#MEAction Response to National Institute of Neurological Disorders and Stroke (NINDS) Request for Information: Soliciting Input on How Best to Advance Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research

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Questions? Email info@meaction.net

NOTE: The response to NINDS RFI was submitted through the official web form and followed NIH guidelines. This document has been reformatted to make it easier for the community to read the entire response. Where there is repetition in the answers we provided across multiple questions, we have simply replaced it with a link to the first instance of our response.

RFI QUESTION	**ASSIGN**
Q1: The most compelling ME/CFS research needs.	
Q2: Strategies for overcoming scientific challenges or barriers to progress in ME/CFS research.	
Q3: Potential research resources, tools, and/or materials that could help advance ME/CFS research or enable early career investigators and senior investigators new to the ME/CFS field to more easily conduct research.	
Q4: Relevant considerations and strategies for clinical ME/CFS research, including the development and validation of data standards and outcome measures.	
Q5: Overcoming challenges or barriers to establishing a career in ME/CFS research for early career investigators and those new to the field.	
Q6: Approaches to strengthen research and career training for ME/CFS investigators.	
Q7: Identifying related scientific areas that may be relevant to ME/CFS and strategies for establishing collaborations with experts in those areas to help advance ME/CFS research.	
Q8: Approaches to reduce barriers that prevent individuals with ME/CFS from participating in research. For example, these might be logistical challenges, such as difficulty traveling to a study site, or might be because of an unwillingness to undergo certain types of research protocols.	
Q9: Strategies for increasing ME/CFS research collaboration and communication between relevant stakeholders.	
Q10: Other approaches that may improve the overall field of ME/CFS research.	

Q1: The most compelling ME/CFS research needs.

MOST COMPELLING RESEARCH NEEDS

The overarching and most compelling research need in ME is to deliver diagnostics and treatments as quickly as possible. It is clear from conference reports and literature that opportunities exist today to deliver on this need within 3-5 years. For instance, with the right plan and political will, it should be possible to deliver one or more clinically viable ME biomarkers within 3 years and at least one FDA-approved symptomatic or disease-modifying treatment within 5 years.

However, NIH's current approach is too narrowly focused on basic disease pathology, planting seeds and hoping they grow. This approach is not only slow but also fails to seize on the present opportunities to quickly deliver patient-focused outcomes and proactively resolve the range of barriers, challenges, and misunderstandings that have stymied ME research for nearly 35 years.

These long-standing barriers and challenges have been extensively documented in NIH's 2011 State of Knowledge Workshop report, the FDA's 2013 PDUFA Drug Development Workshop, NIH's 2015 Pathways to Prevention report, the 2015 National Academy of Medicine report, CFS Advisory Committee recommendations since 2003, and numerous reports and recommendations by patient advocacy organizations over decades. #MEAction submitted a survey-based, patient-led RFI response in 2016; a letter to Director Collins signed by over 7,000 people; and met with and presented recommendations to Francis Collins in December 2018. We have solicited direct input from the community to develop this response, particularly for questions 8 and 9. However, the NIH has failed to act on the majority of recommendations in the past, demanding repeated intellectual labor from a patient community that continues to have the same unmet needs.

Change won't come through watchful waiting. Change can only come through decisive action. Delivering on patient-focused outcomes as quickly as possible will require greater political leadership and commitment from NIH, NIH funding commensurate with disease-burden, and a comprehensive, focused, creative program of parallel initiatives as detailed below. The following components must be included in this program:

1. **Strategic Research Plan:** We must have an outcomes-focused, strategic plan with the necessary funding, coordination, cross-institute commitment, stakeholder engagement, and NIH political leadership needed to make rapid progress. This plan must include parallel components to a) deliver diagnostics and treatments as quickly as possible, b) understand basic disease pathology, and c) address barriers and challenges as further detailed below.

One challenge in developing this strategic plan is that some of the most critical barriers and challenges to be resolved are the remit of other Health and Human Services agencies. For this reason, a Health and Human Services-wide strategy is needed. Director Collins had told President Obama in 2012 that Health and Human Services was "working to develop a Department-wide strategy to address the disease" but that never happened. As NIH develops a strategic research plan, it will need to partner with other agencies in the Department to ensure those agencies are actively addressing these issues.

