

Camenzind, Mark

[...]

Subject: RFI: NIH should fund hyperbaric oxygen study for MECFS since used for several centers in US, & Studies done in Turkey

Hyperbaric oxygen shifts redox potentials and can be toxic to anaerobes.

Turkey did preliminary study of 16 patients (see attached), with positive short term results, but longer term study, more patients, and long term followup are needed.

We know personally two people with ME, incl Willa in NC, who recovered from ME after hyperbaric oxygen treatments, and other treatments, so more controlled studies needed to assess efficacy.

Dr. Mark Camenzind, R&D Advocate to Cure M.E. San Ramon, CA [...]

The efficacy of hyperbaric oxygen therapy in the management of chronic fatigue syndrome

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ABSTRACT

Objective: Chronic fatigue syndrome (CFS) is a chronic disease with social components that ensue secondary to the incapacity of the person to fulfill work, social and family responsibilities. Currently, there is no consensus regarding its treatment. The aim of this study was to determine the efficacy of hyperbaric oxygen (HBO₂) therapy in CFS.

Design: Sixteen patients included in the study were diagnosed with CFS according to the Fukuda criteria. Patients received 15 treatment sessions of HBO₂ therapy over a period of three consecutive weeks (five days per week). The outcome measures (visual analog fatigue scale (VAFS), Fatigue Severity Scale (FSS) and

Fatigue Quality of Life Score (FQLS) were assessed before the treatment and after completion of the 15 sessions.

Results: HBO₂ therapy was well tolerated, with no complications. After treatment, patients' scores were found to have improved with respect to VAFS, FSS and FQLS (all $p < 0.005$).

Conclusions: We may infer that HBO₂ therapy decreases the severity of symptoms and increases the life quality of CFS patients. It may be a new treatment modality for the management of CFS. However, further studies with larger sample sizes and control groups are definitely awaited.

INTRODUCTION

Chronic fatigue syndrome (CFS) is a clinically defined condition characterized by severe disabling fatigue and a combination of symptoms that prominently features self-reported impairments in concentration, short-term memory, sleep disturbances and generalized musculoskeletal pain for more than six months [1]. Its prevalence varies from 0.2% to 2.2% among adults, being twice as common in women as in men and affecting all social classes [2]. Diagnosis of CFS can be established only after other likely causes have been excluded.

Currently, there is no consensus regarding its treatment. Many patients try different therapies to overcome their fatigue, varying from pharmacological (e.g., immunoglobulin or corticosteroid therapy) to non-pharmacological treatments (e.g., massage and osteopathy) [3]. Because the conventional therapies are suboptimal, new

treatment modalities targeting different possible mechanisms of CFS pathogenesis are always drawing attention. Reactive oxygen species (ROS) and lactic acid – generated in active muscles – are suggested to have a critical role in the pathomechanism of fatigue [4-7]. Many mechanisms of action are possible given the susceptibility of proteins to oxidative damage, but current evidence points at the contractile proteins and the Na-K pump as the sites showing the greatest susceptibility to ROS under physiological conditions. Furthermore, the accumulation of lactic acid in muscle has historically been suggested to be the major cause of muscle fatigue [8].

In this regard, the strategies that aim to remove the ROS and lactic acid from the muscle cell seem to be reasonable for the treatment of CFS. One of them could be hyperbaric oxygen (HBO₂) therapy. Previous studies have reported significant decrease in lactic acid

[4,9,10] and ROS [11-16] after HBO₂ treatment. On the other hand, to our knowledge, there is no previous study evaluating the efficacy of HBO₂ in patients with CFS. Accordingly, the aim of this study was to determine the efficacy of HBO₂ therapy in CFS whereby ROS and lactic acid may play a significant role in its pathogenesis.

MATERIALS AND METHODS

This study was conducted at Gülhane Military Medical Academy Haydarpaşa Training Hospital, Department of Physical Medicine and Rehabilitation, Istanbul, Turkey, between 2011 and 2012 and was designed as a prospective clinical study. The study protocol was based on the declaration of Helsinki and approved by the local ethics committee. Before the study, patients gave written consent.

Participants

Patients ($n=16$) included in the study were diagnosed with CFS according to the Fukuda criteria [1] as follows:

- A. Clinically evaluated, unexplained persistent or relapsing chronic fatigue that is of new or definite onset (*i.e.*, not lifelong), is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities.
- B. The concurrent occurrence of four or more of the following symptoms: substantial impairment in short-term memory or concentration; sore throat; tender lymph nodes; muscle pain; multijoint pain without swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep; and post-exertional malaise lasting more than 24 hours.

These symptoms must have persisted or recurred during six or more consecutive months of illness and must not have predated the fatigue.

Patients with any past or current diagnosis of a major depressive disorder with psychotic or melancholic features, patients with contraindications for HBO₂ therapy and patients with physical diseases that could cause fatigue, including morbid obesity, hypothyroidism, Cushing's syndrome, anemia (blood hemoglobin <10 g/L), diabetes mellitus, active neoplastic or infectious disease were all excluded.

Complete blood count, erythrocyte sedimentation rate, C-reactive protein, and hepatic/renal/thyroid function tests were also evaluated. Patients were excluded if they had any abnormal laboratory results.

Treatment

Patients received 15 90-minute therapy sessions with HBO₂ at 2.4 atmospheres absolute (atm abs) on five days of the week (one session per day). No physical therapy or medication was given to ensure standardization among the patients and to detect the efficacy of HBO₂ therapy.

Clinical evaluation

Initially, general physical and substantial neuromusculoskeletal examinations were performed. Additionally, patients were evaluated before treatment and after completion of the 15 sessions in the following way. Fatigue was assessed by using a visual analog fatigue scale (VAFS) where 0 indicated no fatigue and 10 unbearable fatigue (the worst fatigue). Additionally, the Fatigue Severity Scale (FSS) and the Fatigue Quality of Life Score (FQLS) were used to assess the severity of fatigue and quality of life.

The FSS questionnaire contains nine statements that rate the severity of fatigue symptoms concerning respondent's fatigue – *e.g.*, how fatigue affects motivation, exercise, physical functioning, carrying out duties, interfering with work, family or social life. Scale is a 7-point Likert scale, where 1 strongly disagree and 7 strongly agree. Minimum score is 9, and maximum score is 63. Higher scores indicate more severe fatigue.

The FQLS measures how much fatigue affects the patient's quality of life by assessing five characteristics of the person's energy levels. Minimum score is 5, and maximum score is 30. Higher scores indicate more severe fatigue.

Statistical analysis

The numerical variables are presented as mean \pm SD. The Wilcoxon Rank Sum test was used for comparing the clinical variables before and after treatment. The level of statistical significance was set at $p < 0.05$. SPSS software, version 15.0 (SPSS Inc., Chicago, Ill., USA) was used for all statistical calculations. In addition, Pearson Correlation was used to analyze correlations.

RESULTS

All patients (two males, 14 females) completed the study and complications due to HBO₂ were not seen in any of them during the treatment. Table 1 summarizes the baseline clinical and demographic characteristics of the subjects enrolled in the study. Clinical evaluations

TABLE 1. Demographics of the subjects

	Range
Age (year)	44.06±4.62 (34-53)
Symptoms duration (months)	25.06±16.91 (12-60)
Occupation	<i>n</i>
Housewife	10
Worker	5
Retired	1

TABLE 2. Comparative evaluation of the subjects (Mean ± SD)

	Before	After	<i>p</i>
Fatigue Severity Scale	53.20 ± 4.49	14.60 ± 8.81	0.001
Fatigue Quality of Life Score	24.53 ± 2.38	8.66 ± 2.76	0.001
Visual Analog Fatigue Scale	7.66 ± 0.89	2.00 ± 1.73	0.001

of the patients are given in Table 2. After the treatment, patients' scores were found to have improved with respect to VAFS, FSS and FQLS (all $p < 0.005$).

Although there was a strong positive correlation ($r = 0.676$, $p = 0.006$) between FSS and FQLS, none of the clinical evaluation parameters had any correlation with symptom duration of the patients (all $p > 0.05$).

DISCUSSION

In the present study, we aimed to evaluate the efficacy of HBO₂ therapy in patients with CFS. The results showed that HBO₂ therapy decreased the severity of fatigue and increased the quality of life in patients with CFS. To our knowledge, this is the first clinical trial that evaluates the efficacy of HBO₂ in patients with CFS.

Chronic fatigue syndrome is a chronic disease with social components that ensue secondary to the incapacity of the person to fulfill their work, social and family responsibilities. Because the pathophysiology of CFS remains unclear, current treatment modalities mainly seek to alleviate symptoms [17]. To date, there are controversies regarding appropriate strategies for the management of CFS. Because current treatments and medications are often associated with limited clinical benefits [18] and possible undesirable side effects [19], complementary/alternative therapies are frequently used by CFS patients as well [20,21]. However, almost all of them have been suboptimal, because they are

far away from amelioration of the pathophysiology where ROS and lactic acid play a critical role [4-8].

Although, HBO₂ therapy is an old modality, it is relatively new for practitioners of physical and rehabilitation medicine [22]. In addition, there are several studies on HBO₂ therapy in treating musculoskeletal disorders [22,23,24]. HBO₂ therapy is defined as the intermittent inhalation of 100% oxygen in a hyperbaric chamber at a pressure higher than 1 atmosphere absolute (1 atm abs = 760 mmHg, the normal atmospheric pressure at sea level) [25]. HBO₂ therapy is usually administered at 2 to 3 atm abs. Typically, the duration of HBO₂ therapy varies from 30 to 120 minutes. The frequency and total number of HBO₂ sessions are not standard among hyperbaric medicine centers. HBO₂ therapy is administered using monoplace or multiplace chambers. In the former, a single patient is treated and internal pressure is raised with oxygen. Multiplace chambers permit patients to be in the pressure chamber together with health personnel. In multiplace chambers, pressure is raised with compressed air and patients breathe oxygen through masks. HBO₂ therapy causes mechanic and physiologic effects. One of the physiologic effects is to increase evacuation of ROS and lactic acid from the body [9-16].

In this study, a new modality was tried to treat CFS as far as its pathophysiology is concerned. The patients' symptoms improved. On the other hand, although the levels of ROS and lactic acid could not be measured, the improvement in the subjects' complaints is noteworthy. Yet, previous studies have shown that HBO₂ therapy decreased ROS and lactic acid levels in various conditions [9-16]. Therefore, it is possible to say that HBO₂ therapy can be effective and thus be used as a new treatment option in CFS.

Limitations of the present study include the lack of a control group, the lack of a long-term follow-up and the small sample size with female predominance. Nevertheless, the results seem to be significant. In conclusion, we may imply that HBO₂ therapy, an effective and well-tolerated treatment method, decreases the severity of symptoms and increases the quality of life in CFS patients. In this regard, it may be a new treatment modality for the management of CFS. However, further studies with larger sample sizes and control groups are definitely awaited. The long-term and duration of its beneficial effects should be investigated in future studies.

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Subject: Response From European ME Alliance to Notice Number: NOT-NS-16-024 - RFI: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Good Day,

This is a submission from the European ME Alliance regarding **NOT-NS-16-024**.

The European ME Alliance (EMEA) is an organisation of national patient organisations and charities in thirteen European countries (in Belgium, Iceland, Denmark, Finland, Germany, Holland, Ireland, Italy, Norway, Spain, Sweden, Switzerland and UK) campaigning for better research and more funding for research into Myalgic Encephalomyelitis (ME or ME/CFS), as defined by WHOICD-10-G93.3.

We hope you find this useful,

Best wishes,

Richard Simpson

The Chairman and Board of EMEA

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**European ME Alliance Response to RFI
Notice Number: NOT-NS-16-024**

**Request for Information: Soliciting Input for New
Research Strategies for Myalgic
Encephalomyelitis/Chronic Fatigue Syndrome (ME)**

This is a submission from the European ME Alliance regarding **NOT-NS-16-024**.

The European ME Alliance (EMEA) is an organisation of national patient organisations and charities in thirteen European countries (in Belgium, Iceland, Denmark, Finland, Germany, Holland, Ireland, Italy, Norway, Spain, Sweden,

Switzerland and UK) campaigning for better research and more funding for research into Myalgic Encephalomyelitis (ME or ME/CFS), as defined by WHO-ICD-10-G93.3.

