

Department of Health and Human Services  
Chronic Fatigue Syndrome Advisory Committee (CFSAC)  
Research Work Group  
Background for Recommendations

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## Introduction

The ME/CFS Researcher and Clinician-Scientist Recruitment Workgroup was established during the May 22 – 23, 2013 meeting and was charged with the following:

The Research Work Group was charged with the specific task of identifying problems and barriers to increasing research in ME/CFS. The primary goal of the work group was to provide an evidenced-based and actionable set of recommendations to the Secretary aimed at “increasing awareness among basic and clinical researchers about ME/CFS research and suggesting strategies to increase the number of interested researchers who will apply for current and future research funding opportunities”.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating illness that is characterized by persistent symptoms of fatigue, pain, cognitive impairment, sleep disturbance and muscle weakness and is associated with signs of autonomic, immune and central nervous system abnormalities (Carruthers et al., 2003; Fukuda et al., 1994). ME/CFS is estimated to affect roughly one million men and women in the United States of America and 17 million worldwide (Jason et al., 2008; Johnston et al., 2013) and may be more prevalent among minority groups and those with low socioeconomic status (Dinos et al., 2009; Jason et al., 1999). The social and economic impacts of ME/CFS are staggering with billions of dollars in health care costs, family strife and lost productivity (Jason et al., 2008; Reynolds et al., 2004). There are no known causes of ME/CFS and there are no verified efficacious treatments for the illness. Research has demonstrated abnormalities across a multitude of biological systems including the autonomic nervous system (Cauwenbergh et al., 2014), the hypothalamic pituitary adrenal axis (Papadopoulos and Cleare, 2011), the immune system (Klimas et al., 2012), and the brain (Chen et al., 2008; Natelson, 2013). Evidence of the heritability of ME/CFS is emerging (Albright et al., 2011). The multitude of systems involved in the pathophysiology of ME/CFS and the diversity of abnormalities identified within these systems was recently highlighted at the National Institutes of Health, State of the Knowledge Work Shop – Myalgic encephalomyelitis /Chronic Fatigue Syndrome ([http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH\\_SKW\\_Report.pdf](http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH_SKW_Report.pdf)). Noting the wide array of scientific disciplines that are relevant for the study of ME/CFS the workshop concluded with two key mechanisms for “moving forward”.

The first was –

“The study of ME/CFS can benefit from an interdisciplinary collaborative approach using well-connected clinical and research networks. Moreover, additional highly qualified investigators must be attracted to study ME/CFS.”

The second was –

“To capture the extensive information from such studies (clinical trials), a centralized interactive database, using common data elements and accessible to everyone, is sorely needed to collect, aggregate, store, and analyze results.”

## Rationale and Evidence for the need for a Data Sharing Platform and a Request for Applications

The Research Work Group for the CFSAC was charged with providing an evidence-based recommendation to the Secretary of Health and Human Services (HHS) specifically addressing: (1) the dearth of awareness among various research communities about ME/CFS; and (2) an effective mechanism to increase the number of investigators who apply for ME/CFS research funding. After much deliberation and debate the committee came to the conclusion that the most effective way to increase awareness and to attract the best and brightest researchers was to provide robust research opportunities. The first critical step would be to establish the infrastructure necessary to accelerate CFS research. This would take the form of a data sharing platform (e.g. National Database for Autism Research (NDAR) example below) to harness both completed and future ME/CFS research. The second critical step would be to release a Request for Applications (RFA) that is informed principally by the evidence reported during the *State of the Knowledge Work Shop – Myalgic encephalomyelitis/Chronic Fatigue Syndrome*, but could also be informed by the various efforts of the federal government to advance ME/CFS including but not limited to the FDA drug development planning series for ME/CFS and the Pathways to Prevention (P2P) program for an ME/CFS evidenced-based methodology workshop (<https://prevention.nih.gov/programs-events/pathways-to-prevention/upcoming-workshops/me-cfs/working-group>). Thus, any RFA should capitalize on the past and current efforts of the National Institutes of Health (NIH).