2. **Rapid Expansion of Pool of ME Expert Clinicians:** One of the most significant research needs, especially given the definitional issues discussed in responses to other questions, is for rapid expansion of the pool of expert clinicians who can accurately diagnose people with ME . While developing the workforce of ME expert clinicians may not appear to be within NIH's remit, NIH will be unable to ramp up research with proper ME cohorts until this issue is addressed. NIH must provide the political leadership with its partner agencies within Health and Human Services and with the leadership of medical organizations to resolve this issue swiftly before these disease experts retire. NIH needs to creatively use every lever at its disposal to support the rapid expansion of the pool of disease experts.

   In addition to expanding the ranks of expert clinicians, it is essential that we capture ME expert clinicians' knowledge to expedite and inform research, including but not limited to knowledge about diagnosis, subtypes, outcome assessment, intervention effectiveness, and symptomology. NIH needs to provide tangible financial and structural support for current efforts targeted at capturing, organizing and disseminating this information before it is lost.

3. **Case Definition, Instrumentation and Research Tools**
   a. **Case Definition and Methods**: The 2011 NIH State of Knowledge report indicated that lack of consensus on the research case definition and methods to operationalize the application of the case definition threatens "the entire scientific enterprise." This issue has never been resolved and study participant selection criteria and methods still lack the necessary rigor to ensure the selected research cohorts all have ME. In fact, the NAM report stated that the Fukuda Criteria, one of the most commonly used research criteria, includes patients who do not have ME. The artificial heterogeneity resulting from non-specific case definitions has complicated the task of understanding the disease and hampered progress toward biomarker discovery and effective clinical trials. This has created confusion as to whether the observed heterogeneity is intrinsic to the disease or purely an artefact of mischaracterization. This circular problem of selection criteria impacting research and research needed to inform selection criteria will not resolve itself organically; proactive interruption of this cycle is necessary to progress the field.

      While NINDS' Common Data Elements Initiative established common data elements for research, it did not explicitly address this issue. Given the current crisis with knowledgeable clinicians, it is essential that NIH sponsor a meeting as soon as

possible for expert ME clinicians and researchers to reach consensus on the core criteria and methods used to accurately assess whether a given study participant has ME. Until this is completed, patient selection in NIH-funded research must use the 2003 Canadian Consensus Criteria (CCC) and/or the 2011 ME-International Consensus Criteria (ICC-ME) and must use the NIH CDE approved DSQ to assess symptom profiles. Post-exertional exacerbation is a hallmark of the disease and required for diagnosis according to the NAM report, CCC and ICC-ME; therefore it is essential that NIH-funded researchers ensure that all patients in cohorts labelled with ME exhibit this clinical feature.

b. **Instrumentation:** In addition to selection criteria and assessment methods, the field needs further evolution of basic instrumentation for assessing symptoms and outcomes. Numerous needs have been identified in NINDS' ME/CFS Common Data Elements initiative. These needs should be prioritized and funding made available to address them.
c. **Diagnostic Biomarkers:** To improve diagnostic accuracy of ME, we need at least one diagnostic biomarker, even if it's not unique to this disease. This has to be one of the highest priorities for the field. To make this happen quickly, NIH will need to issue a targeted funding opportunity with set-aside funding.
d. **Data Repository and Biobank:** Finalize a clearly articulated plan to establish and maintain NIH-funded centralized data and biospecimen repositories, which can store anonymized clinical and research data, including imaging data and biospecimens collected from well-characterized patients in past, current, and future research studies. These repositories should be fully operational within two years and accessible by outside researchers. The repositories can be extensions of existing repositories that are storing ME data and biospecimens or built from scratch. The current efforts focused on just the data generated by the NIH supported CRCs must be expanded to include institutions not funded in the CRC grant, provided they share their inclusion criteria and specifics regarding the manner in which the specimens were gathered and stored.

4. **Intrinsic Complexity and Heterogeneity of the Disease:** In addition to the issue of artificial heterogeneity, this disease, by its very nature, is heterogeneous in presentation, history, and response to treatment. This complexity impedes progress in research. To make progress in understanding this level of complexity, a plan must advance the following:
    a. Richer subtyping strategies and standards for recording and reporting those subtypes in databases and published literature. Key dimensions of subtyping include but are not limited to duration, severity, nature of onset, comorbidities, and concomitant medications
    b. Study designs and outcome measures that account for the impact of post-exertional malaise and the waxing and waning of the disease
    c. Biomarkers associated with those various subtypes to improve subtype identification

d. Study designs that include more study participants and are multi-disciplinary in nature in order to understand the interactions across systems that may be driving the disease and its heterogeneous presentation

5. **Targeted Clinical Intervention Initiatives:** ME expert clinicians have identified opportunities for clinical trials of drugs already being used off-label in clinical practice to relieve symptoms and improve patients' quality of life. In March 2019, attendees at the ME/CFS Clinician Summit called for action on this front, stating:

   "The field of ME/CFS needs evidence-based treatments. The combined clinical experience of ME/CFS clinicians supports efficacy of several treatments that have potential and warrant testing. Appropriate funding mechanisms are warranted. In addition, funding should support a clinical trials consortium."