We hope you find this useful,

Best wishes,

The Chairman and Board of EMEA

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ASSUMPTIONS

The IOM and P2P reports are recent reports and we assume that the good findings from these reports are built upon in these future plans being developed. It is also recognised that the IOM performed a literature search on ME already and we therefore have not provided research references.

Much of the content in this response has already been discussed and documented by the European ME Research Group (EMERG) which set an overall goal to define a sound research strategy to address the research issues and constraints for ME – more details from Professor Simon Carding at UEA/IFR.

Emerging needs and opportunities that should be considered as new ME research strategies are developed.

Biomarker discovery:

Establishing reliable biomarkers would be a major boost for all research, treatment and perception around the disease.

Therefore, consideration and a collaborative action plan should be given to the following –

- The use of comprehensive and validated scales, instrumentation and measurements for agreeing biomarkers
- Identification of the most promising marker(s) (antibodies, soluble, cellular, microbial or genetic markers) should be targeted as lines of research
 - Biomarkers should always be (cor)related with symptom patterns (see database later) Mapping back to patient stratification
 - Cross matched vs. relevant controls to identify specifics to ME
 - Disease controls – other fatigue-related illnesses, sedentary individuals, different ME case definitions?
 - “Healthy” controls – related, same household, unrelated (age/sex/race matched) individuals – defining criteria?
 - Also to be stored and correlated by gender, age and length of illness
- Multinational cohort studies
- Reference labs should be established
- Imaging:
 - Studies on specific brain findings need to be replicated and expanded

Clinical trials:

A need for multi-national clinical trials is present. This allows replication, verification and direct paths to possible treatments.

Currently the following might be viewed as potential, initial trials

- Rituximab, Ampligen, LDN, FMT

What is important, for whatever trials are conducted, are the following -

- Defining meaningful endpoints for trials
- National and international collaboration in multinational trials

It is suggested that a rituximab trial could combine existing projects underway in Norway (Haukeland University Hospital) and UK (EMERG/Invest in ME UK rituximab trial) to form a multi-national, multi-site clinical trial set – or knowledgebase, and could be used as a template for future collaboration.

This itself would give a boost for this collaboration as well as sending out strong signals to the research, academic and clinical communities – as well as to patients and their families. This is also achievable as links are already established between the groups undertaking this work. This sort of research needs to be performed in clinical trials and data made available rather than being performed on an ad-hoc basis by individual doctors.

Longitudinal studies

There needs to be consideration for longitudinal studies to elucidate the natural history of ME. Due to failings of the past by funding organisations we start from a position of a lack of any coordinated strategy for research and we need to build in this component to ensure future research can be augmented by this type of data. Such studies help to evidence how ME changes over time and may also help inform of the risk of relapses for people who are supposedly recovered or in remission?

Distinct plasma immune signatures in ME are present early in the course of illness, but differ in long-term patients and such differences could be investigated further.

Changed content of immune proteins a few years after the onset of ME.

Challenges or barriers to progress in research on ME.

Diagnosis

A central issue to all of the research into ME is correct diagnosis. Currently a vast number of wildly disparate and arbitrarily used case definitions and criteria exist for ME and CFS research and diagnostic purposes. A substantial body of evidence suggests that these definitions do not all represent the same disease and that there are significant differences in patient populations, making some of these definitions highly unreliable and inaccurate. Evidence reviews and such like usually don't acknowledge the differences, nor the consequent problems and risks, and therefore often present their findings in such a way that the uninformed reader is led to believe that their conclusions are applicable to all patients meeting any CFS or ME definition regardless of the research criteria used in a particular study.

The lack of standard, up-to-date and accurate criteria being used in all ME research has impacted on the reliability of research in the past, as well as directly increasing the risk of harm to patients due to flawed "results" (e.g. the PACE trial).

Standard diagnostic criteria must be used for diagnosis – with standard sets of research criteria being formed from within these criteria.

These criteria need to be as refined as possible to avoid misdiagnosis and should evolve as research data is gained and confirmed.

A starting point should be the criteria which have been commonly used in recent years – CCC, ICC, IOM. The definition from Ramsay is favoured by many patients but they have not been used in research or properly evaluated. Yet from these sources a standard could be decided.

Comparative studies of different ME definitions may be necessary to achieve this.

Since post-exertional malaise/muscle weakness is a key feature of ME then it is important that future research is based on criteria where PEM is a required symptom. The effects of exercise should be taken into account in research.

Patient Stratification

Patient stratification is required for all research into ME to ensure well-defined patient cohorts – and this should include full disease spectrum/subgroups and inclusion/exclusion criteria.

The diagnosis must be accurate, reliable, universal, useful using standard diagnostic guidelines.

Appropriate (disease) control groups must be established.

The quality and standards of sample collection must be formulated for all to use and take into account the types of samples required, when and how often they are taken, and how many.

Also it has to be decided on what patient stratification is made – is it via onset type, severity, by biomarkers?

Databases of patients need to be set up and maintained. These need to consider

- Individuals
- Demographics
- Clinical Features
- Treatment History
- Systematic studies of patients' health history, including which infections the patient has undergone before the onset of ME, needs to be recorded.

The database may be used to identify/define sub-groups – such as

- Differences in biological pathologies
- Duration of illness
- Symptom clusters
- Level of severity
- Acute vs gradual onset
- Infectious vs non-infectious onset
- Triggers
- Pathogens
- Single vs cluster outbreaks
- Fluctuating pattern vs progressive decline
- Increased susceptibility to infection vs decreased susceptibility to

infection since onset of ME

Data collection approaches are an issue with questionnaires not being sufficient, and questionnaires + patient visits may be subject to variation depending on the level of expertise of visiting nurses/research assistants.

Data Protection

This will be a challenge when working across different national or continental boundaries.

Ethics

This will be a challenge when working across different national or continental healthcare systems?

Sample Standardisation

National and international collaboration in setting standard operating procedures would be beneficial such as -

- Standard Operating Procedures (SOPs) –
 - Collection
 - Transport
 - Storing
 - Distribution
 - Sample Life History
 - Samples linked to documentation relevant to ME
 - Sample Types: Blood, Urine, Stool, Tissue, Spinal Fluid
 - Sample Quality and Frequency (of samples)
 - Challenge of selecting and “assuring” cohorts, comparable with epidemiology
 - Universal analysis protocols and quality control procedures

Bio/Tissue/Sample banks

These should include comprehensive samples with protocols which are standardised for ME research.

Many academic institutions have already established this facility so what is necessary is to standardise the registry and collection processes so that all can be assured of the provenance of the samples and they can be joined for research purposes.

The standardisation of registry and collection for biobanks to allow all academic biobanks to be joined as one resource for ME research rather than concentrating on single biobanks is the way forward.

This would allow, and encourage, sharing and collaboration and could reduce costs and avoid unnecessary “ownership” issues from being built up which become another obstacle to collaboration and progress.

It would also guarantee the provenance of sample definition and maintenance. These sample bio/tissue banks in research organisations should be viewed as a necessary resource and not as an economic function.

Lack of funding

The need for more funding for biomedical research into ME has been recognised by many patient organisations around the world – but also by the recent IOM and P2P reports. The lack of appropriate funding for mainstreaming ME research makes it impossible to resolve this disease.

A substantial uplift in funding for biomedical research into ME would, we suggest, encourage new researchers to enter the field as well as create the necessary environment to allow causality to be established and treatments to be developed.

One of the later points regarding collaboration between NIH consortium and EMERG would provide a huge boost to the chances for increasing in funding for research into ME.

This investment would, in turn, save far more money than is spent by giving patients their lives back and reducing costs on healthcare.

Education

The Involvement of doctors in ME research needs to be encouraged.

A method of distributing knowledge of current and planned research to enable healthcare professionals to be made aware of ME needs to be looked at.

Existing methods seem not to be working.

The curriculum for medical students needs complete overhaul.

In the UK, for example, the education of medical students is based on erroneous information and borders on negligence by academic institutions responsible for setting the curriculum, and by the overriding regulatory body that governs this.

All of the above affect public and political perception and treatment of the disease.

They affect the likely interest of new researchers in participating in research into ME.

Gaps and opportunities across the research continuum from basic through clinical studies

Sample sharing

- This helps with research, establishes academic links between institutes and researchers and facilitates collaboration and standardisation
- If linked to sample standardisation then validation of results from small groups is possible
- “Freshness and validity” of samples and over time can be made possible across

multiple centres and storage conditions

- Epidemiology: natural course of the disease progression and cross-checking definitions. Epidemiological studies are long overdue despite data being collected by healthcare services.

Database of Research

The database of research needs also to be built up and available to all researchers and not dependent on Journal publication alone. It needs to consider inclusion of negative results also – which may be useful for future research.

This is obviously affected by the results of research being published. But it is one area that needs to be analysed.

Paediatric research

Paediatric biomedical research has been poorly served by research funding bodies.

A view is held by some that children often improve and the prognosis for children is much better for children than for adults.

Yet many children are ill for a long time, often very ill for a very long time. So where is the evidence for this?

Could it be that the prognosis for children actually isn't as good as currently claimed, or do they become long-term sufferers because they aren't receiving adequate help or are often removed from the healthcare system due to apathy or decide to withdraw as a self-protection measure?

The lack of attention to paediatric ME research allows false beliefs about the disease to creep into healthcare systems and prejudice and ignorance is allowed to be built up (an example being the ridiculous use of the term "pervasive refusal syndrome" which is attributed to children with ME).

A subgroup to be studied should eventually include children and look at aspects that may affect the prognosis (acute vs gradual onset, type of trigger, subgroup, symptom clusters, severity, severity during the first 5 years, degree of PEM, frequent over-exertion, genetics etc.)

What proportion of children with ME become severely affected long-term? How is their illness changing over time?

Such studies overlap with epidemiological studies, education of doctors (and researchers) and even social considerations.

As a great deal of abuse from clinicians (and some researchers) towards children and young people with ME is based on this unproven expectation of recovery within 3-5 years then this warrants further research.

But it is also important with regards to health insurance, in dealing with schools and social services and other authorities etc.

It is also necessary to investigate heritability and familial associations - e.g. do symptoms differ between children and adults, and if so in what way?

Replication and validation of existing biomedical studies

Initial small studies are rarely followed up by larger or complementary confirmatory studies, due to lack of any longer term strategy and/or funding. The strategy for research needs to consider this point.

Centres of Excellence

The NIH have intimated that a number of Centres of Excellence for expert clinical care, biomedical research and clinical trials, may be established.

Similar plan exists in UK in Norwich Research Park which would link EMERG work. These should collaborate and build on a research foundation that could fast-track biomedical research and eventual treatments for ME.

General Comments

The lack of consistency in research criteria, the flawed policy of funding psychiatric theories and the failure to even standardise on methods and terminology are all shown to contribute to the mediocrity and lack of vision that has characterised research into ME for the last decades, until perhaps the last couple of years.

Characterization and evaluation of the hallmark symptom post-exertional malaise (PEM) in carefully designed high-quality studies with large cohorts is absolutely essential.

Fatigue is often misleadingly stated to be the most important and/or characteristic symptom of ME, whereas in fact leading experts agree that the actual cardinal symptom of ME is post-exertional malaise (PEM), also called post-exertional amplification of symptoms or post-exertional crash.

'Fatigue' fails to capture the essence of this complex condition. Reducing a complex multisystem illness such as ME to just one single diffuse symptom that can also be found in a myriad of other illnesses, that can't even be measured objectively, is valueless.

Recognizing PEM as a distinguishing symptom is important in improving both the research field and clinical care for ME patients.

ADDITIONAL POINTS

The overriding themes which pervade all of these considerations are the following

-

Collaboration:

It was evident from the Invest in ME International Colloquium and Conference events in London in June 2016 that USA and European researchers (and patient groups) can work together, and are doing so.

We would suggest that the NIH use the European ME Research Group (EMERG) as partners in research. This can begin immediately and will create a very powerful research potential which includes major European research institutions.

We would also suggest that NIH can use the European ME Alliance (EMEA) as partners for patient related considerations. It is extremely important that the NIH can work with a European patient organisation as this will bring major benefits for the research which is undertaken.

There is a great need for international collaboration in order to tackle this disease. This is an easy route

for fast tracking research and improving education and awareness.

This will also expand research, force correct education of healthcare professionals and open up new avenues for research funding.

