidence indicates immunologic and inflammatory pathologies, neuroendocrine findings, and abnormalities in gene expression of energy and other related proteins post-exertionally in ME/CFS patients, which differ from findings among age and sex matched normal control populations. Additionally, there is reproducible evidence of abnormalities in functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies.

  "Research has clearly shown that ME/CFS is not a psychiatric or a psychological disease. ME/CFS is a distinct pathological entity that can affect both sexes and all racial, age, and socioeconomic groups regardless of education, financial security, or social standing. The U.S. Centers for Disease Control and Prevention (CDC) reports over 1 million adults with ME/CFS in the United States, and recent evidence has shown a higher prevalence in females compared to males. Certain racial/ethnic groups have also been found to be at an increased risk for ME/CFS; most notably Native American and African American populations.

  "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. When considering indirect costs to society as a whole, the annual estimate jumps to between $18.7 and $23 billion in the U.S. alone. ME/CFS results in major disability for a large proportion of patients and in its most severe form, can lead to individuals becoming housebound, dependent on wheelchairs, or bedbound and forced to turn to caregivers for all basic activities of daily living. Limited knowledge and research funding creates an additional burden for patients and health care providers.

- Line 6: *"Economic burden estimated to be greater than $1 billion."*
  This is very misleading and needs to be corrected. The most widely accepted estimate of

economic impact is from Jason, who estimated it at $19-24B.[2] No sources support an estimate of $1B.

Requested modification: change $1B to $19-24B.

- Line 10: *"ME/CFS is an area where the research and medical community has frustrated its constituents by failing to assess and treat the disease and by allowing patients to be stigmatized."*
  The research and medical community who study and treat ME are not the ones that have frustrated its constituents. HHS has frustrated this community as outlined above. The clinicians and researchers who treat this disease have had their hands tied.

  Requested modification: "HHS and other federal agencies in addition to the general medical and research community has frustrated this patient population by failing to assess and treat the disease and by allowing patients to be stigmatized."

- Line 50: "*163 symptoms have been associated with ME/CFS."*
  This is an error. At the P2P workshop, Dr. Nacul said that there were 163 different combinations of Fukuda symptoms of which only 35 had PEM.[3] This is a critical distinction and was discussed by Dr. Nacul in the context of demonstrating how overly broad Fukuda is.

  Requested modification: "Numerous symptoms have been associated with ME/CFS."
  Requested addition after line 40: "Like Oxford, Fukuda also encompasses a substantial number of other conditions beyond those encompassed by the Canadian Consensus Criteria and the ME-ICC."

- Line 67: *"Patients are frequently treated with psychiatric and other inappropriate drugs that may cause harm."*
  This line is targeted at drugs but some of the greatest harm comes from non-pharmacological treatments like CBT and GET which try to convince patients they are not really sick. On the other hand, there are a number of drugs that can be used to treat some of the core symptoms like Fluorinef for orthostatic intolerance.

  Requested modification: "Patients are frequently treated with psychiatric and exercise therapies that may cause harm."

- Line 113: *"Existing treatment studies (cognitive behavioral therapy [CBT] and graded exercise therapy [GET]) demonstrate measurable improvement."*
  The AHRQ Evidence Review acknowledges that these have never been tested in CCC and ME-ICC patients. Given the dramatic differences in inclusion and exclusion criteria between Fukuda/Oxford on the one hand and CCC/ME-ICC on the other, what evidence justifies a call to use these therapies in patients that meet CCC/ME-ICC based on testing in Oxford? Its important to note that while PACE claims they used an ME criteria, they used a non-standard version of an unpublished, little used criteria. They did not use CCC or ME-ICC.

  This statement will create confusion because both CBT and GET have dual meanings. As applied by PACE and the biopsychosocial approach to CFS, CBT is not about coping but rather convincing patients they have a maladaptive fear of exercise.

  Requested modification: "Treatment studies of cognitive behavioral therapy (CBT) and graded exercise therapy (GET) have demonstrated modest improvement in patient populations selected by Oxford and to a much lesser extent, Fukuda. But these treatments have not been tested in patients selected by the Canadian Consensus Criteria or the ME-ICC and therefore it is impossible to state what effectiveness these therapies have in these patients. However, given the post-exertional exertion and the questionable ethics of recommending CBT to convince patients with a neuroimmune disease that they are not ill, these therapies should not be recommended."

