

Response to National Institutes of Health Notice Number: NOT-NS-16-024  
Request for Information: Soliciting Input for New Research Strategies for Myalgic  
Encephalomyelitis/Chronic Fatigue Syndrome.  
June 24, 2016.

Thank you for the opportunity to provide information to NIH as it develops new strategies to guide NIH's research efforts and priority setting for ME/CFS research. This response addresses the topics "Challenges and barriers to making rapid progress" and "Gaps and opportunities across the research continuum."

As NIH knows, thirty years of neglect have left the basic research infrastructure in this field in significant disarray – few researchers, academic centers, or pharmaceutical companies; little biomedical research; a polluted evidence base; and even lack of clarity on who the patients are. Significant investment from NIH will be required to correct these problems and establish the kind of research ecosystem required to make rapid progress.

There can be little question that there are many scientific opportunities to advance research in this field and make rapid and substantial improvements in diagnostics and treatment. What is not clear is whether NIH will make the magnitude of commitments needed to do this in a timescale that matters to patients whose lives are being destroyed. For the sake of patients, NIH must quickly address the institutional, process, policy, and funding challenges and barriers that have both left this field in disarray and are impeding the ability to make rapid scientific progress.

If you need any additional information, don't hesitate to contact us through Mary Dimmock.

Signed:  
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## **I. Challenges and barriers to making rapid progress**

- A. **Quickly ramp up committed budget:** Dr. Collins has indicated that funding for ME/CFS will be "substantially greater" than current levels and that NIH is going to "ramp this up." NIH has announced new initiatives and indicated that additional initiatives are coming. However, NIH has not said how much money each of the key institutes intends to provide annually, starting with 2016. What little is known suggests that the funding provided in each of the next three to five

years will be far short of what is needed to accelerate research and achieve meaningful outcomes in the short term for these terribly disabled patients.

At the CFSAC in May of 2016, Stanford's Dr. Montoya challenged NIH to quickly come up with the \$100 million that is required to get this field going. Estimates based on burden of disease and economic impact suggest \$250 million is needed. This level of funding is justified by scientific opportunity and researcher demand. But it is also needed to proactively establish the research ecosystem and infrastructure needed to make rapid progress. A tripling of the budget or even a budget of \$30 or \$40 million is woefully inadequate given the magnitude of the need.

To achieve the needed level of funding, each key NIH institute needs to make a substantial financial commitment to this disease on an ongoing basis, starting with 2016. NIH can take advantage of the infusion of \$2 billion new dollars in 2016 to work around the long lead-time of NIH's normal budgeting process and the concern voiced that dollars have already been allocated to other diseases, dollars that should have been allocated to this disease all along.

Obviously, money alone will not solve the substantial problems in this field. But a plan that has been throttled because of a lack of funds and commitment will not solve these problems either. NIH and its institutes need to make the level of financial and strategic commitment - starting immediately - that is required to make substantial progress. These patients should not have to continue to wait for more years because of the failure to do so.

## **B. Address NIH institute, process, and policy barriers**

- i. Institute Commitment and Home: NIH has decided to organizationally position ME/CFS only in a trans-NIH Workgroup and not in an institute, with the rationale that ME/CFS is a multi-system disease. A review of trans-NIH disease-specific workgroups suggests that few if any other diseases, including other multi-system diseases, exist only in a Trans-NIH Workgroup and not also in a home institute. Using a non-standard organizational approach for ME/CFS risks leaving this disease outside the normal NIH budgeting and strategic planning processes, which are largely institute-based.

Further, while NINDS has provided reinvigorated leadership to the Trans-NIH ME/CFS workgroup, it is not yet clear how the use of a Trans-NIH Workgroup will translate into the financial and strategic commitment that must be made by each of the key institutes. How much budget is each key institute willing to commit? Will each key institute make this disease part of its core mission and strategic goals and consider the disease as such at grant review time?

The lack of a committed "home" institute and the lack of financial commitment of the other key institutes have impeded progress on this disease for many years. NIH will need to demonstrate to the community how this model has worked effectively for other diseases and that NIH is able to generate the needed financial and strategic cross-institute commitment for ME/CFS. Otherwise, NIH needs to place ME/CFS in the appropriate institute.

- ii. Support for hypothesis-generating research: As a result of the lack of research, little is known about the pathology and etiology of this disease. Because of the state of the field, hypothesis-generating research is essential. However, NIH reportedly prefers to fund investigator-initiated research that is based on defined hypotheses.<sup>1</sup> Generating those

hypotheses requires funding from private sources, something that is difficult to obtain in this field because of the level of stigma and misunderstanding associated with this disease. To help quickly jump-start this field, NIH needs to provide a mechanism to fund investigator-initiated hypothesis-generating research in the short term while the community builds the capacity to attract private funding for this purpose.

- iii. Fertilizing research: To its credit, NIH recognizes the disarray of the field and the need to build up the research infrastructure, which is largely absent. The recently announced consortium concept is a great step in the right direction. However, NIH's planned implementation of this concept will only establish a few consortia/sites initially followed by additional consortia/sites in later years, which would then eventually allow for clinical trials. Such an approach will take too long to deliver treatments to patients. NIH needs to expedite the timeframe for implementation of the consortium concept.

Further, NIH's announced consortium plans do not provide funds for the clinical care component, which will limit the effectiveness of these centers in both basic research and clinical trials. In other diseases, the community often funds this component but as noted above, the ME/CFS community is limited in its ability to raise funds because of the level of stigma and misunderstanding that was specifically noted in the 2015 report from the Institute of Medicine. While it is understood that NIH does not fund clinical care, NIH's leadership could encourage other funding sources, including HHS and private sources, to fund this essential component in the short term. This could help position the community to take on the support for this component over time.