This all leads to improved chances for translating research into effective treatments which will lead to improvements in the lives of patients and their families.

Standardisation:

By now it is clear that standard protocols, diagnostic and research criteria and terminology should be used by the international research community. So this issue must be tackled – and it would certainly be possible if the previous Collaboration theme was to be embraced.

Biomarkers and Subgroups

As indicated earlier the discovery of biomarkers and possible determination of subgroups would be of great help in the daily lives of patients since this would allow impartial validation that a patient had ME following tests, would underline the fact that ME is a serious disease, allow healthcare professionals to work with the patient rather than against them and would be helpful in gaining aid from social services etc. – all serving to dispel mistrust with which many patients are confronted.

The Future

We hope that the NIH will involve the EMERG group and EMEA in future collaboration and cooperation. There is a real chance being created here to do things right for patients – and EMEA will be willing to play a full role on progressing this opportunity based on solid and progressive biomedical research and international collaboration.

Dimmock, Mary

[...]

Subject: NIH RFI NOT-NS-16-024

Attached please find the response to NIH RFI NOT-NS-16-024 on ME/CFS

Thank you for the opportunity to provide input. Do not hesitate to let me know if you need additional information from us.

Mary

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 at [...].

Signed:

Massachusetts CFIDS/ME & FM Association
Pandora Org.
Solve ME/CFS Initiative

[...], patient
[...] California
Mary Dimmock, Connecticut
Claudia Goodell (Race to Solve ME/CFS)
[...] Arizona
Cort Johnson (Health Rising)
Denise Lopez-Majano (Speak Up About ME)
Bob and Courtney Miller, Nevada
Billie Moore, Advocacy Chair, NJME/CFSA, Inc.
[...] Delaware
[...] Florida
Jennie Spotila, J.D. (OccupyCFS)

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.¹ 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."² 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 disease³ 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.

- ¹ Newby, Kris. “Immune System Disruption. The Search for Answers.” *Stanford Medicine. Balancing Act*. Fall 2014. <http://stanmed.stanford.edu/2014fall/immune-system-disruption.html>
- ² Ibid.
- ³ 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.

HsuBorger, Ben

[...]

Subject: MEAction Survey Response to ME/CFS Request For Information

Greetings,

I'm submitting the attached document as a summary of a [survey](#) #MEAction conducted to collect information for this RFI among our constituents. I appreciate the extra time afforded to #MEAction to submit this document. If you have any questions please let me know.

Regards,

Ben

1. Introduction: The #MEAction Survey

#MEAction created a survey of questions about Myalgic Encephalomyelitis (M.E.) that it sent out to its patient community via its online platform meaction.net. #MEAction is a global grassroots community of M.E. patients and advocates open to everyone. The survey was also posted on the online M.E. community forum Phoenix Rising.

Created through Google Surveys, the survey contains 109 questions allowing responders to rate the importance of each item 1-5, in which items marked '1' are least important to research and items marked '5' are most important to research. The survey provided a neutral summary of the potential significance of each item, and responders were encouraged to skip items they did not feel they understood rather than choose an 'average' value. An item that rated 4/5 or better was considered to be of significant concern. The survey also contained 13 questions about demographics and open-ended responses for each section, allowing responders to add additional comments and concerns.

Items were added to the survey at the request of community members, and responders had the option to skip items they did not understand, which creates some heterogeneity in the number of responses per item. The lowest number of responses for any item 1-5 was 980 responses, and the greatest number of responses for an item was 1800.

Survey questions were divided up into the following categories:

- Specific barriers to research
- Specific solutions to these barriers
- Symptoms
- Testing
- Treatments
- Additional hypotheses for research

Data was gathered anonymously, marked only with time completed. Data was scrubbed to eliminate accidental double-submissions and to more accurately calculate numerical values, e.g. if a responder wrote that they contracted ME in "1998 or 1999" the figure 1998.5 was substituted in order to estimate average time of onset for all responders.

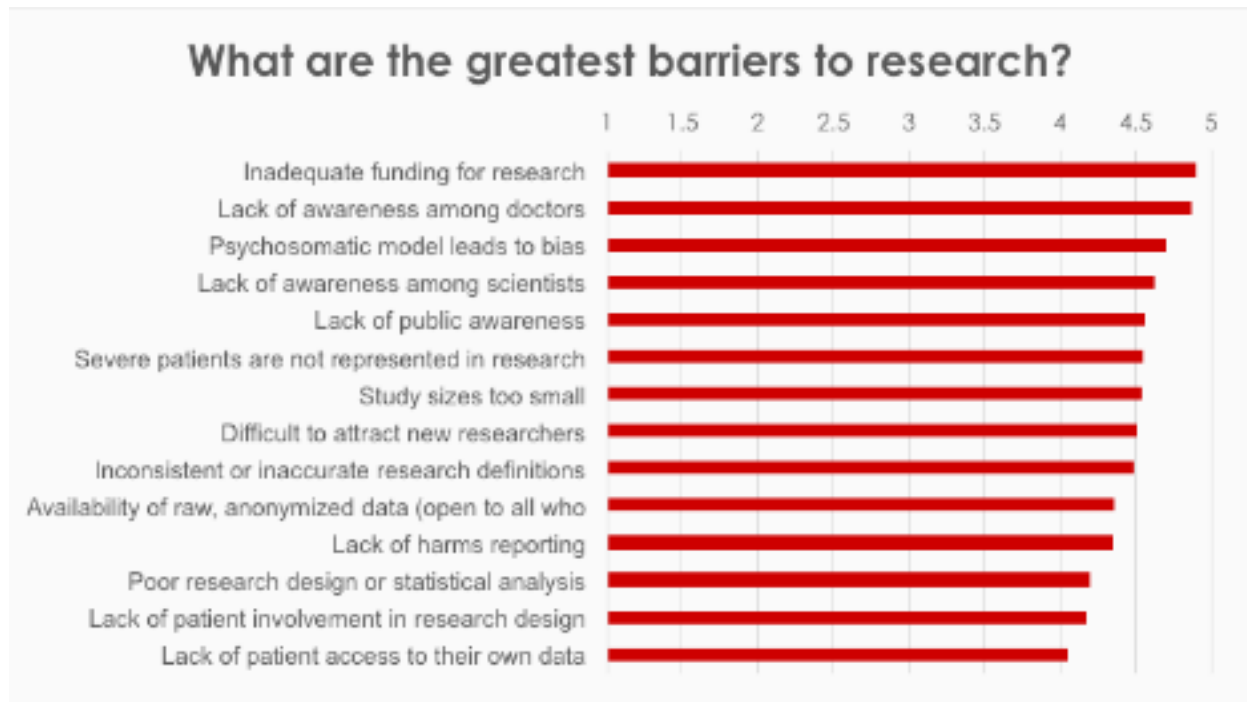
Responders self-identified as 92% white, 82% female, and were generally of European descent.

Limitations of the survey include that it was only provided in English, the limited period of time allotted to respond, which may have preferentially selected for retired or disabled responders. The act of completing a 100+-question survey may have been untenable for severe and very severe patients. Here 'severe' is defined as housebound, and 'very severe' is defined as bedbound. This creates the possibility that responders are generally healthier than the referent population.

In order to gather information from individuals with a variety of perspectives, clinicians and caregivers were also encouraged to respond.

2. Specific Barriers to ME Research

In the below chart the survey respondents rated the barriers to ME research as follows.



The single item that received the highest overall score in any category was the challenge of inadequate funding for research (4.901). However, all of the barriers respondents were surveyed about received an average score of 4 or higher demonstrating the perceived multidimensional and interdependent nature of the barriers facing ME research.

Some responders further commented on these barriers noting the following:

“Lack of money and stigma/poor understanding are intimately related. They create a feedback loop with lack of researchers and lack of good information. Until we push money at this in a big way, along with good information, these barriers will remain.”

“NIH needs to recognize that fishing expeditions are needed, and that well-posed single hypothesis/single outcome studies are not the only ones needed to advance ME/CFS research.”

“Because this disease has been sorely neglected for 30 years, the ME community knows more about it than the scientific community as a whole, and NIH in particular. You need to work with specialists OUTSIDE NIH, researchers such as Ron Davis at Stanford,

clinician/researchers such as Dan Peterson of Incline Village, Jose Montoya of Stanford, and John Chia in L.A. You need to work with patients who have a scholarly background.

“Finally, there has been a CFS Advisory Committee to HHS since 2003 (before that there was a CFS Coordinating Committee). The public members on CFSAC have worked hard to produce a set of recommendations every year, and every year it has been ignored. It would be a good first start to take those recommendations seriously.”

“Mostly I would say the stigma the illness has as a result of years of medical insistence on a psychosomatic basis and the lack of interest in further investigation. This has led to little doctor training in the illness, the lack of awareness in the medical community of the very real biomedical evidence that is out there and the dismissing of patients as individuals unwilling to get well - when even a quick Google search reveals patients who like me were robust, adventurous highly active individuals prior to getting sick.”

“The bifurcated literature - psychiatric v. biomedical - has been an enormous barrier to advancing knowledge about this disease... the quality of the psychiatric literature is very questionable, whereas that of most of the biomedical research is not. The psychiatric literature starts with the assumption that the patients have "medically unexplained symptoms" - the existing biomedical literature is proof that it is not so unexplained. But they never cite the biomedical literature.”

“There are many people who would like to be involved in the actual physical research or have the technical data simplified so they can read and digest it easily. Many people with CFS/ME can understand the research and will be able to offer a more inciteful view if they were more hands on and able to participate in a more proactive way.”

“More people need to give data, there needs to be an easier, clearer call to allow sufferers to chance to take part”

“Remember that patient participation can be genuine or token - we don't need the equivalent of greenwashing, a token blessing on the design of studies by a tame and ill informed group of patients. After being alternately ignored and denigrated for so long, patients are going to want real input.”

3. Specific Solutions to ME Research Barriers

A) NIH Potential Actions:

Survey respondents rated several potential solutions to overcoming these barriers to ME research as follows:

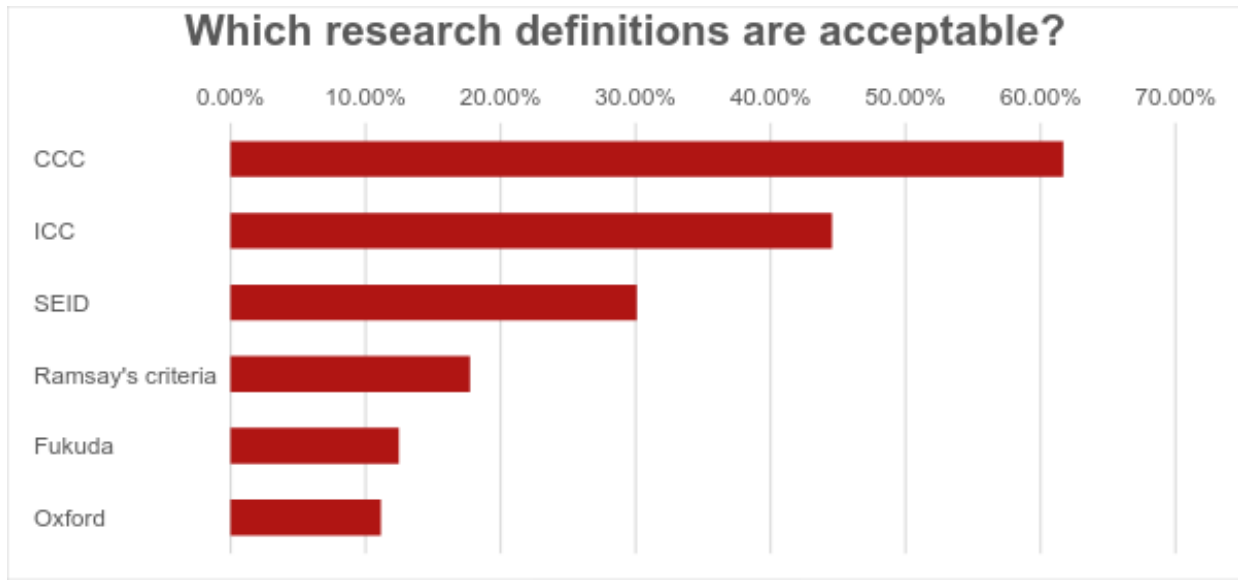


B) Preferred Research Definitions:

The survey asked respondents about the acceptability of using any of the following criteria to further research the disease:

- The Ramsay Criteria (ME, 1988)
- The Oxford Criteria (CFS, 1991)
- The Fukuda Criteria (CFS, 1994)
- The Canadian Consensus Criteria (ME/CFS, 2003)
- The International Consensus Criteria (ME, 2011)
- The IOM criteria (SEID, 2015)

The #MEAction survey revealed that patients overwhelmingly prefer the Canadian Consensus Criteria (CCC) definition of myalgic encephalomyelitis (62%) or the International Consensus Criteria (ICC) (45%) over other proposed criteria, including the IOM's 'SEID', Ramsay's criteria, Fukuda and Oxford. The Fukuda and Oxford criteria were considered the least favorable criteria by responders, at 12% and 11% approval rates, respectively.