- Line 130: "*In general, little attention was given to how self-management may empower and improve health and QOL for patients with ME/CFS."*
  It is unclear where this came from, what evidence has been used to support this statement, or how self-management is expected to "improve health." Are you talking about little attention in research, little attention by the general medical community or little attention by patients.
  Are you talking about pacing/energy envelope. Patients excel at that.
  Additionally, this statement will divert scarce resources studies into needed biological treatments.
  Requested modification: If you are calling for doctors to receive training on pacing/energy envelope, state that. Otherwise, delete the sentence.

- Line 166: "*The symptoms patients consider clinically meaningful are not in the scientific literature; this discordance must be rectified."*
  This is not true. The symptoms are in the literature. The problem is that because of the way the AHRQ Evidence Review was performed and the P2P agenda shaped, you didn't see them. The other huge problem is that limited NIH funding keeps the studies that have been done from being replicated.
  Requested modification: "While not covered in AHRQ's Evidence Review, the symptoms that patients consider clinically meaningful (e.g. PEM, cognitive dysfunction) have been covered in the scientific literature but funding from NIH is needed to replicate the studies. This issue must be rectified."

- Line 181: "*Overall, there has been a failure to implement what we already know for patients with ME/CFS while it steals their health and well-being."*
  Is this intended to be a call to implement CBT and GET? If so, this is dangerous and unacceptable for ME patients given their adverse reaction to exercise, the fact that these therapies have not been tested in ME specific populations and the questionable ethicality of using CBT to convince a patient with the kind of neuroimmune problems seen in ME that he is really not sick and should ignore his symptoms.
  Requested modification: If the intent is to implement CBT and GET, then I ask you to carefully look at how those therapies have been studied in CFS as discussed above and below.
  These terms have been used ambiguously and/or interchangeably and have resulted in great confusion. I respectfully ask that you not perpetuate this confusion.

- Line 191: *"The dissemination of diagnostic and therapeutic recommendations should focus on primary care providers."*
  What is the basis of this recommendation? Are primary care doctors expected to be the focal point for treating multiple sclerosis and do they have the needed expertise? Do the training and business practices of primary care doctors support the amount of time and expertise necessary to work with ME patients? At the very least, other specialists must be listed as in the CFSAC submission to P2P.
  Requested modification: Adopt the language submitted by CFSAC. *"The dissemination of diagnostic and therapeutic recommendations should focus on primary care providers and all other health care providers dealing with symptoms specific to this disease including but not limited to cardiologists, endocrinologists, neurologists, rheumatologists, psychiatrists, clinical immunologists and infectious disease specialists."*

- Line 282: "*Studies addressing biopsychosocial parameters (including the mind-body connection), function, and QOL should be encouraged."*

Note that the biopsychosocial model for "CFS" (as in the PACE trial and CBT and GET trials) postulates that CFS is maintained by factors like maladaptive fear and avoidance of activity, excessive focusing on symptoms and perfectionism. According to this model, patients have developed a fear-based avoidance of activity, which resulted in deconditioning and an excessive focus on bodily symptoms, which causes the symptoms of the disease.[4] In this model, CBT is used to eradicate false illness beliefs, not to help patients cope and GET is used to push beyond a patients limits; patients are encouraged to ignore their bodily symptoms and to push to the predefined targets.[5] It is not about gentle stretching.

Are the authors stating that this treatment approach is appropriate for patients with the neuroimmune disease described by CCC and ME-ICC? If that is true, then given the history of how this term has been used in this disease, the term "biopsychosocial" should not be used in this Executive Summary.

Requested modification: Delete this sentence and replace as recommended by CFSAC: "Use of outcome measures such as QOL and function should be encouraged in the studies of immunologic, neurologic and genomic factors as well as the other valuable studies outlined in the "Create New Knowledge" section of this workshop draft Executive Summary."