   Advancing such trials has the potential to not only improve patients' quality of life and insurance reimbursement for clinical care but could also advance our understanding of disease mechanisms and improve trial enrichment strategies and outcome assessment methods. NIH should also leverage all funding opportunities including both clinical efficacy trials for interventions already being used off-label and for exploratory trials to identify responder/non-responder subgroups and investigate underlying biological variables driving disparate outcomes.

   To best leverage this opportunity, we recommend NIH issue a targeted funding announcement with set-aside funds to support the establishment of a Clinical Trials and Interventions Consortium to develop the network of clinical sites who participate in trials and to further develop the instrumentation, methods, and trial design to ensure success of these trials. We also recommend NIH institutes prioritize and provide funding for intervention trials already being used off-label in clinical practice.

6. **Insufficient knowledge about the disease:** The National Academy of Medicine was pointed in its conclusion that there's a remarkable lack of knowledge about the epidemiology and pathophysiology of ME. Efforts such as the NIH intramural study are important but have a narrowly-focused patient population and have been slow to recruit patients and yield results. The Collaborative Research Centers are too few, underfunded, and narrowly focused. Most studies focus on adults and are lacking in diversity, leaving children and minorities underrepresented. CDC has reported plans to undertake epidemiological research using surveys of patient reports of receiving a clinical diagnosis of "CFS." This method is unlikely to deliver the quality and range of data needed, particularly given the rates of clinical underdiagnosis and misdiagnosis seen in this disease. As outlined in our responses to other questions, additional efforts must be undertaken to understand the multi-system breadth of disease pathology and lay an accurate foundation of knowledge about prevalence, demographics, risk factors, natural progression and prognosis and ultimately prevention.

7. **Insufficient NIH funding:** The disparity between NIH's ME funding and the burden of disease, estimated at about $200M, is well-known. NIH has stated that funding will increase when more researchers submit meritorious applications. In response to the low number of submissions, NIH has called on the patient community to recruit researchers.. But without a substantial year-on-year funding commitment from NIH, researchers are unlikely to leave existing funded research programs and risk their careers on such a challenging and uncertain area. This is a point that researchers and CFSAC have made on numerous occasions: researchers are hesitant to enter the field because of challenges securing funding for ME studies and NIH's lack of substantial, sustained and dedicated financial commitment to ME. To overcome this barrier, CFSAC had repeatedly recommended that NIH issue disease-specific RFAs.

   The NIH funded 3 centers in the late 1990s, issued one RFA in 2006 and another in 2017 for the collaborative research centers. But these grants have been miniscule compared to the magnitude of the disease burden and research needs, and they have been too sporadic. The number and frequency of RFAs and the level of funding provided have not been sufficient to attract the number of researchers and the breadth of expertise needed to accelerate research.

   If NIH is serious about increasing the number of researchers, ramping up the level of funding, and accelerating growth in this field, then NIH must issue multiple, disease-specific, multi-year funding opportunities with set-aside funding. As listed below, there are numerous opportunities for RFAs that could address key issues in the field and rapidly generate breakthroughs that will produce impactful outcomes for patients.

   Beyond RFAs, NIH must issue disease-specific funding announcements for investigator-initiated studies and leverage all other funding options, including supplemental grants, to grow the field and attract senior researchers with expertise in adjacent areas. The argument that this would not be fair to other diseases is not an acceptable rationale, given the unique challenges that the field needs to overcome and the debility of ME patients.

8. **NIH Administrative Structure and Review Processes:** In spite of assurances to the contrary, it is not clear that any NIH institute has taken strategic accountability for ME. While NIH has reinvigorated the Trans-NIH Working Group, NIH is ultimately an institute-driven organization and it seems unlikely that the Trans-NIH structure can compensate for lack of strategic accountability for ME by one of the institutes. For instance, it is unclear how Trans-NIH Working Group recommendations translate into institute-specific strategies, goals, resource commitments, and actions. Even NINDS, which leads the Trans-NIH Working Group, does not list ME in the list of diseases it studies and its financial commitment is less than that of NIAID. Further, as has been reported by NIH staff, the number of Center grants awarded was throttled by the low level of financial commitment that NIH institutes were willing to offer.