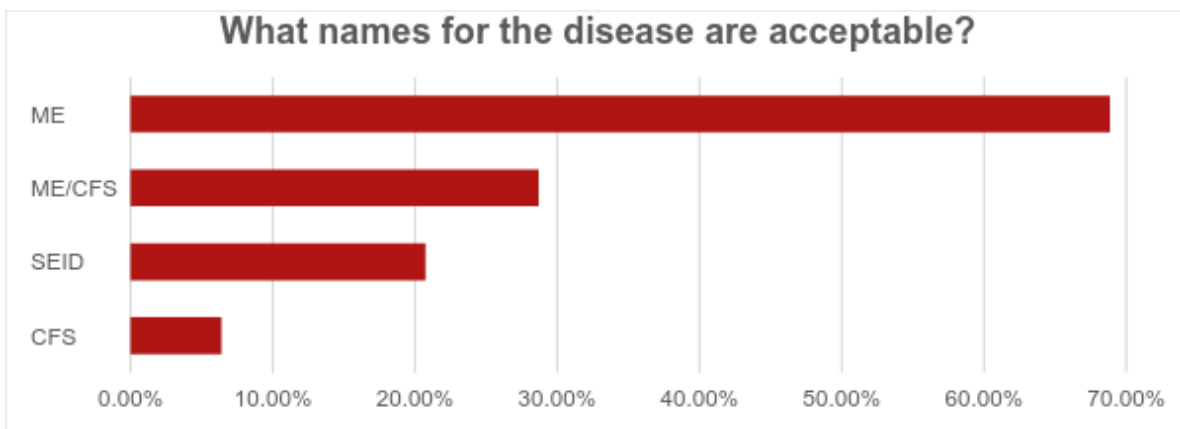


Approximately 30% of responders agreed that patients should meet multiple different criteria; however, responders considered it extremely important that NIH studies use one, consistent definition in clinical trials (4.45 / 5). This reflects the idea that, while multiple definitions may be useful clinically, research definitions should be more stringent and consistent, so that it is clear which illness is being studied, and to what patient population data may apply.

C) Preferred Disease Names:

The survey asked respondents which names for the disease are acceptable:

- Chronic Fatigue Syndrome (CFS)
- Myalgic encephalomyelitis (ME)
- Myalgic encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS)
- Systemic Exertion Intolerance Disease (SEID)



The responders strongly prefer the name ME, though both ME/CFS and SEID were rated as acceptable by a smaller, but significant portion of responders. Some responders provided the following comments on the issue of acceptable disease names:

“The fact that M.E. appears to me to be an umbrella title for half a dozen sub groups means that history of the symptoms is critical. What caused one type of M.E. would not be responsible for all sub groups so research results should be split to show which sub group responded best to which treatment. My M.E. differs from others that I know so it is important to know what results are relevant to which sub group.”

“...we should NOT hold this disease to a higher standard than all others by hunting for one, elusive biomarker or by insisting that results that are frequently abnormal and may be sensitive but not specific are useless. We could probably get very close to diagnosis with panel of 3-5 commercially available tests: e.g., natural killer cell function (properly prepared and executed), sed rate, cognitive testing and where available, an exercise test. It's also very important that patients be tested for individual pathogens to help determine what antivirals/antibiotics, etc. may be of some benefit to them.”

D) Preferred NIH Institute Location:

When asked where the disease should be housed, 81.49% stated ‘in a new institute for complex neuro-immune diseases’ (n = 1529). NINDS, NIAID, and the Trans-NIH working group were also choices selected by a smaller proportion of patients.

New institute for Complex neuro-immune diseases	81.49%
NINDS	34.60%
NIAID	23.22%
Trans-NIH	22.89%

These are numbers without full explanations, and may require additional feedback from the community to characterize them accurately. However, as one responder put it,

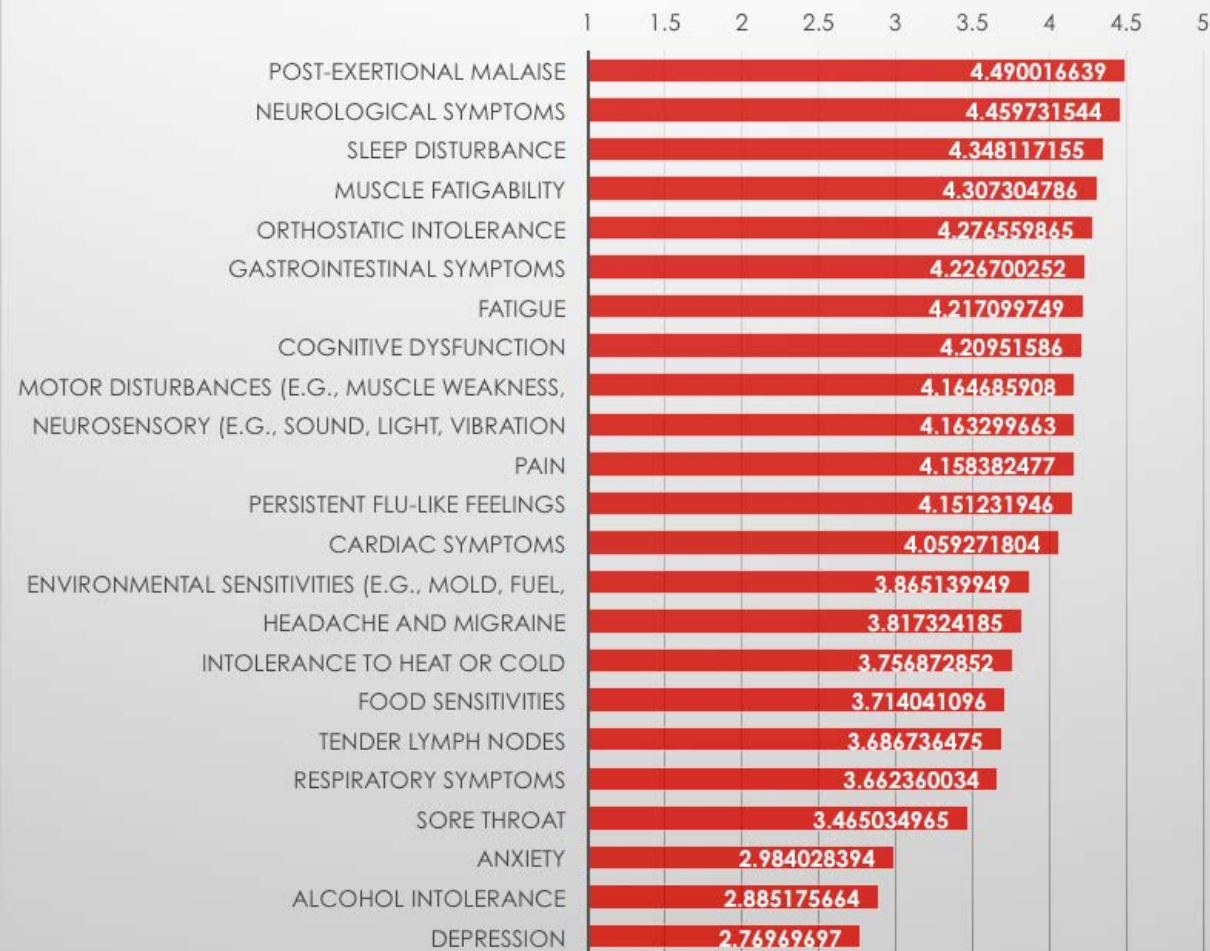
“Belongs to no one, no organized discipline. We are homeless orphans.”

4. Suggested Areas of Study: Symptoms

In the below chart the survey respondents rated the symptoms of ME that they were most interested in

having studied.

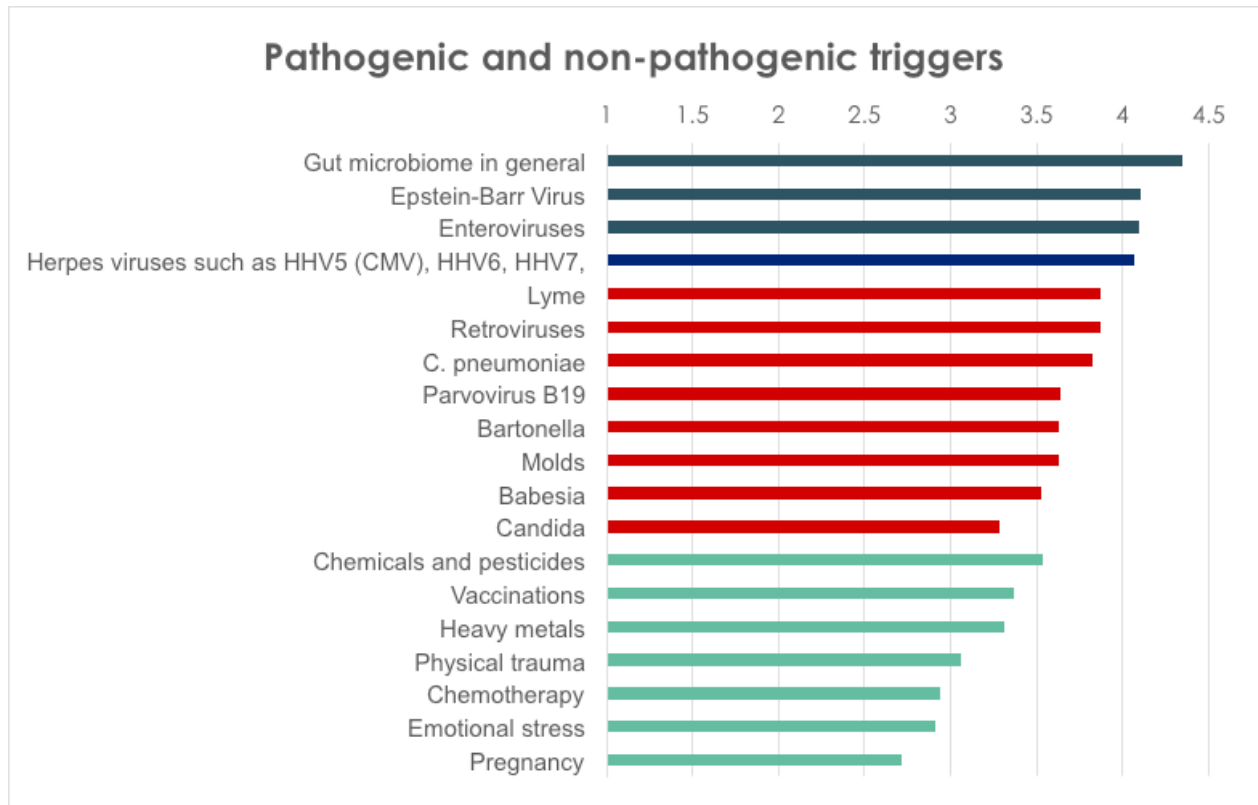
What are the most important symptoms to study?



It should be noted that while patients rate PEM as a high research priority, the ethical considerations of testing for and studying patients with PEM are considerable, as is reflected in respondents low rating of the desirability of performing second-day exercise testing (3.69/5).

5. Suggested Areas of Study: Testing

In the below chart the survey respondents rated the pathogenic and non-pathogenic triggers of ME that they were most interested in having studied.



Some responders further commented on pathogenic and non-pathogenic triggers stating the following:

“EBV, and to a lesser degree other HHVs are correlated with ME. Reactivation is either a cause or an effect of ME.”