- Line 313: "*We believe ME/CFS is a distinct disease that requires a multidisciplinary care team (e.g., physicians, nurses, case managers, social workers, psychologists) to optimize care."*
  As written, especially given the history of this disease, this can easily be interpreted to mean that disease specialists – neurologists, immunologists, cardiologists, etc. are not needed.
  Requested modification: *"We believe ME/CFS is a distinct disease that requires a multidisciplinary care team (e.g., primary care physicians, clinical immunologists, neurologists, endocrinologists, rheumatologists, infectious disease specialists, nurses and case managers) to optimize care.*"

- Line 317 – 319: HRSA currently facilitates training but it has used the CDC CFS Toolkit which CFSAC and patients alike have recommended be taken down because it miseducates doctors. Given this situation, any training recommendations must also clearly state what training material is to be used and be clear on the disease.

  Requested modifications:
  - "Using educational material that reflects the disease described by CCC and ME-ICC, Health professional licensing and accreditation agencies to ensure a curriculum that facilitates ME/CFS knowledge acquisition"
  - "Health Resources and Services Administration (HRSA) to facilitate training using educational material that reflects the disease described by CCC and ME-ICC. The IACFS/ME Primer is one source of educational material that accurately describes this disease."

- Line 327: *"Patients—in addition to the medical therapies they are receiving, patients must become active participants in their overall treatment."* (line 327)
  It is unclear what you are implying here. Patients already are very active participants. The problem is that they are often doing it on their own, with no medical support. As stated, the line implies that they are not active participants or that they only want drugs and don't want to do their part. This is simply not true.
  Requested modifications: Clarify. Accurately reflecting the degree to which patients have had to be active – and typically sole – participants in their medical care.

- Line 328-339 Find new sources of funding. This section recommends a number of sources but avoids stating the obvious source – NIH. NIH funding is obscenely inadequate and far below the disease burden. This situation has persisted 30 years.

  Requested change: Add a sentence on line 330 to state "NIH must provide a fair share of funding that is commensurate with the burden of this disease. Given the amount of money spent in multiple sclerosis, a similarly disabling disease with lesser prevalence, it is anticipated that that funding should be over $120M/year. Additionally, NIH must take active steps to address the institute and researcher barriers that have impeded the expansion of research in this field."

- Line 359: *"Studies examining the role of self-management techniques as part of a comprehensive treatment plan for patients with ME/CFS during and after clinical interventions should be explored. The modest benefit from CBT should be studied as adjunct to other modalities of treatment such as self-management. Future treatment studies should evaluate multimodal therapies."*

  The singular focus on psychological and behavioral treatments in this section to the virtual exclusion of disease modifying treatments would be unacceptable in cancer and multiple sclerosis and is completely unacceptable for this disease. It will harm patients and will set the science of this disease backwards. This is particularly true when you consider how the biopsychosocial approach, CBT and GET have been applied as discussed above. It is of questionable ethics to use such treatments with patients who have the neuroimmune disease described by CCC or ME-ICC. This also sends an inappropriate message to the medical community that this is a psychological illness.
  See note about self-management above in line 130.

  For years, most treatment studies have focused on such psychological and behavioral factors with little benefit to patients. As a first priority, scarce resources must instead be aggressively focused on the study of potential biomedical treatments, such as drugs currently being used off label, so that patients no longer have to find a way to cope with such a miserable quality of life.

  Requested change: Revamp this section to remove the call for study of self-management, the further study of CBT and multimodal therapies and to replace it with the study of disease modifying treatments like antivirals, immune modulators, autoimmune treatments and treatments used in neurodegenerative diseases

- Line 365: "*We recommend that the NIH and the FDA convene a meeting on the state of ME/CFS treatment."*
  The FDA already held a drug development workshop in 2013. What are you expecting a new meeting to address, particularly when pharmaceutical companies are by and large staying away in droves because so little basic research has been done and so few academic centers have studied the basic biology.

  Requested modifications: If the intent is to have this meeting cover psychological and behavioral treatments, this should be removed. Otherwise, it needs to be clarified.

- Line 373: *"Patients and their advocates may benefit from education on how to effectively communicate their symptoms and concerns to clinicians."* (line 373).
  Given the challenges that patients have faced with even getting doctors to believe they are really sick, this statement is offensive and far misses the mark of the problems that these patients face (insurance, medical business practices like concierge, doctors who don't believe them, inappropriate treatment recommendations like GET).