NIH has said it has chosen the Trans-NIH approach because ME is a multi-system disease. To our knowledge, the use of the Trans-NIH structure for ME is unique situation in that while such Working Groups do exist for other diseases, those diseases are primarily housed in a given institute even when they are multi-system.

To ensure that ME is not at a disadvantage in strategic planning and funding decisions, NIH should maintain the Trans-NIH Working Group but also formally house ME in the National Institute of Neurological Disorders and Stroke and formally include ME in the strategic goals of the National Institute of Allergy and Infectious Diseases.

If NIH continues not to house ME in NINDS, then NIH must implement the necessary organizational structures to ensure progress is effectively achieved within its institute-driven organization. One approach is to establish and fund an Office of ME Research within the Office of the Director to drive the strategic planning, coordination, resource commitment, stakeholder engagement, and monitoring across institutes and with other key stakeholders that are required to get this field moving. Continuing to use part-time staff and the Trans-NIH structure to implement our country's response to this disease is inadequate and must be urgently revised.

Grant Review Processes: Given the challenges that researchers have reported in getting grant applications approved for ME, it is important to assess in what ways these processes may be impeding access to funds. Specific concerns with the review processes include:

1. What is NIH doing to address the dearth of reviewers on the SEP who both:
    a. thoroughly understand ME as a disease and
    b. have sufficient knowledge and expertise about the given area of science being studied (e.g. immunology, metabolomics, genomics, etc.) and the type of technology being used (e.g. imaging technology, computational modeling)?
2. Is the ad hoc nature of the SEP reviewers resulting in challenges with getting grants approved because the grantee is faced with new reviewers and new concerns if he or she has to resubmit the application.
3. Are applications being scored poorly by SEP reviewers and reviewers of clinical trials because:
    a. The reviewer has a personal opinion that the research is unimportant but that personal opinion does not reflect the actual priorities of the field?
    b. The reviewer has an expectation for preliminary data, size of supporting studies, etc. that is not realistic given the state of ME research?
4. Are experienced researchers with broad success in getting grants in other fields still having their ME applications scored poorly and if so, why?
5. Why are researchers having difficulty getting applications approved for clinical trials, even following multiple applications? Given that these are institute-specific processes, it is unclear whether the issue is lack of strategic commitment to the disease by that institute, or whether one of the issues above might be at play.

6. Do the program offices in each involved institute have the time, expertise, and interest to support applications that intersect with their institute and thus come their way? Have their institutes made this disease a priority in their strategic planning and goal setting?

NIH should formally evaluate the effectiveness of the review processes and whether they are creating an unnecessary impediment to the goal of accelerating research.

9. **Bold Leadership to Drive Rapid Change:** Two of the key barriers to forward progress are:
    a. the widespread stigma and misunderstanding about the disease and
    b. the critical lack of engagement by major academic centers, researchers, the pharmaceutical community, and the medical community and its leadership, as well as relevant federal agencies and NIH institutes.

As noted above, making progress on research is further complicated by the fact that some of the most critical barriers are within the remit of other agencies.

The ME patient community has done its part but does not have the political power, physical capacity, or financial resources to change the research landscape. It is the NIH that has the unique organizational position and political capital to influence the other Health and Human Services agencies and the research, industry, and medical communities to do what is needed to advance research. NIH must leverage its position and capital in an aggressive and creative outreach plan to these agencies and organizations to accelerate research.

10. **Stakeholder Engagement and Transparency:** NIH has implemented the Trans-NIH Working Group as a structure for coordinating ME initiatives. However, the activities of this group lack transparency and accountability to the community. With little buy-in as shown by the small financial commitments from relevant NIH institutes in recent years (resulting in funding of only 3 CRCs), this mechanism is insufficient to drive the needed scale of participation and commitment from across NIH. Finally, this group's work is not informed by the vital perspectives of those living with and studying ME.

With the recent dissolution of CFSAC, no formal venue exists for engagement of ME stakeholders with federal agencies responsible for addressing needs of patient community, research groups and other institutions. In a field where agency-interdependent issues have long been critical bottlenecks to advancement, it is unacceptable that a venue does not exist for the communication and coordination of actions to address interrelated needs.