“The viruses in the herpesvirus family to study are NOT HSV1 or HSV2. There are already known correlations with HHV-6 Variant A and to a lesser extent HHV-6 Variant B - NIH must study the difference - HHV-5 (Cytomegalovirus, or CMV), and HHV-7. EBV clearly plays a role in the onset of the disease for many patients, but perhaps there is a more virulent strain of it that causes more trouble than others. Finally, the British have suspected a polio-like virus, enterovirus, for decades (remember, this was first called atypical polio), and have studied Coxsackie B. Recently John Chia has studied Coxsackie B as well. But there is no treatment.”

“EBV has been implicated in a significant % of people with ME. And, any one of the above infections, could just be the start of a cascade of infections. ME sufferers have been found to have a number of infections. Due to the large number of GI problems, the enteroviruses would be especially important to study. But I would say we need to study ALL of these bugs!”

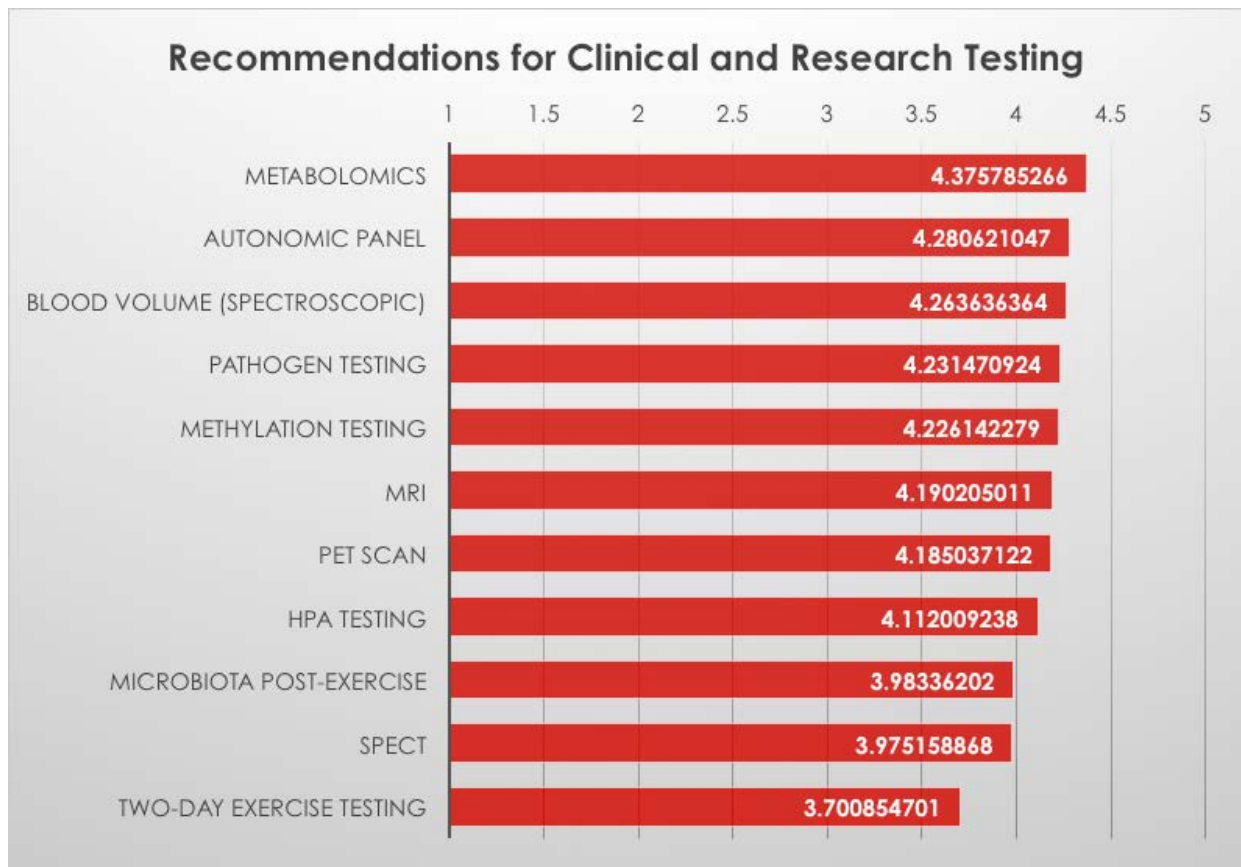
“Lyme related illnesses constitute a separate diagnosis and should be exclusionary. Mold exposure and candida cause fatigue, maybe chronic fatigue, but should also be exclusionary. EBV is ubiquitous and opportunistic in the weak and immune-challenged but

has been extensively studied already. Further research on EBV seems unlikely to provide breakthrough understandings of any of the subtypes of this illness (or group of illnesses)...

Therefore more large-scale research is needed to see what's going on with... other pathogens, and whether early testing, at the beginning of the illness, could help patients and doctors toward a more accurate evaluation and prognosis.”

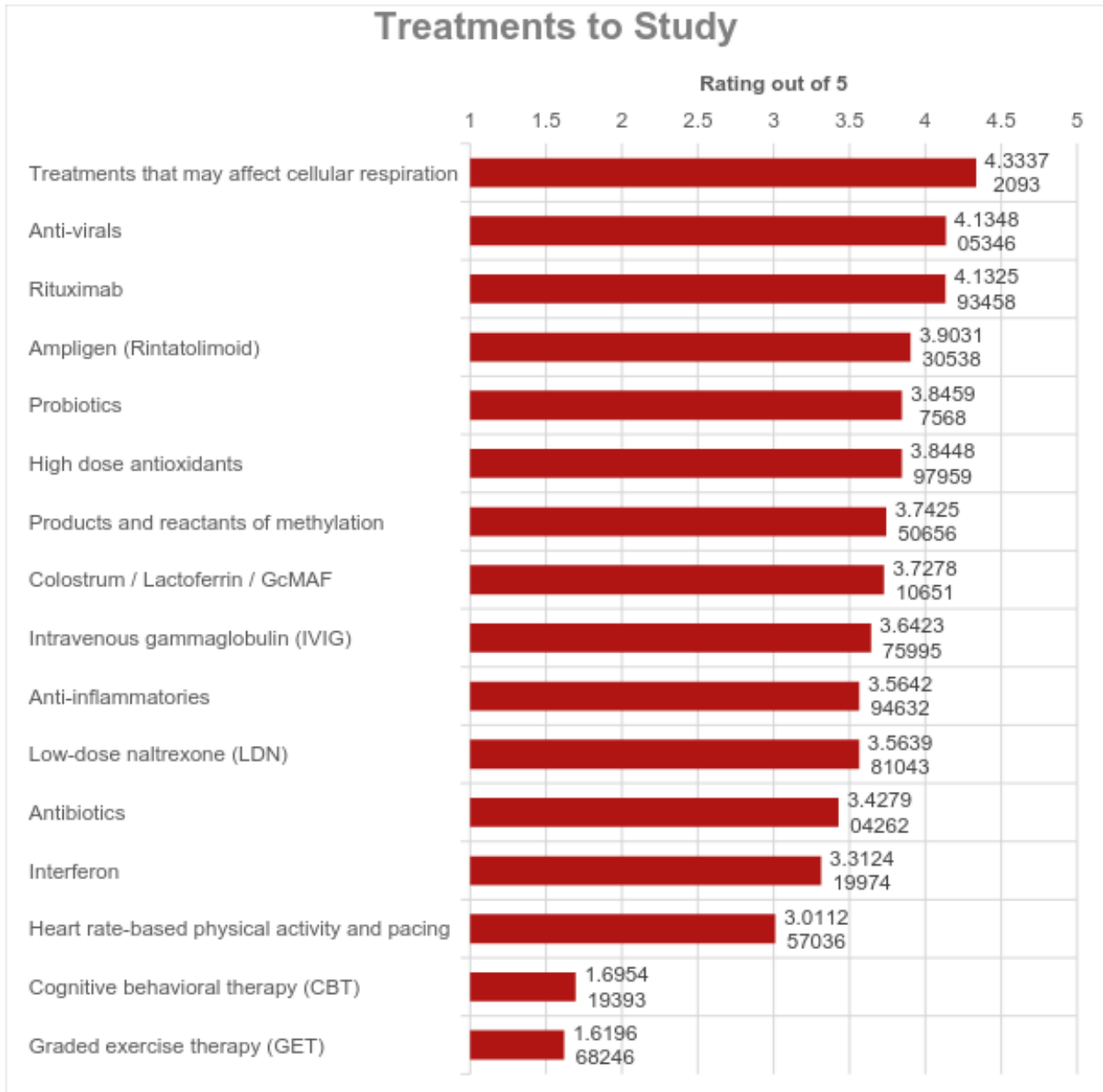
“Different pathogens are identified by different patients as triggering their ME. I feel mostly neutral about studying specific pathogens, I think there is something wrong with the immune system response or underlying energy system (mitochondria) in those that develop ME. The question is more likely, what is wrong with the mitochondria or immune system of the patients that get ME as opposed to, what are the pathogens that cause ME. Why do some people recover from the pathogen and move on, while others are never the same?”

In terms of recommendations for clinical and research testing, performing second-day exercise testing, has the lowest ranked method among responders.



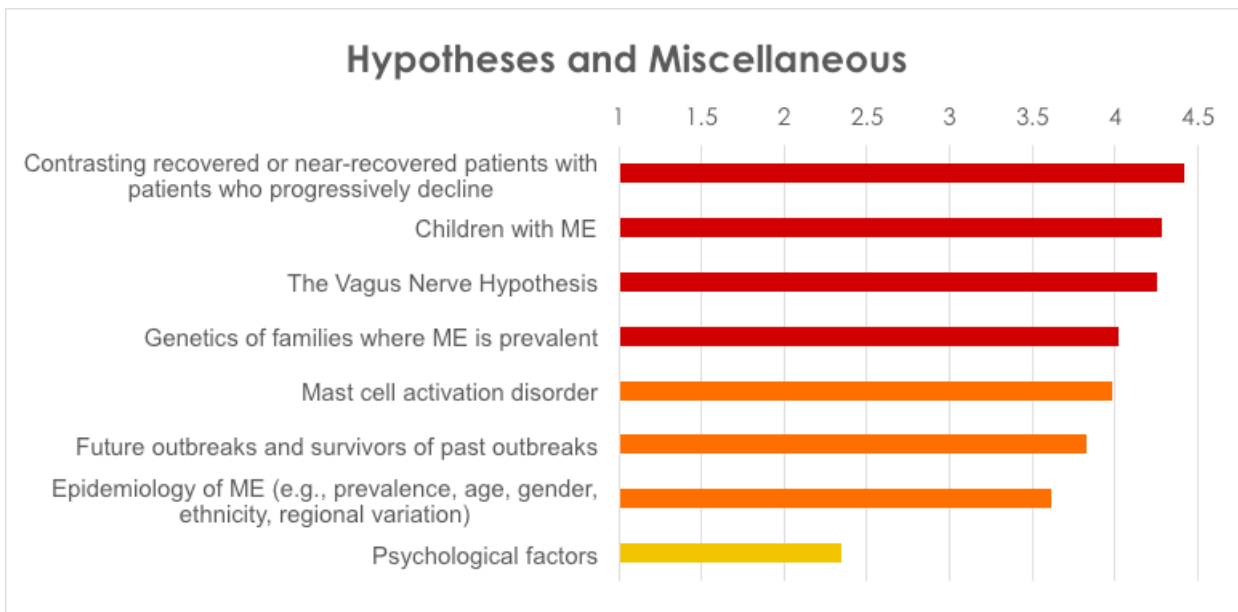
6. Suggested Areas of Study: Treatments

In the below chart the survey respondents rated potential treatments of ME that they were most interested in having studied. Cognitive Behavioral Therapy (CBT) and Graded Exercise Therapy (GET) were the treatments options that responders had the least desire to have studied.



7. Suggested Areas of Study: Medical Hypotheses

Responders to the #MEAction survey were also asked about possible other avenues of research that they were interested in having studied. The below chart shows how they rated the following medical hypotheses.



Regarding the interest in the genetics behind ME, it should be pointed out that 27.96% of #MEAction survey responders stated they had at least one family member with ME or CFS (n=1266).

Miller, Courtney

[...]

Subject: RFI Response NOT-NS-16-024: Research Ramp-Up Ideas

In response to NOT-NS-16-024, I am resubmitting a collection of recommendations prepared by a group of ME/CFS organizations and leaders outlining a coordinated set of actions to ramp-up NIH's research strategy for our disease. We submitted them on March 1, 2016 and know they have been reviewed, however I would like to submit them formally as a response to the RFI as well.