  Requested modifications: Remove this sentence

- Line 384: "*We believe there is a specific role for multimodal therapy."*

Various sources describe multimodal therapy as an approach to address psychological problems. There are no studies that have demonstrated that such therapy will help patients who meet CCC or ME-ICC.

Requested modifications: Remove this sentence or else provide an explanation of the nature of the therapy that you are recommending, the evidence that supports that claim, the expected therapeutic impact and mechanism.

Line 379: "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."

This Executive Summary must call for the CCC and also call out the problems with Fukuda

Requested modification: "Thus, for needed progress to occur we recommend (1) that the Oxford definition be retired and Oxford studies not be used to inform treatment recommendations (2) that Fukuda be retired (3) that the CCC be universally adopted until such time that updated criteria are accepted (4) that the ME/CFS community review the clinical diagnostic criteria recommendation produced by the Institute of Medicine and then agree on a single clinical diagnostic case definition, even if its not perfect, to be used by all health care providers caring for patients with ME/CFS (5) that the single clinical diagnostic case definition be followed by development of a research case definition for use by all conducting research on ME/CFS and (6) that patients, clinicians, and researchers agree on a definition for meaningful recovery."

B. Further details on impact of NIH institutional barriers and research funding decisions

NIH budgets $5M for this disease out of a total NIH budget of $ $30.1B, placing this disease at #226 out of 234 diseases funded by NIH. Hay fever gets twice as much and MS, a disease with roughly half the prevalence, gets $115M. NIH has said that the budget will not increase until there are more investigators applying for grants. But paltry funding combined with stigma against the disease at both NIH and at the researcher's institutions has discouraged investigators from going into this field. CFSAC members have raised this issue with NIH staff many times over many years, calling for an RFA to attract new investigators and for NIH to apply approaches used to jump-start other fields.[6] Neither has happened. The most recent RFA recommendation (June 2014) was rejected because "there remains a lack of definitive evidence regarding the etiology, diagnosis and treatment."[7]

The second factor is a set of NIH institutional issues resulting from this disease being administered by the NIH Office of Research on Women's Health. While it is true that the Trans-NIH Working Group does not have a member from each institute (line 209), most of the key institutes are covered. The more fundamental issue is that ORWH itself has no budget and has to beg the different institutes for funding. The challenges this creates have been discussed at CFSAC, most recently in 2011 when Dr. Klimas stated,

"Using an interagency coordinating committee to try to patch together the funding has dramatically limited access to program projects and center grants. That must be tackled head on. It has been a recurrent theme. We have mentioned it many, many, many times."[8]

Cross-institute issues likely affect more than just funding. It would be similarly difficult to cobble together a strategy, given the narrow slices of self-interest expressed by the various institutes in the different funding announcements posted on the Trans-NIH ME/CFS website.

References

[1] Ramsay issued two articles on the definition, one in 1986 and one in 1988.
Ramsay, M. "Myalgic Encephalomyelitis: A Baffling Syndrome With a Tragic Aftermath." Published 1986. http://www.cfids-me.org/ramsay86.html

Includes the following core symptom "One of the Muscle fatigability, whereby, even after a minor degree of physical effort, three, One of four or five days, or longer, elapse before full muscle power is restored and constitutes the sheet anchor of diagnosis."
Ramsay, M. *Myalgic Encephalomyelitis and Postviral Fatigue States: The Saga of Royal Free Disease,* Gower Medical Publishing Corporation, London, 2nd ed. 1988.