- iv. Foster multi-disciplinary research: An article from Stanford noted that funding of NIH grants are "awarded through medical specialty groups that tend to favor research that tests one narrow hypothesis about a disease," an approach that is slow and can take years to "build on discoveries."<sup>2</sup> Research initiatives by both Drs. Montoya and Davis demonstrate the value of this multi-disciplinary approach for this disease. Unfortunately, these efforts have only happened because these scientists have been able to attract some private funding.

NIH's recently announced consortium concept could address this need although the NIH presentation on the concept primarily focused on its role in building research infrastructure and capacity. If the consortium will not address this need, NIH should examine what other approaches will.

- C. **Provide for meaningful engagement of the experts and patient advocates**: NIH has announced its intent to have patient advisory boards as part of its consortium concept. NIH has also held teleconferences with the community, has issued this request for information, and has stated that it is meeting with researchers. All of these are positive steps. However, NIH's planning efforts to date have appeared to be largely internally focused to NIH and HHS and NIH's intramural study has raised concerns with the choices made in case selection and study design. This is unfortunate as the community of researchers and patients have substantial knowledge about the disease. As NIH refines its approach to engaging experts and the patient community, it is essential that NIH provide mechanisms that proactively tap into the expertise of researchers and patients in the planning stages before decisions are made on strategy, priorities, study design, and research approaches.

- D. **Establish Rigorous Research Standards:** NIH, together with CDC, has announced plans to convene a meeting or series of meetings of researchers to agree on common data elements and methods for measuring them. This is good. However, common data elements alone do not specify what inclusion and exclusion criteria are mandatory and as a result, cannot ensure that the patients selected for ME/CFS research actually have the core features of the disease.

The impact of inaccurate case selection is huge in both research and in clinical care. As was clear in the 2015 AHRQ Evidence Review, what we think we know about the disease has been based on studies that included patients who did not have the disease. Many groups have recognized the need for a consistent research case definition. The 2011 State of Knowledge Workshop, the 2014 AHRQ evidence review, the 2015 P2P report, the 2015 IOM report, and the CFS Advisory Committee have all explicitly acknowledged the lack of diagnostic accuracy with CFS definitions such as Fukuda, Reeves, and Oxford that do not require core features of the disease<sup>3</sup> and/or called for a common research case definition.

To ensure accurate selection of patients with the disease described by the IOM, NIH must adopt not only common data elements but also and just as importantly, define the mandatory core inclusion and exclusion criteria that are required to accurately select patients. Fifty international experts have recommended that the Canadian Consensus Criteria be used in research, as has CFSAC. This case definition is already being used in much of the promising research being produced across the world today. At the Pathways to Prevention Workshop, Dr. Luis Nacul noted Fukuda's lack of specificity and recommended that patients satisfy both the Canadian Consensus Criteria and Fukuda, at least until a biomarker is validated. The alternative is to specify the minimum mandatory inclusion criteria that must be present in all research in this disease. At the least, this minimum set must include post-exertional malaise and other core features - such as cognitive impairment and unrefreshing sleep - that are required by all the ME definitions. Patients who do not meet these core criteria should not be identified as having the disease described by the IOM.

One additional note: To avoid confusion, cohorts that meet these core inclusion and exclusion criteria must be given a different label from those who do not - in studies as well as in sample repositories. For instance, the biobank developed by Dr. Nacul of the London School of Hygiene and Tropical Medicine includes both patients who meet the Canadian and also patients who meet Fukuda but not the Canadian Criteria. However, the biobank reportedly uses different labels for these two groups of patients to allow them to be distinguished.

## **II. Gaps and opportunities across the research continuum from basic through clinical studies.**

- A. **Speed delivery of treatments** - NIH's current plan for its intramural study has multiple phases that look at disease pathology, then at biomarkers, and finally at clinical trials. The consortium concept description included phases, with clinical trial "readiness" being a longer-term objective. However, such serial execution means that patients, many of whom have been waiting for decades for some kind of treatment, will need to wait for many more years before treatments are studied and finally approved. This is not acceptable, especially given the effectiveness already seen in current ME/CFS clinical trials and in off-label use of certain drugs, including immune modulators, B-cell depleting agents, and antivirals. These drugs have already demonstrated that they can deliver significant improvement in

functioning and quality of life for some patients but are largely inaccessible unless a patient is able to pay out of pocket and potentially relocate.

In partnership with FDA and disease experts, NIH needs to adopt a strategy that accelerates clinical trials *in parallel with* research into basic disease pathology and identification of biomarkers. Not only will this achieve the important goal of speeding delivery of treatments to patients, it will also help address the barriers in e.g. patient selection and outcome measures that are currently impacting clinical trials and investment by the pharmaceutical industry. This strategy can be successful but will of course require that NIH quickly address some of the other barriers discussed above, particularly in funding, the consortium concept, and the research case definition.

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<sup>1</sup> Newby, Kris. "Immune System Disruption. The Search for Answers." *Stanford Medicine. Balancing Act*. Fall 2014. <http://stanmed.stanford.edu/2014fall/immune-system-disruption.html>

<sup>2</sup> Ibid.

<sup>3</sup> At NIH's P2P Workshop, Dr. Luis Nacul pointed out that only 20% of the 163 unique combinations of Fukuda symptoms require PEM while Jason pointed out that in a review of 53 studies, as few as 25% of the patients in a given study had PEM and as few as 16% had unrefreshing sleep, criteria that are both mandatory according to the IOM. Jason has also pointed out that patients with mental illness but no physical impairment can also satisfy Fukuda because they can experience fatigue and satisfy Fukuda criteria such as impaired memory. Fukuda is clearly too non-specific to continue to be used as a research case definition for this disease.