Thank you for your work,

Courtney Miller

[...]

March 1, 2016

Dear Dr. Koroshetz, Director, NINDS:

The ME/CFS community is united in its goal of reaching NIH funding commensurate with the burden and costs of our disease, and on par with research funding for diseases like multiple sclerosis. We seek a strong NIH research program that builds on existing expertise, recent findings, new technology and a growing understanding of subsets within the ME/CFS disease.

As you lead the Trans-NIH Working Group to form a strategic plan for ME/CFS research and execute the first intramural research study in our disease in decades, the patient community seeks to engage in a two-way process with your team. We bring not only the patient experience, but also disease research expertise, ideas, and a unique understanding of the complexity of our disease.

With a strong investment in NIH research, ME/CFS patients are within reach of diagnostic tests and FDA-approved treatments. It is essential that these next few years incorporate the deepest understanding of the disease to date and minimize pitfalls, so that your renewed commitment can build an NIH program that works to provide scientific answers to patients. Below are elements recommended by a broad group of ME/CFS advocates to inform your work to ramp-up ME/CFS research.

Elements of a Plan of Coordinated Activities to Ramp-Up ME/CFS Research

1. Utilize ME/CFS clinical and research experts – for example those who have collaborated in recent NIH or CDC multi-site ME/CFS studies – in the diagnosis of patients to enroll in the NIH Clinical Center study, and its design, execution, and publications.
2. Collaborate with the patient and expert community to generate a two-way process for permanent engagement in development, execution and monitoring of an ME/CFS Strategic Plan.
3. Convene current ME/CFS disease experts to reach agreement on a consensus research definition and study standards, as recommended in the NIH P2P report, and incentivize studies utilizing the consensus definition and its subsets. Reconvene the expert panel on an ongoing basis (at least quarterly) to produce and validate consensus definitions of ME/CFS subsets.
4. Identifying and characterizing subsets is critical to making progress in ME/CFS science. Therefore, contract with statisticians and CDC to analyze extensive data and samples already collected by CDC's Multi-site Clinical Assessment Study and privately-funded data sources and biobanks.
 - a. Identify and publish measures to produce homogeneous subsets for research. Identify and publish potential biomarkers for development of diagnostic tests and interventions in these subsets.
5. Conduct a review of the ME/CFS grant-making process, including study section/institute assignment, review panel composition, scoring, Council review and final funding decisions. Identify barriers and biases that make it difficult for ME/CFS proposals to secure funding. Identify specific action items to overcome these barriers and correct for biases. Share this information with the public, either through the CFS Advisory Committee or other means.
6. Issue RFAs every year for 5 years specifically for ME/CFS, targeting identification and validation of biomarkers, diagnostic tests, outcome measures, and identifying potential treatments. As recently as August 2015, CFSAC made detailed recommendations about the types of RFAs urgently needed to move the field forward. We seek RFAs totaling \$7-10 million per year during this ramp-up period. Historically low levels of ME/CFS grant applications received using Program Announcements indicates RFAs are needed at least initially to stimulate researcher interest and bring new researchers into this field. The Trans NIH Working Group should set specific goals for the number of ME/CFS grant applications it receives and funds. The power of RFAs to stimulate researcher grants is unparalleled, and they are utilized by NIH for HIV, diabetes, cancer, Brain Initiative and Precision Medicine Initiative, as examples.
7. Model Dr. Ian Lipkin's involvement in ME/CFS. Dr. Lipkin was drafted by NIH leadership to solve the XMRV retrovirus controversy; his team created a multi-site collaboration with expert clinicians to collect samples and controls, and subsequently extended that model in execution of multiple immunological studies with groundbreaking new findings.

- a. We recognize that the NIH Clinical Center study, led by a top infectious neurologist, will produce substantial data and follow-up research questions in immunology, neurology, genetics and exercise physiology to use as a stimulus for the extramural grant program for ME/CFS. As part of an overall strategic plan, we propose the Trans-NIH Working Group prepare a strategy for collaborating with and drafting leading extramural geneticists, exercise physiologists, and neurologists to carry this work forward, similar to the model of work done by Dr. Lipkin's team.
8. Coupled with limited scientific research, there is an extremely limited availability of accurate diagnosis and care of ME/CFS patients. In collaboration with expert ME/CFS clinicians who lead the field in diagnosing, treating, and running clinical trials, partner with other agencies at HHS to establish Centers of Excellence in order to expand and model the highest standard of care available, integrate high-quality translational research, and provide rigorous settings to test scientific findings and potential treatments.
9. Because the few ME/CFS expert clinicians now practicing are aging, training the next generation of ME/CFS clinician-scientists is critically needed. Establish ME/CFS training grants and fellowships to train the next generation of expert clinician-scientists, including those outside the university setting.
10. Use ideas the Trans-NIH team raised in recent meetings and others below to pursue a communication strategy to create the understanding in the research community that ME/CFS is now a funding priority at the NIH:
 - a. Produce a campaign that emphasizes the NIH's new commitment to solving ME/CFS in order to bring new researchers into the field: "NIH needs you to help solve ME/CFS" or "NIH wants your grant applications on ME/CFS" "Dr. Collins: ME/CFS is solvable. Send us your grant applications."
 - b. Send notifications to University Department Chairs of Microbiology, Immunology, Neurology and Genetics, copied to grant administrators: "NIH wants your grant applications for ME/CFS"
 - c. Proactive messaging at scientific conferences: Immunology, Neurology, NK cell conference, Autoimmunity, Genetics
 - i. Booths with publications available re: ME/CFS
 - ii. Poster display of cutting edge research re: ME/CFS
 - iii. Dr. Koroshetz encourage scientific associations to invite ME/CFS experts to speak at conferences.
 - d. Have Dr. Collins or Dr. Koroshetz write an op ed, and provide it and messaging materials to patient/expert community to disseminate in research and scientific publications.

Respectfully submitted,

Courtney and Robert Miller obtained Pres. Obama's promise to elevate ME/CFS
Solve ME/CFS Initiative, Los Angeles, CA, national association

Health Rising, online patient community

Massachusetts CFIDS/ME & FM Association Quincy, MA
ME Action Network, online patient community

Open Medicine Foundation, Agoura Hills, CA

Pandora Org, Inc., Traverse City, Michigan

ProHealth, online patient community
Simmaron Research, Incline Village, NV
Wisconsin ME and CFS Association, Inc.
Workwell Foundation, Ripon, CA

Mary Dimmock, CT

Jennifer Spotila, JD

Claudia Goodell, Race to Solve ME/CFS, online network

Billie Moore, New Jersey ME/CFS Association Advocacy Chair

Lily Chu, MD, MSHS - Independent Consultant - San Francisco, CA

[...] Patient Advocate

Denise Lopez-Majano, Speak Up About ME

[...], Oakland, CA

[...], MPIA

Miller, Courtney

[...]

Subject: Response to RFI NOT-NS-16-024: Community Integration Recommendations

In response to NOT-NS-16-024, I am resubmitting a collection of recommendations prepared by a group of ME/CFS organizations and leaders to integrate the expert and patient community into the process of forming a research strategy for our disease. We submitted them in April 2016 and know they have been reviewed, however I would like to submit them formally as a response to the RFI as well.

Thank you for your efforts,

Courtney Miller

[...]

ME/CFS Community - NIH Integration Recommendations

We, the undersigned ME/CFS organizations and advocates, offer these recommendations to NIH with the goals of:

1. Supporting NIH staff in implementing an intramural study with the most meaningful and credible outcomes possible.

2. Providing ongoing input to the Trans NIH Working Group from highly knowledgeable and experienced patient, clinical and research experts.
3. Creating meaningful communication between NIH and the patient community.

We are supportive of NIH's current efforts to improve integration with our community, including the recently noted seminar series that will bring ME/CFS scientists and clinicians to the Bethesda campus to speak to NIH staff. Choosing experts well-recognized by the ME/CFS community is important to such an effort and is at the root of this set of recommendations. We encourage NIH to implement a number of other initiatives, and some of the suggestions below may overlap with what NIH staff is already considering. We are glad for the overlap of ideas and look forward to continuing to deepen the engagement of NIH and the ME/CFS community with each other.

Note: ME/CFS experts referenced in this document mean those who have extensive experience and deep expertise in this disease and are recognized as such by our community.

1. Conduct a series of staff-patient-expert roundtables
 - a. Hold quarterly roundtable discussions that include NIH staff, patient advocates and ME/CFS experts. The purpose of these discussions is to have two-way conversation on details of the intramural study, NIH Working Group initiatives, an ME/CFS Strategic Plan, and implementation progress.
 - b. Begin roundtables in May 2016, using video or tele-conferencing and in person meetings when feasible.
2. Cross-fertilize the Trans-NIH Working Group
 - a. ME/CFS Experts:
 - i. Invite expert ME/CFS clinician-researchers to make presentations
 - ii. Review 5 years of recommendations made by CFSAC, a longstanding committee of ME/CFS experts (as a background presentation)
 - b. Patients:
 - i. Invite presentations by advocates
 - ii. Summarize meetings publicly, noting input from experts, so patients can follow
 - c. Provide for a timeline and a public comment period on a draft Strategic Plan
3. Interview series: In addition to inviting presentations at Trans-NIH Working Group meetings, staff from the core institutes should conduct interviews for additional input from the following:
 - a. ME/CFS experts (goal: 15-20 experts, one-on-one and/or in focus groups)
 - i. Clinical presentation and diagnostic testing
 - ii. Symptom treatment, clinical trials they have participated in
 - iii. Research directions they recommend
 - iv. How to set up more advanced clinical care centers, translational centers of excellence
 - b. Patient advocates (goal 12-15, one-on-one and/or in focus groups)
 - i. What concerns patients have about past, current, and future research
 - ii. What types of research, outcomes, or results are important to them
 - iii. Why it is important to meet with clinicians and researchers our community identifies as experts
4. Community Communication Methods:
 - a. Community Update Conference calls: quarterly & widely accessible

- b. Create a new Listserv:
 - i. ME/CFS community is more likely to read email, used well by CFSAC
 - ii. Notify listserv when initiatives are released publicly (for example: the Notice of Administrative Supplement on ME/CFS)
 - c. Webpage: easy to find (one place), post details, initiatives, protocol, summaries of Trans-NIH Working Group meetings, Q&As
 - d. CFSAC meetings. Provide a substantive update on Trans-NIH Working Group efforts and the intramural study at CFSAC meetings: a widely watched webcast in the community, providing a wide communication opportunity.
5. Federal Partners Meeting on P2P recommendations (referenced in revised response to CFSAC)
 - a. ME/CFS experts: invite participation for a portion of meeting
 - b. Publish a report summarizing the next steps for partner agencies from that meeting.
 6. Convene ME/CFS expert clinicians and researchers in 2016 or early 2017:
 - a. Agree on research definition and approach to subset definitions
 - b. Agree on key methods and standard data elements
 - c. Collaboratively develop a research Strategic Plan with defined milestones and share it publicly to get feedback from the community.

NIH Clinical Center Intramural Study Integration Recommendations:

Inclusion of ME/CFS experts on the Executive Committee and a proposed Expert Panel is of vital importance to the fullest success and accuracy of the intramural study.

1. Expand Executive Committee from Drs. Lipkin and Unger:
 - a. Add 2 clinicians identified as experts by patient community with publications in post-infectious ME/CFS: such as Dr. Daniel Peterson, Dr. Nancy Klimas, Dr. Jose Montoya.
 - b. Add a patient advocate.
 - c. Our understanding is that the Executive Committee will determine each subject's eligibility for the study, including confirmation of the ME/CFS diagnosis.
2. Establish a focused ME/CFS Expert panel to vet the proposed protocol and study design, and advise on all phases of the study, including these two specialized researchers: Chris Snell (or Staci Stevens), for exercise physiological assessment of post-exertional malaise, and Leonard Jason, for highly precise symptom assessment methods.
3. To minimize inconsistent diagnosis, select at least 75% of ME/CFS patients from the 9 expert clinicians participating in the CDC or Lipkin multi-site studies. Seek outside diagnostic review from Dr. Peterson, Dr. Klimas, or Dr. Montoya of all ME/CFS patients selected from other sources.
4. Urge the leadership of the intramural study to:
 - a. Visit a clinical site in the CDC multi-site study before enrollment begins, preferably one that conducts exercise testing.
 - b. Meet with expert clinicians, researchers, and patient advocates.