Papers on CPET include

- Davenport TE, Stevens SR, Baroni K, Van Ness M, Snell CR. "Diagnostic accuracy of symptoms characterizing chronic fatigue syndrome." *Disabil Rehabil* 2011; 33(19-20): 1768-75. PMID: 21208154 http://dx.doi.org/10.3109/09638288.2010.546936
- Snell C, Stevens S, Davenport T, Van Ness M. "Discriminative Validity of Metabolic and Workload Measurements for Identifying People With Chronic Fatigue Syndrome." *Physical Therapy* November 2013; 93(11): 1484-1492. PMID: 23813081. http://dx.doi.org/10.2522/ptj.20110368
- VanNess JM, Stevens SR, Bateman L, Stiles TL, Snell CR. "Post-exertional malaise in women with chronic fatigue syndrome*." J Womens Health (Larchmt)* February 2010; 19(2): 239-44. PMID: 20095909. http://dx.doi.org/10.1089/jwh.2009.1507
- Replication studies by Keller and Vermeulen.
  - Keller, B., Pryor, J., Giloteaux, L. Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO2peak indicates functional impairment. Journal of Translational Medicine April 2014, 12:104. PMID: 24755065. http://dx.doi.org/10.1186/1479-5876-12-104
  - Keller B, Micale F. "Exercise Testing to Quantify Effects of Fatigue on Functional Capacity in Patients With CFS." Abstract of presentation given at IACFS/ME Biennial Conference; Translating Evidence Into Practice. 2011. Ottawa, Ontario, Canada. http://iacfsme.org/LinkClick.aspx?fileticket=%2BG6GTkbP33I%3D&tabid=499
  - Vermeulen RC, Kurk RM, Visser FC, Sluiter W, Scholte HR. "Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity." *J Transl Med,* 2010. 8: p. 93. http://dx.doi.org/10.1186/1479-5876-8-93
- Snell, C. "Repeated CPET Results as Clinical Endpoints for ME/CFS Research." Presentation to U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). "Drug Development For Chronic Fatigue Syndrome And Myalgic Encephalomyelitis: Public Workshop. Day Two. Scientific Drug Development Meeting." April 26, 2013. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM355406.pdf (Page 201) Video http://www.tvworldwide.com/events/fda/130425/globe_show/default_go_archive.cfm?gsid=2251 Starting at
- Keller, B., Pryor, J., Giloteaux, L. Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO2peak indicates functional impairment. Journal of Translational Medicine April 2014, 12:104. PMID: 24755065. http://dx.doi.org/10.1186/1479-5876-12-104
  "ME/CFS patients currently represent a unique class of ill patients who do not reproduce maximal CPET measures, unlike individuals with cardiovascular disease, lung disease, end-stage renal disease, pulmonary arterial hypertension and cystic fibrosis."

"CFSAC recommends that you will promptly convene (by 12/31/12 or as soon as possible thereafter) at least one stakeholders' (Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS)experts, patients, advocates) workshop in consultation with CFSAC members to reach a consensus for a case definition useful for research, diagnosis and treatment of ME/CFS beginning with the 2003 Canadian Consensus Definition for discussion purposes

[2] The best estimate of economic impact comes from Jason's study, which was based in part on numbers from Reynolds et al (a CDC study). Jason reported estimated lost productivity at $17B. Jason also estimated direct medical costs at $2,342 per patient in a community based sample and $8,675 per patient for patients in a tertiary setting. Using the prevalence of 836,000 patients, he estimated direct medical costs ranging from $2B to $7B and an estimated total economic impact of $19B to $24B for lost productivity and direct medical costs.

- Reynolds, K., Vernon, S., Bouchery, E. and Reeves, W. "The economic impact of chronic fatigue syndrome." *Cost Effectiveness and Resource Allocation* 2004, 2:4. PMID: 15210053. http://dx.doi.org/10.1186/1478-7547-2-4
- Jason LA, Richman JA, Rademaker AW, Jordan KM, Plioplys AV, Taylor R, McCready W, Huang, CF, Piloplys, S. "A community-based study of chronic fatigue syndrome." *Archives of Internal Medicine* October 1999; 159(18): 2129-2137. PMID: 10527290. http://dx.doi.org/10.1001/archinte.159.18.2129
- Jason L, Benton M, Valentine L, Johnson A, Torres-Harding S. "The Economic impact of ME/CFS: Individual and societal costs." *Dynamic Medicine* April 2008, 7:6. PMID: 18397528. http://dx.doi.org/10.1186/1476-5918-7-6

[3] Nacul, L. Presentation at the P2P workshop. http://videocast.nih.gov/summary.asp?Live=14723&bhcp=1 Time 2:28

"The first question we need to answer is What. What are we interested in studying? What is ME/CFS? And I am sure that each and every one of you in this audience will have a concept in your own minds of what ME or CFS means. But I doubt many of you will agree with each other about what this concept is. So basically, we are not sure what we are studying. And this is the main limitation to describe the epidemiology of any condition." "Let me illustrate what I mean. If we use the Fukuda criteria, CDC 1994, which is probably the most widely used criteria, its quite non-specific. It's a negative criteria." It mentions in this criteria not explained by disease, not relieved by rest, not due to exertion and so on."