A major limitation to ME/CFS research progress has been a lack of infrastructure that facilitates the use of common data elements and allows sharing of data between researchers. By using the word “infrastructure” we mean a platform where data can be federated<sup>1</sup>, aggregated, collected, stored and analyzed. Data types would include phenotype data (similar to what is collected in a registry) and biological data (e.g., genomic, neuroimaging, etc.). Currently there are several smaller independent data collection efforts ongoing including those being done by the Centers for Disease Control and Prevention, a private effort called the Chronic Fatigue Initiative, the SolveCFS BioBank and the NIH’s small collection of biological samples. A centralized data sharing platform would greatly accelerate research discovery for ME/CFS; federation among these smaller efforts would be an ideal start.

Overall, the existence of a relatively small research community combined with a heterogeneous patient population has resulted in a multitude of inconsistent and often conflicting data. As a result, potential biomarkers have not been validated, no FDA approved treatments exist for this patient population, and neither the etiology of the disease nor the causes of symptom maintenance and/or exacerbation are well-understood. Thus, our recommendation requests that NIH leverage existing internal/intramural infrastructure technology to establish a data sharing platform for ME/CFS research. Collaboration within the existing ME/CFS research community and opportunities for new scientists to enter the field needs to be fostered by a central platform that lowers the barriers to conducting ME/CFS research. As an example, we provide evidence from the NDAR.

### An Example of Infrastructure: NDAR

- NDAR (<https://ndar.nih.gov/ndarpublicweb/aboutNDAR.html>) is a joint initiative sponsored by the NIMH, NICHD, NINDS, and NIEHS and supported through federation with several private partners including the Autism Tissue Program Autism Speaks,

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<sup>1</sup> Federated data are external databases that can be acquired and shared virtually while the original data remain at the host site.

(<http://www.autismtissueprogram.org/site/c.nIKUL7MQIsG/b.5183271/k.BD86/Home.htm>), the Autism Genetic Resource Exchange (<https://research.agre.org/>) and the Interactive Autism Network at the Kennedy Krieger Institute (<https://www.ianresearch.org/>). NDAR is a prime example of how research infrastructure can accelerate discovery and provide a pathway for collaboration and transdisciplinary research. NDAR was named one of the top 10 research advances of 2011 (<http://www.nimh.nih.gov/about/director/2011/nimhs-top-10-research-advances-of-2011.shtml>) and was awarded an HHS Innovates award from Secretary Sebelius that same year. NDAR is a biomedical informatics system designed to optimize autism research through data sharing. The NDAR platform has several attractive features that would benefit ME/CFS research and that would attract new investigators. These include:

1. A data sharing platform that creates a large database for hypothesis testing and research discovery using a standardized and adaptable data entry interface;
2. A common data dictionary and data standards that can be applied across studies thereby creating a mechanism for collaboration among researchers that use differing methodologies;
3. Opportunities to connect with other public and private data repositories through federation (i.e. linking data);
4. Protection of patient privacy through globally unique identifiers (GUIDs);
5. Protection of investigator intellectual property by allowing collaborations to occur within the protected large database environment.