- c. Encourage attendance at IACFS/ME Conference in October by investigators on intramural study.
- d. Read IOM full report, P2P findings, IACFS/ME Primer for Clinical Practitioners, and literature based on Canadian Consensus Criteria definition.
- e. Recognize that both ARHQ and the NIH P2P independent panel recommended retiring the Oxford definition, and recognize that IOM questioned the selection of cohorts based on the Reeves 2005 definition (sometime called the Empirical definition). Therefore, all literature based on these definitions should be cautiously interpreted, and are suspect in their applicability to ME/CFS patients.
 - i. The P2P report noted: "In particular, continuing to use the Oxford definition may impair progress and cause harm. Therefore, for progress to occur, we recommend that this definition be retired; the ME/CFS community concur on a single case definition (even if it is not perfect); and patients, clinicians, and researchers agree on a definition for meaningful recovery."
From: <http://annals.org/article.aspx?articleid=2322804>
 - ii. The IOM report noted, "A study suggesting a role for childhood trauma in ME/CFS used the broad empirical definition of ME/CFS, which resulted in a biased sample with overrepresentation of individuals with depression and posttraumatic stress disorder (PTSD). The unusually high proportion of subjects with serious psychiatric problems likely explains the study finding of an association between ME/CFS and adverse childhood experiences. No other studies have suggested a higher rate of childhood trauma in those with confirmed ME/CFS as opposed to nonspecific chronic fatigue."

Respectfully submitted,

Courtney and Robert Miller obtained Pres. Obama's promise to elevate ME/CFS
Solve ME/CFS Initiative, Los Angeles, CA, national association

Health Rising, online patient community

Massachusetts CFIDS/ME & FM Association Quincy, MA
New Jersey ME/CFS Association, Florham, NJ

Open Medicine Foundation, Agoura Hills, CA

Pandora Org, Inc., Traverse City, Michigan

ProHealth, online patient community
Wisconsin ME and CFS Association, Inc., Patricia Fero, MEPD, President

Jennifer Spotila, JD

Mary Dimmock

Lily Chu, MD, MSHS

[...]

Claudia Goodell, Race to Solve ME/CFS

[...], Patient Advocate

Denise Lopez-Majano, Speak Up About ME

[...]

Nahle, Zaher (Solve ME/CFS)

[...]

Subject: RFI ME/CFS - Solve ME/CFS Initiative

Please find attached.

Zaher Nahle

June 24, 2016

National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892

Re: Request For Information (RFI) Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) – NOT-NS-16- 024

Dear Sir or Madam:

The enclosed document is the submission of the Solve ME/CFS Initiative in response to the above indicated Request for Information. It reflects a genuine effort on our part to outline some of the ME/CFS research needs and priorities. Notably, we have utilized the language, formatting, and style of the NIH itself to communicate these points. We welcome the use of this content in any manner that would be helpful for the ongoing efforts at the NIH to bolster ME/CFS research. To reiterate, this is a creation of the Solve ME/CFS Initiative, inspired by the NIH and does not represent any actual actions conducted by the NIH to date.

If you have any questions, we welcome a conversation. Please feel free to contact me anytime using the information provided below. Respectfully yours,

Zaher Nahle PhD, MPA

Vice President of
Research &
Scientific
Programs Solve
ME/CFS Initiative

(www.solvecfs.or

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Part I Overview Information

Response to Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Participating Organizations

The Solve ME/CFS Initiative (SMCI)

Notice Number: NOT-NS-16-024

Key Dates

Response Date: June 24, 2016

Related Announcements

In response to the NIH RFI (NOT-NS-16-0024), The **SOLVE ME/CFS INITIATIVE** designed and authored this mock FAO using existing NIH format, style, language and content. We limit our edits to the section labeled Part II in this mock FAO for specificity. **Disclaimer: This is not an actual announcement or a part of any actual NIH issued RFA.** This is for informational and educational use only.

Title: **Chronic Fatigue Syndrome: Pathophysiology and Treatment**

Part II - Full Text of Announcement

Section I. Funding Opportunity Description

1. Research Objectives

Purpose

This Funding Opportunity Announcement (FOA) issued by the National Institute for Neurological Disorders and Stroke ([NINDS](#)), the Trans-NIH working group on ME/CFS, and the co-sponsoring Institutes and Centers (ICs) of the National Institutes of Health (NIH) listed below encourages investigator(s)-initiated applications to study the etiology, pathophysiology, diagnosis, and treatment of chronic fatigue syndrome (CFS), also known as Myalgic Encephalomyelitis (referred to thereafter as ME/CFS). Proposals are solicited to investigate all age groups, including the pediatric and adolescent patient population, and across the spectrum severity to include the housebound and bedbound groups requiring tailored and condition-appropriate study design. The NIH is particularly interested in funding interdisciplinary research that will enhance our knowledge of the disease process and provide evidence-based solutions to improve the diagnosis, treatment, and quality of life of all persons with ME/CFS. This interdisciplinary research will include the building of scientific teams to develop biomarkers and/or innovative treatment interventions. Applications submitted under this mechanism should be exploratory and novel, and should break new ground or extend previous discoveries toward new directions or applications.

National Heart, Lung, and Blood Institute

([NHLBI](#)) National Institute on Aging ([NIA](#))

National Institute of Allergy and Infectious Diseases ([NIAID](#))

National Institute of Arthritis and Musculoskeletal and Skin Diseases

([NIAMS](#)) National Institute of Biomedical Imaging and Bioengineering

([NIBIB](#))

Eunice Kennedy Shriver National Institute of Child Health and Human Development

([NICHD](#)) National Institute on Dental and Craniofacial Research ([NIDCR](#))

National Institute of Diabetes and Digestive and Kidney Diseases ([NIDDK](#))

National Institute on Drug Abuse ([NIDA](#))

National Institute of Environmental Health Sciences ([NIEHS](#))

National Institute of Mental Health ([NIMH](#))

National Institute of Nursing Research ([NINR](#))

National Library of Medicine ([NLM](#))

National Center for Complementary and Integrative Health

([NCCIH](#)) National Center for Advancing Translational
Sciences ([NCATS](#))

Specific Areas of Research Interest

Applications that address gaps in knowledge of energy system defects, biochemical processing of ATP-bound substrates, nutrients sensing and signaling mechanisms, neuro- inflammation, Endocrine biology, cellular and systemic Immunity, host/pathogen interaction, gut/brain axis, Microbiome research, Post Exertional Malaise (PEM) and other characteristics of ME/CFS like Orthostatic Intolerance (OI), sleep abnormalities alongside environmental and biological risk factors are all encouraged. More specifically,

- *Bioenergetics-type projects* encompassing cellular and biophysical processes regulating energy production, the adaptation to metabolic and genotoxic stress conditions, mitochondrial dysfunction, aerobic and anaerobic bioenergetics, cellular signaling of substrate uptake, storage and processing (Fat, glucose, amino acids and complex lipids), tissue oxygen delivery, REDOX biology, biochemical and free radicals toxicity, DNA damage response, reactive oxygen species (ROS), and other structures affecting ATP generation and utilization, including nutrient/gene interaction in the regulation of energy source acquisition transport, mobilization and expenditure are welcomed.
- *Neuroendocrine-focused investigations* addressing adrenergic and non-adrenergic pathways, the Hypothalamic-Pituitary-Adrenal axis (HPA), Glucocorticoids regulation and signaling, Catecholamine's, energy 'rheostats' systems and energy balance like Leptin, Ghrelin alongside regulatory components of nucleotides, metabolites, substrates and precursors synthesis directly associated with energy production (mitochondrial and otherwise), as well as enzymes regulating Glucose and fatty acid oxidation, glycolysis, TCA cycle biology, nutrient shuttle and shunting mechanisms and the transcriptional regulation of cell metabolism, hormonal response, feed-forward and feed-back adaptive response and the role of regulatory complexes (transcriptional, enzymatic

and otherwise) important for the regulation of homeostatic energy systems across multiple tissues and organs are solicited.

- *Immunity and Inflammation* proposals including the area of immune-surveillance and immune-senescence biology are welcomed. That is in addition to studies addressing defined aspects of pathogen/host interaction, autoimmunity, immunotherapy and the pathologies of chronic inflammation in ME/CFS. Studies that will synergize, inform or complement existing national efforts at the NIH and the CDC (e.g., the intramural ME/CFS study at the National Institutes of Health and the clinical multisite study at the CDC) are welcomed.

In addition, investigations addressing hemodynamic changes (e.g., reduced blood volume in ME/CFS patients) and studies of *organ system physiology* nature particularly cardiovascular, cardiopulmonary, nephrology, exercise physiology, muscle contractility, neuromuscular and associated functions as well as the detoxifying roles of the kidney and immune surveillance are welcomed. A better understanding of signaling pathways cross talk and integration between multiple organs functioning and organelles biology (e.g., ER, mitochondria) in ME/CFS using interdisciplinary studies will promote the knowledge of how cells sense and respond to genotoxic and environmental stresses or triggers. This will also identify system perturbation in the adaptive response to pathological insults that is likely deficient in ME/CFS. Furthermore, possible determinants of heterogeneity including endogenous and exogenous stressors such as toxic metals, pesticides and air pollution components as well as disease-associated genetic mutations (gain- or loss-of-functions), chromosomal deletions translocations, point mutations, polymorphism including Single Nucleotide Polymorphisms (SNPs) genetic variants, inherited traits and epidemiological studies that address the natural history of the disease using strong patients registries or large epidemiological studies are also invited. Studies that build on current knowledge in identifying biomarkers, innovative treatment modalities, and/or the modifiable risk and protective processes specifically targeted by preventive and/or treatment interventions are encouraged. Innovative platforms using modern investigative tools such as RNA interference, iPS, CRISPR, single-cell-analysis or large scale, high-throughput and deep-resolution profiling, identification and screening of metabolic, immune, genetic, pathogenic and phenotypic signatures in ME/CFS using imaging, NMR, Mass Spec, calorimetric and other technologies are welcomed. The NIH is interested in funding interdisciplinary research that will enhance our knowledge of the disease process and provide evidence based solutions to improve the diagnosis, treatment, and quality of life of all persons with ME/CFS.

Background

Investigating ME/CFS is a top priority area at the NIH with the recognition of all urgent and unmet needs both at the clinical and translational side as well as in the basic sciences. It is now recognized that this disease has been disenfranchised and misunderstood - even stigmatized - for so long. In fact, the Institute of Medicine (IOM) was commissioned by several federal agencies including the NIH alongside AHRQ, CDC, FDA, SSA and others to establish clear clinical diagnostic

criteria for the disease and evaluate the current 'state-of-the-science' in ME/CFS. In 2015, the IOM released its 300-page report sounding the alarm regarding the dearth of investment and investigations in ME/CFS, pointing to the severe gaps in knowledge when it comes to this debilitating disease. The report underscored the complexity of ME/CFS as a multifactorial disease affecting up to 2.5 million Americans and advocated for the need of funding, collaborations, patient registries and studies that investigate the Pathophysiology of ME/CFS. Notably, the report stated that the committee was "struck by the relative paucity of research on ME/CFS" and "was unable to define subgroups of patients or even to clearly define the natural history of the disease" to specifically recommending that "Studies aimed at assessing the natural history of the disease and its temporal characteristics (onset, duration, severity, recovery, and functional deficits) are essential for a better understanding of ME/CFS and also are important to further refine the diagnostic criteria proposed in this report." In a press release on October 29, 2015 the NIH announced that is taking actions to bolster research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and NIH Director, Francis S. Collins, M.D., Ph.D., stated that "Of the many mysterious human illnesses that science has yet to unravel, ME/CFS has proven to be one of the most challenging." He went on to say "I am hopeful that renewed research focus will lead us toward in identifying the cause of this perplexing and debilitating disease so that new prevention and treatment strategies can be developed." This sentiment was echoed in the NIH Pathway to Prevention (P2P) report published in December 2015, with similar conclusions to those stipulated of the IOM report.