"[Unclear]… asks for the need for 4 out of 8 symptoms to be present so that definition is met. And this means 163 combinations of symptoms or possible combinations of symptoms that patients may have to be classified as having CFS. If for example we added post-exertional malaise as one of the criteria, a compulsory criteria, then the number of combinations of symptoms that make a diagnosis would drop to about 35. SO it seems that there may be an advantage of having more restrictive criteria.

[4] Papers describing the biopsychosocial model and the postulated role of psychological factors in perpetuating the disease and putting patients at risk

- Flo, E., Chalder, T. "Prevalence and predictors of recovery from chronic fatigue syndrome in a routine clinical practice." Behavior Research and Therapy. December 2013. 63:1-8. doi:10.1016/j.brat.2014.08.013

  "Our original cognitive behavioural model of CFS suggested that an initial trigger such as a virus may contribute to a vicious cycle in which the individual avoids activity for fear of making symptoms worse. In an effort to manage symptoms people become hypervigilant and this so called symptom focusing can exacerbate symptoms. Surawy and colleagues subsequently added to the model by suggesting that pre-morbid characteristics such as conscientiousness and perfectionism contributed to individuals becoming vulnerable. In addition, patients with CFS were more likely to hold the belief that showing emotions was unacceptable. Cognitive behavioural therapy (CBT) addresses these factors but in particular focuses on encouraging patients to become more consistent in engaging in activity before increasing activity thereby challenging fearful cognitions such as fear avoidance beliefs and catastrophising whilst simultaneously addressing symptom focussing."
- Larun L, Odgaard-Jensen J, Brurberg KG, Chalder T, Dybwad M, Moss-Morris RE, Sharpe M, Wallman K, Wearden A, White PD, Glasziou PP. "Exercise therapy for chronic fatigue syndrome (individual patient data)." *Cochrane Database of Systematic Reviews* April 2014, Issue 4. http://dx.doi.org/10.1002/14651858.CD011040

  "The biomedical model explains the illness as caused by abnormalities of the immune, central nervous or endocrine systems and/or a persistent infectious agent. The multifactorial biopsychosocial model distinguishes between precipitating and maintaining factors. Precipitating factors may include acute infective illness and/or excessive stress, while the illness is maintained by the interaction of behavior, thoughts, emotions and physiology. For example, after a severe infection or other illness, attempts to get back to normal life may result in bursts of activity punctuated by the need to rest up to recover, known as all-or-nothing behavior. These periodic bursts of activity may exacerbate symptoms and result in failure, which further reinforces sufferers' belief that they have a serious, ongoing illness. As time goes by, efforts to meet previous standards of achievement are abandoned and patients become increasingly inactive and distressed by their ongoing symptoms. Inactivity in turn leads to physiological changes such as cardiovascular and muscular deconditioning, dysregulation of the hypothalamic-pituitary-adrenal axis and disrupted circadian rhythms. In this deconditioned state, any activity is liable to produce symptoms, the experience of which reinforces the fearful beliefs and hence reinforces the avoidance of activity (fear avoidance)."Pace model of CBT and GET is based on the biopsychosocial model

[5] Pace model of CBT and GET is based on the biopsychosocial model

White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M. "Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial." *The Lancet* March 5, 2011; 377(9768): 823-836. PMID: 21334061. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext

- The study report states that PACE subscribes to the "fear avoidance theory of chronic fatigue syndrome" that "assume that the syndrome is perpetuated by reversible physiological changes of deconditioning and avoidance of activity." Page 825
- Additional information is provided in the PACE trial manuals, available through the PACE Trial information website http://www trial.org/trialinfo/
  - PACE trial CBT Manual
    Burgess M, Chalder T. "PACE Manual for Therapists. Cognitive Behavioral Therapy for CFS/ME." MREC Version 2. November 2004. http://www.pacetrial.org/docs/cbt-therapist-manual.pdf
    The manual states "It is important to include the precipitating factors, e.g., illness, life-events, working excessively hard, perfectionist personality etc. It is also important to discuss the maintaining factors, e.g., erratic or reduced activities, disturbed sleep patterns, unhelpful illness beliefs and any other unhelpful cognitions etc." (Page 81)
  - PACE trial GET Manual
    PACE Trial Management Group. "PACE Manual for Therapists. Graded Exercise Therapy for CFS/ME.".Version 2. http://www.pacetrial.org/docs/get-therapist-manual.pdf . Last accessed December 2014.

The manual makes the following statements:

"GET assumes that CFS/ME is perpetuated by deconditioning (lack of fitness), reduced physical strength and altered perception of effort consequent upon reduced physical activity." (Page 20).

"The aim of this treatment is to reverse the physical inactivity that helps to maintain CFS/ME, and to re-engage the participant in physical activity." (page 20)

"Planned physical activity and not symptoms are used to determine what the participant does." (Page 21)

- Chalder T, Goldsmith K, White P, Sharpe M, Pickles A. "Rehabilitative therapies for chronic fatigue syndrome: a secondary mediation analysis of the PACE trial." The Lancet. January 13, 2015 http://dx.doi.org/10.1016/S2215-0366(14)00069-8

[6] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. November 9, 2011. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac_min-11092011.pdf (page 30)

[7] U.S. Department of Health and Human Services CFS Advisory Committee. "CFSAC Recommendations - June 16-17, 2014." CFS Advisory Committee. June 16-17, 2014. *CFS Advisory Committee Website.*

- Recommendation from CFSAC to Secretary Burwell.
  http://www.hhs.gov/advcomcfs/recommendations/06142014.html
  "CFSAC recommends that the NIH issue a Request for Applications (RFA) for ME/CFS by November 1st, 2014, or as soon as feasible, to address the gaps in ME/CFS knowledge and research. The RFA should consider current known gaps in knowledge for the following areas:
  - "Provocation designs where symptoms are triggered through standardized challenges involving exercise, cognitive tasks, and mental stressors. These designs appear to be more likely to identify symptom to biology relationships in comparison to assessments done in resting states."
  - "Ambulatory monitoring of symptoms, activities, behaviors, and physiological states that identify associations between biological and behavioral measures, e.g., daily fatigue ratings and cytokine fluctuations."
  - "Network analysis of dysregulation of multiple bodily systems, such as the neuroendocrine system, the central nervous system, the autonomic nervous system and the immune system."
  - "Natural history studies aimed at identifying the genetic triggers and causal factors of ME/CFS."
  - "Treatment trials that address both clinical and biologic outcomes. This RFA may also be informed by the gaps identified in the 2011 NIH State of the Knowledge Workshop, the Pathways to Prevention Program for ME/CFS research panel report or any relevant source, including but not limited to, the IACFS meeting summary. This RFA should encourage investigators to use the NIH data and biobank sharing platform (subject of an accompanying recommendation to this recommendation), if such a platform is established at the time of release or becomes available during the time awards are made on this RFA."
- HHS response from Secretary Burwell to Dr. Susan Levine (Chair CFSAC). October 29, 2014.
  http://www.hhs.gov/advcomcfs/recommendations/letter-to-slevine-from-sburwell-june-2014-recommendations.pdf

HHS Response

"Unfortunately there remains a lack of definitive evidence regarding the etiology, diagnosis, and treatment for ME/CFS. As such, issuing a Request for Applications (RFA) would not be an effective strategy as RFAs generally encourage a narrowly defined research area that addresses more specific gaps in scientific knowledge. RFAs are designed to build upon recommendations that have been identified through cutting- edge research findings in the extant literature, that address unmet NIH Institute mission-specific objectives, or that incorporate findings from workshops and conferences on specific topics"

[8] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. November 9, 2011. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac_min-11092011.pdf (page 30)