#### **The success of NDAR:**

1. NDAR currently reports data sharing for 77,000 patients and recently federated with Simons Foundation Autism Research Initiative to provide access to 10,000 autism patients.
2. Currently, there are 350 terabytes of exome data in the NDAR cloud that are being used for validation of genomic findings. This highlights the power of a data sharing platform; importantly these data are being analyzed using standardized and consistent data definition and analytic approaches.
3. Researchers have run 12 years' worth of computations in each of the last two months, demonstrating how research can be accelerated in the presence of a large data sharing and informatics platform.
4. NDAR provides the ability to query data. For example, within NDAR, investigators can query omic<sup>2</sup> data ([http://ndar.nih.gov/query\\_data.html?showOmics=true](http://ndar.nih.gov/query_data.html?showOmics=true)) for studies with options for the alterations of interest and type, the chromosome and cytoband of interest and the biological region (e.g. IL-1) and type (e.g. gene, protein, etc.) The value of this capability for ME/CFS research cannot be understated. A platform similar to this for ME/CFS research could harness current and future tax-payer funded research.
5. The ability to validate imaging results using several different pipelines is another strength NDAR has with relevance for ME/CFS research.
6. A large increase in approved scientists accessing autism data has been documented. In 2011, there were 20 approved scientists. In 2013, there were about 350 scientists from 7 countries and 80 labs. Notably, new investigators accounted for much of the increase.
7. Finally, the NDAR platform has begun to be adopted by other institutes within NIH.

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<sup>2</sup> "Omics" informally refers to a field of study in biology ending in *-omics*, such as genomics, proteomics or metabolomics.

## **Rationale for a Request for Applications (RFA)**

Our recommendation to the Secretary is that the NIH dedicates money to ME/CFS research in the form of a RFA – one that capitalizes on the past efforts of the State of the Knowledge Workshop ([http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH\\_SKW\\_Report.pdf](http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH_SKW_Report.pdf)), the current efforts of the P2P Program for ME/CFS research (<https://prevention.nih.gov/programs-events/pathways-to-prevention/upcoming-workshops/me-cfs/working-group>) and the current efforts of the Institute of Medicine (IOM) Committee (<http://www.iom.edu/~media/Files/Activity%20Files/Disease/ME/CFS/Maier%20IOM%20ME/CFS%20Presentation.pdf>). Thus, the RFA should be informed by the State of the Knowledge Workshop and the P2P panel report and should address the critical gaps in ME/CFS research identified therein. Depending on the timing of release, the RFA could also be informed by the IOM Committee's report concerning diagnostic criteria for ME/CFS (<http://www.iom.edu/Activities/Disease/DiagnosisMyalgicEncephalomyelitisChronicFatigueSyndrome.aspx>).

Attracting new researchers requires people dedicated to the task. A NIH RFA for ME/CFS research would supply the dedicated NIH staff necessary manage the funding opportunities. They could write the funding announcement, assist with recruiting investigators, recruit peer reviewers and screen letters of intent. Combined with robust infrastructure and a data sharing platform, an RFA could result in rapid scientific discovery. Simply stated, an entity such as the NIH is necessary not only for providing the funds to attract new investigators interested in ME/CFS research, but also providing the experience to market the call and manage the opportunity. This could include staff dedicated to helping craft a funding opportunity that targets scientists doing the most impactful and relevant research and then marketing the opportunity to those investigators. The existing Trans-NIH ME/CFS Research Working Group is ideally positioned to promote this type of research opportunity (<http://orwh.od.nih.gov/research/me-cfs/index.asp>) and indeed has been set for such a role following the State-of-the-Knowledge workshop.

We are aware that CFSAC has made this recommendation on numerous occasions; however recent efforts at both federal and local levels demonstrate the need and timeliness of this recommendation (i.e. it is time to capitalize on past and current investments). In particular, the evidence contained within our work group report highlights the need for a new RFA, one that takes advantage of the projects described above and that leverages these efforts within a powerful data sharing platform.

The most recent CFSAC recommendation for a RFA for ME/CFS research occurred at the October 3-4, 2012 public meeting and recommended that the Secretary “instruct the NIH to issue an RFA (funded at the \$7-10 million range) for projects to establish outcomes measures for ME/CFS diagnosis, prognosis and treatment which would include but not be limited to biomarker discovery and validation in patients with ME/CFS”. The Secretary's response can be found here - (<http://www.hhs.gov/advcomcfs/recommendations/response-from-ash-10-2012.pdf>). Highlighted within this response were the current and past investments by the NIH and several other federal agencies and many of these are detailed within this recommendation.