It is now widely documented that ME/CFS (ME/CFS) is a debilitating, multifactorial disease that affects many complex body systems. It is characterized by profound fatigue that is not improved by bed rest and may be exacerbated or re-kindled by physical or mental activity. Persons with ME/CFS most often function at substantially lower levels of activity from their pre-onset capacities. In addition to these defining characteristics, a diverse array of other symptoms is associated with ME/CFS. These symptoms include cognitive deficits, impaired sleep, myalgia, arthralgia, headache, gastrointestinal symptoms, and tender lymph nodes. Neither a specific cause(s) nor any specific diagnostic test(s) have been identified for this illness. The range of symptoms, however, suggests that there may be subtle perturbations in at least two systems of the body that are important for homeostatic regulation and in the multiple physiological pathways through which these systems communicate. These dysregulations may be triggered by diverse causes such as infection, stress, brain structure abnormalities, hormone levels, pro-inflammatory cytokines, etc. Evidence is needed to detail the immune mechanisms and/or mechanisms of microbial pathogenesis involved in ME/CFS.

Epidemiological evidence also requires further study. Existing data suggest that approximately up to two and a half million people in the United States are afflicted. ME/CFS is said to occur more frequently among women than men and among white Americans than in Americans of other racial/ethnic groups although large scale and methodical natural history studies are lacking. More recent studies narrow the gap between the sexes, as well as among racial/ethnic population subgroups. In addition, the prevalence of ME/CFS in children should be carefully investigated as it requires a range of additional considerations of sensitive nature. The role of dietary factors, background diets, and body compositions in study participants and persons with ME/CFS also

remains to be studied, along with differences according to race and gender across the lifespan.

Recent reports identified distinct immune signature in ME/CFS and implicated a dynamic disease kinetic where duration of illness could be very relevant in understanding disease prognosis. Another study identified altered metabolomics patterns in ME/CFS patients. A number of studies have also described mitochondrial dysfunctions in ME/CFS. Epidemiological data reveal ME/CFS, as well as other disorders that share pain as a common symptom, is often associated with chronic urologic pelvic pain syndromes. This relationship remains to be further elucidated through epidemiological and basic-science research.

Detection and treatment of ME/CSF also merit further study. Promising research to date has focused on identification of biomarkers for diagnosis of ME/CSF; nonetheless, more work is needed for a clinically applicable detection method. Studies of innovative treatment modalities and their relationship(s) to pathophysiology of ME/CFS and to co-morbid conditions are also needed.

Innovative, well designed studies are needed to provide a better understanding of ME/CFS, prevalence, pathogenesis, and pathophysiology, with the goal of developing improved diagnostic and intervention strategies. The heterogeneity of the ME/CFS population should be recognized in both basic, translational and clinical research; thus, sex, age/developmental stage, racial and ethnic variations should be considered along with any subtyping of ME/CFS in the study designs. This FOA encourages the integration of basic research with clinical observations in forming study hypotheses. The multisystemic nature of the disorder will benefit from a collaborative multidisciplinary (across scientific disciplines) team approach that will lead to the interdisciplinary solutions necessary to provide a foundation for understanding, diagnosing and treating this complex illness.

Applicants are encouraged to review the Institute of Medicine (IOM) released February 2015 and entitled “Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness, February 2015 (http://www.nationalacademies.org/hmd/~media/Files/Report%20Files/2015/MECFs/MECFs_ReportBrief.pdf) and the Trans-NIH ME/CFS Working group (<https://www.nih.gov/mecfsNIH><https://www.nih.gov/mecfs>) as well as the NIH, Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, December 9–10, 2014 (<https://prevention.nih.gov/programs-events/pathways-to-prevention/workshops/mecfs>). Other information on the CFSWG Web site (<http://orwh.od.nih.gov/cfs.html>) as well as recommendations from an NIH-sponsored CFS science summit held in October 2000 at Arlington, VA. May be helpful. This document may be found at (http://orwh.od.nih.gov/cfs/cfsWkshopSummary_6-03.pdf). They also are encouraged to review the summary of the scientific workshop: Neuroimmune mechanisms and chronic fatigue syndrome:

understanding central mechanisms, which may be found at (<http://www4.od.nih.gov/orwh/cfs-newhome.html>). Applicants also are referred to the Agenda for Research on Women's Health for the 21st Century, volume 2" (NIH Publication No 99-4386, http://orwh.od.nih.gov/pubs/agenda_book_2.pdf), as well as Exploring the Biological Contributions to Human Health. Does Sex Matter" (National Academy Press, Washington DC, <http://www.nap.edu/>), to ensure responsiveness to all aims of this FOA.

The evolution and vitality of the biomedical sciences require a constant infusion of new ideas, techniques, and points of view. These may differ substantially from current thinking or practice and may not yet be supported by substantial preliminary data. By using the R21 mechanism, the NIH seeks to foster the introduction of novel scientific ideas, model systems, tools, agents, targets, and technologies that have the potential to substantially advance biomedical research.

The R21 mechanism is intended to encourage new exploratory and developmental research projects. For example, such projects could assess the feasibility of a novel area of investigation or a new experimental system that has the potential to enhance health-related research. Another example could include the unique and innovative use of an existing methodology to explore a new scientific area. These studies may involve considerable risk but may lead to a breakthrough in a particular area, or to the development of novel techniques, agents, methodologies, models, or applications that could have a major impact on a field of biomedical, behavioral, or clinical research.

Applications for R21 awards should describe projects distinct from those supported through the traditional R01 mechanisms (which will also be announced separately for ME/CFS research). For example, long-term projects, or projects designed to increase knowledge in a well-established area, will not be considered for R21 awards.

Applications submitted under this mechanism should be exploratory and novel. These studies should break new ground or extend previous discoveries toward new directions or applications. Projects of limited cost or scope that use widely accepted approaches and methods within well-established fields are better suited for the R03 small grant mechanism. Information on the R03 program can be found at <http://grants.nih.gov/grants/funding/r03.htm>.

Additional areas of studies suitable for larger granting mechanisms such as the Research Project Grant Program (R01):

Epidemiology

- Conduct studies to define the natural history of the disease
- Explore whether pathogenesis and pathophysiology differ relative to age, sex, developmental period, racial/ethnic background, and co-morbid conditions.

- Compare the diagnostic criteria and symptomatology of ME/CFS in children and adolescents with those of adults.
- Describe the epidemiology of ME/CFS in older adults and explore the relationship of ME/CFS to general complaints of fatigue and exhaustion in the elderly.
- Conduct case-control comparisons of ME/CFS with syndromes such as fibromyalgia, interstitial cystitis/painful bladder syndrome, chronic prostatitis/chronic pelvic pain syndrome, irritable bowel syndrome and other multi-systemic illnesses that have similar or overlapping symptoms.
- Conduct genetic, epidemiologic, and cellular biologic studies investigating whether polymorphisms in clock-related genes alters cellular function in peripheral cardiovascular tissue or mediates abnormalities in peripheral endocrine function that are characteristic of the autonomic nervous system dysfunction associated with ME/CFS.

Diagnosis

- Develop novel and objective biological markers for the diagnosis of ME/CFS.
- Develop and validate techniques for linking biomarkers to behavioral responses associated with ME/CFS.
- Develop/refine objective measures for fatigue or sleepiness and severity of associated sleep disturbances.
- Develop/refine technologies to improve the identification and measurement of precipitating factors.
- Conduct longitudinal studies and studies with multiple sampling points to capture the progression of ME/CFS symptomatology.
- Explore the role of neuroimaging modalities in the diagnosis, treatment and progression of ME/CFS.

Physiologic Interactions

- Study the role of bioenergetics and energy system defects in ME/CFS
- Conduct large scale diet composition studies in ME/CFS
- Study the role of neuroendocrine and neuroimmune functions in ME/CFS pathogenesis and pathophysiology.

- Study the role of neuro-cardiovascular regulation in the loss of the normal control of blood pressure, heart rate and contractility in ME/CFS patients.
- Study the action of mediators (i.e., cytokines, chemokines) on the multiple, interacting, feedback-controlled systems that are dysregulated in ME/CFS (pathogenesis and pathophysiology).
- Study the mechanisms and consequences of dysregulation in the major physiologic control systems to better understand the multi-system symptoms among ME/CFS patients.
- Study the role of oxidative stress in the pathogenesis of and marginal nutritional deficiencies in the etiology of ME/CFS.

Treatment and Quality of Life

- Conduct clinical trials in ME/CFS patients to determine the efficacy of reliable and valid strategies that are used to improve quality of life in other chronic diseases.
- Conduct definitive trials to determine the effectiveness of currently prescribed pharmacologic, behavioral and other treatments used in ME/CFS.
- Develop and test new pharmacologic and nonpharmacologic strategies for managing symptoms, improving function, reducing disease burden and enhancing quality of life in patients with ME/CFS.
- Develop and test the efficacy of interventions that address issues particular to older ME/CFS patients.

Methodological Considerations

- Collaborations and networking: Collaborative arrangements with ongoing studies that provide patient populations, biospecimens, and data are encouraged if they meet the research needs of the project. Such arrangements should be clearly delineated in the application.
- Study Design: Improper study design and underpowered studies have made it difficult to compare or reproduce results from multiple studies. Careful stratification of patients and matching of controls, accurate collection of data and samples at specific time-points, and use of quantifiable outcome measures will facilitate comparisons between studies. Studies using a longitudinal approach, validated biomarkers, genetic whole genome analyses, or animal models also create opportunities for advancing a deeper understanding of ME/CFS. The inclusion of or focus on pediatric patients provides information on this important subpopulation.
- Interdisciplinary Research: ME/CFS is a complex illness requiring an interdisciplinary research approach. A large core of clinical and basic researchers will provide the expertise needed to studies a complex disease such as ME/CFS. Multidisciplinary studies and collaboration among investigators with expertise in appropriate disciplines are encouraged.
- Systems Biology: The incorporation of large amounts of data into computer models of disease may prove to be a powerful approach for studying ME/CFS. Systems biology can identify distinguishable patterns and networks from complex data which may help identify patients with di

fferent forms of disease. Such information will improve diagnosis, prognosis, and therapy.

Section II. Award Information

1. Mechanism of Support

This FOA will use the NIH Exploratory/Developmental Research Grant (R21) award mechanism (Note: Other FAO for two additional mechanisms: NIH High Priority, Short-Term Project Award (R56) and NIH Research Project Grant Program (R01) will be announced separately). The Project Director/Principal Investigator (PD/PI) will be solely responsible for planning, directing, and executing the proposed project.

This FOA uses Just-in-Time information concepts see [SF424 \(R&R\) Application Guide](#)). It also uses the modular as well as the non-modular budget formats (see the Modular Applications and Awards section of the [NIH Grants Policy Statement](#). Specifically, if you are submitting an application with direct costs in each year of \$250,000 or less (excluding consortium Facilities and Administrative [F&A] costs), use the PHS398 Modular Budget component provided in the SF424 (R&R) Application Package and SF424 (R&R) Application Guide (see specifically Section 3.4, Modular Budget Component, of the Application Guide).

U.S. applicants requesting more than \$250,000 in annual direct costs and all foreign applicants must complete and submit budget requests using the Research & Related Budget component.

2. Funds Available

Given the utmost urgency associated with ME/CFS and the decades of deficit in research investment and spending on the disease, The NIH has committed a sum of 250 million dollars as an initial investment in these RFAs (R21, R56 and R01). This excludes funding for consortium, program projects and other mechanisms or initiatives that could be announced separately at later dates. The nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. While typically awards pursuant to this funding opportunity are contingent upon the availability of funds and the submission of a sufficient number of meritorious applications, in this instance however the financial

plans of the Institutes and Centers (ICs) stipulated a firm commitment to providing support for this program.

The total project period for an application submitted in response to this funding opportunity may not exceed 2 years. Although the size of award may vary with the scope of research proposed, it is expected that applications will stay within the budgetary guidelines for an exploratory/developmental project; direct costs are limited to \$275,000 over an R21 two-year period, with no more than \$200,000 in direct costs allowed in any single year. Applicants may request direct costs in \$25,000 modules, up to the total direct costs limitation of \$275,000 for the combined two-year award period. Other granting mechanisms (e.g., R01) have different budget structure, NIH grants policies as described in the [NOT-00-00000](#).

This is not an actual announcement or a part of any actual RFA. This document was prepared and submitted by Dr. Zaher Nahle, Vice President for Research and Scientific Programs at the Solve ME/CFS Initiative using existing material from the NIH website as well as original opinions and content. This document is intended for informational use only and is a mo