It is clear that the HHS and the NIH have taken significant steps towards addressing the patient and research needs of the ME/CFS community. Our current recommendation is intended to capitalize on this effort, continue the momentum generated by these efforts and make significant progress towards increasing investigator awareness and participation in ME/CFS research. An RFA that continues the momentum generated by the NIH State of the Knowledge workshop, is guided by the P2P report and that is fueled by the

availability of a data sharing platform (i.e. infrastructure) will be both timely and focused on the research questions that are most pressing for this patient population and will establish a much-needed “road map” for ME/CFS research.

### **Examples of what a RFA might contain (subject to P2P report)**

The work group recognizes and appreciates the current investment by the NIH, FDA, CDC and IOM towards identifying gaps in our current understanding of ME/CFS pathophysiology (<http://orwh.od.nih.gov/research/me-cfs/> & <https://prevention.nih.gov/programs-events/pathways-to-prevention>), determining the parameters of drug development for ME/CFS (<http://www.fda.gov/Drugs/NewsEvents/ucm319188.htm>), expanding research on symptom constructs (<http://www.cdc.gov/cfs/programs/clinical-assessment/index.html>), and addressing the uncertainty of disease definition (<http://www.iom.edu/Activities/Disease/DiagnosisMyalgicEncephalomyelitisChronicFatigueSyndrome.aspx>). These efforts reflect current research efforts occurring across the country and demonstrate that CFS is in the midst of a period of great discovery. Advances over the past decade in biomedical and behavioral research in chronic conditions have indicated the utility of several methodologies in illuminating the dynamic interplay of symptoms and biology that may increase our understanding of the mechanisms related to causation and perpetuation. These methodologies include:

1. 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.
2. 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.
3. 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.
4. Natural history studies aimed at identifying the genetic triggers and causal factors of ME/CFS.
5. Treatment trials that address both clinical and biologic outcomes.

These advances in research were highlighted during the International Association for Chronic Fatigue Syndrome’s (IACFS/ME) International meeting this year in San Francisco (<http://www.iacfsme.org/Conferences/2014Conference/tabid/532/Default.aspx>) where the world’s leading experts on ME/CFS gathered to showcase and discuss the current state-of-the-knowledge based on innovative research and future needs of ME/CFS research. An elegant audio summary of the meeting was provided by Dr. Anthony Komaroff and can be accessed from the following link (<https://www.dropbox.com/s/vame7msb9h6nnfs/DrKomaroff.MP3>). The importance of an RFA for ME/CFS was quickly recognized by Congress who wrote an open letter to Dr. Francis Collins urging the NIH to invest in ME/CFS research, as well as the Board of Directors for the IACFS/ME. Both letters are included as appendix materials for the Secretary (See attached). The Director of the Office of Research on Women’s Health recently responded (See attached) to the open letter by detailing the efforts that have been taken by NIH and other federal agencies following the 2011 State-of-the-Knowledge Workshop. Highlighted within the letter was that an RFA should be informed by the current P2P and IOM efforts. Our recommendation to the Secretary is sensitive to this issue and appears consistent with the expectations of the NIH for ME/CFS research.

## **Evidence Gathered to Support Our Recommendations**

As part of the Research Work Groups charge, we sought to provide evidence showing a need for “basic and clinical researchers” to solve the puzzle that is ME/CFS and to propose a mechanism to increase the number of interested researchers who will apply for current and future research funding opportunities. The evidence gathered is detailed below.

### ***ME/CFS Research Publication Rates:***

We examined publications rates of CFS research and compared them to publication rates from other similar illnesses, including fibromyalgia and general fatigue unspecified. The report analyzed the annual number of peer-reviewed, published articles over the past decade in the subject areas (Search Terms) of Fatigue, Fibromyalgia, and Chronic Fatigue Syndrome. Medline-indexed articles were included that contained at least one of these search terms in the title. All non-peer reviewed material (e.g., letters to the editor) was excluded.

What we discovered was revealing. Publication rates for ME/CFS research have been relatively flat for the past decade, while publication rates for fibromyalgia and general fatigue have risen over the same time period. When quantified, publication rates for the decade rose 81% for fatigue, 101% for fibromyalgia and 39% for CFS. These results show remarkably small increases in ME/CFS publication rates over the past decade in comparison to fibromyalgia and fatigue. These data suggest that research output in the field of ME/CFS is considerably below related illness conditions. This may be attributable to (a) low levels of research funding; (b) a small number of active research scientists in the field; and/or (c) few new researchers entering the field. Regardless, low publication rates lead to low awareness of the state-of-the-knowledge among the scientific community. There is a clear need for increased publication rates in ME/CFS. The most direct solution to correct this deficit is to provide new researchers with a data sharing platform that encourages collaboration, exploration, and funding opportunities (i.e. a RFA) to support both analysis of existing data and collection and sharing of new data.

### **Barriers and Solutions to Increasing ME/CFS Research**

The Research Work Group was fortunate to have several patient organizations involved in the discussions. Based on their combined experience, we detailed the barriers and solutions to fulfilling our charge. Barriers that were identified included:

- Potential new investigators avoid studying ME/CFS because they lack critical knowledge about the illness. This directly and negatively impacts the rate of new investigators entering the field and limits the number of applications for ME/CFS research funding. Establishing a data sharing platform such as NDAR clears many of the hurdles by providing standardized clinical information, psychometric instruments, and a community of researchers with whom to collaborate.
- There is currently a lack of partnerships within and between agencies and patients/advocacy organizations and there is a need to do a better job of communicating with patients and the advocacy groups. Thus, there is limited access to a pool of well-characterized patients which directly limits the number of investigators capable of conducting ME/CFS research and provides a major barrier to proposing fundable projects (i.e. no proof that patients can be recruited).
- There is a current lack of funding that translates into tangible outcomes. The lack of infrastructure/data sharing has had a significant and negative impact on ME/CFS research. In reality, there are many interesting research findings in ME/CFS, but these data have not been archived or shared in a way that allows us to understand the disease.

- The lack of infrastructure/data sharing has also led to lack of valid data standards, endpoints and outcomes. This is despite the fact that fatigue is a universal symptom.
- The lack of a patient registry is a major barrier to studying a disease that is heterogeneous with respect to its symptom complex and where patients have trouble finding doctors to provide a valid diagnosis. Thus, the field lacks a database of well-characterized patients. In addition, the field also lacks access to biological material from well-characterized patients.
- A poor funding history is also a recognized barrier to further CFS research.

In order to overcome these barriers we need to:

- Create a supporting infrastructure (e.g. data sharing platform) that optimizes collaborative research opportunities for ME/CFS.
- Provide funded research opportunities that encourage/require data sharing within the established data sharing platform.

Such a robust research strategy would lead to the formation of new partnerships and enhance those that currently exist. The expansion of the ME/CFS research community would accelerate research progress and thus increase the likelihood of a scientific break-through for this debilitating disease. Current efforts of the Solve ME/CFS Initiative (SMCI: formerly The CFIDS Association of America) are a smaller scale example of what is possible when researchers are given the opportunity to collaborate and share data. During the past 4 years, twelve ME/CFS research projects have been conducted using the clinical information and biological samples available in the registry and biobank (SolveCFS BioBank - <http://solvecfs.org/solvecfs-biobank/>) that the SMCI started in 2010. All but one of these research investigators are new to ME/CFS research and include some of the brightest investigators (a Lasker laureate and an HHMI investigator) from some of the best medical institutions (Harvard, Columbia). Several of these investigators are applying innovative technologies they developed to the samples in the repository. There is an urgent need for a larger scale effort such as NDAR accomplished for Autism research for ME/CFS research.

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