NIH is in a strategic position to rectify this deficiency and should therefore develop a structured, NIH-led venue that engages community, academic, federal agency and industry stakeholders in a holistic and comprehensive approach to advancing research. This structure should also serve as a platform for facilitating movement on shortcomings that are outside NIH's purview but which gravely impact the community and represent critical barriers for growth.

In addition to establishing such a venue, there is a need for NIH to leverage its position and capital in pressing for restoration of CFSAC by HHS in order to reestablish a space for all cross-agency and community partnership, and resume the critical work that was underway in CFSAC subcommittees. This trans-agency mechanism, which included participation by multiple Health and Human Services, the VA, DOD, Social Security Administration, and the Department of Education, is essential to fully informing a broader federal strategy to address ME needs, and NIH is a critical player in this approach.

MOST COMPELLING SCIENTIFIC OPPORTUNITIES

The above issues are primarily focused on the initiatives needed to address the challenges and barriers. In parallel, there are compelling scientific opportunities that are immediately actionable and could make a big difference for the field if funding and researchers were in place. To seize these scientific opportunities and simultaneously grow the workforce, RFAs could be issued immediately to pursue these domains. We don't need to wait for the CRC and intramural studies to deliver findings to begin pursuing these opportunities. These scientific opportunities include:

1. Identification of objective sensitive and specific biomarker(s)
2. Analysis of disease-modifying treatment efficacy, symptomatic treatment efficacy, and exploratory intervention clinical trials
3. Characterization of spectrum of disease severity and associated features, development of standardized scale and terminology
4. Cross-sectional studies to understand subgroups, breadth of symptoms, spectrum of severity
5. Cross-sectional studies to define spectrum and prevalence of onset types, triggers
6. Exhaustive objective and subjective characterization of the pathophysiology underlying PEM (e.g. metabolites, cytokines, cellular composition, cardiopulmonary and metabolic dysfunction, etc.)
7. Development of in vitro models (e.g. serum transfer studies)
8. Characterization of metabolic dysfunction, mitochondrial function in energy metabolism and host defense
9. Measurement of of neuroinflammation, impaired functional connectivity, hypoperfusion, neurocognitive impairment
10. Characterization of autonomic, orthostatic and vascular dysfunction
11. Characterization of immunologic dysfunction (e.g. autoreactivities, immunodeficiencies, chronic inflammation)
12. WGS, GWAS to identify predisposing and symptom-associated risk variants, subset stratification
13. Analysis of the mechanisms of central and peripheral asthenia
14. Blood omics: cytokines, metabolomics, proteomics, transcriptomics, methylation profiles, exosome profiles, cellular integrity and function (e.g. NK cytotoxicity, RBC deformability, B cell maturity, T cell clonal expansion)

15. Measurement of functional impairment: CPET alternatives, orthostatic intolerance measures (e.g. NASA lean, cerebral hypoperfusion), activity meters, survey instrumentation
16. Additional CRCs to improve research domain diversity, accelerate progress
17. Development of disease-specific instrumentation, subjective and objective assessment methods, outcome measures
18. Diagnostic instrument development and validation (for clinical and research use)
19. Prospective longitudinal studies following triggering events (infectious and non-infectious)
20. Retro- and prospective longitudinal observational studies to define disease progression (develop a prognosis framework), incidence of progression to other diseases (e.g. autoimmune disease, cancer, cardiac disease, endocrine dysfunction, metabolic disease), causes of premature death
21. Prospective study of impacts hormonal change (e.g. pregnancy, menopause, HRT, puberty) on disease status

Q2: Strategies for overcoming scientific challenges or barriers to progress in ME/CFS research.

EPIDEMIOLOGIC KNOWLEDGE

Barriers:

- Lack of basic epidemiologic assessments characterizing disease landscape precludes informed construction of subgroup cohorts for exploratory and clinical research
- Given that CDC's plan for epidemiologic research is BRFSS, which is self-report phone survey based, there is a need for NIH to lead comprehensive epidemiologic studies that adequately capture this disease population
- Lack of patient engagement with medical care/survey capture due to stigma, uninformed practitioners, psychosomatic narrative polluting literature/medical practice
- Lack of centralized patient registry portal for engagement with research data capture efforts
- DMCC only includes CRC data and omits many large cohorts with extensive phenotyping data
- Sex, race, age, socioeconomic biases in existing data and research cohorts, males, minorities, poor, youth underrepresented (and underdiagnosed)

Strategies:

- Conduct exhaustive, comprehensive epidemiologic study, using appropriate patient selection methods, to define: demographics; prevalence; natural history, onset types, triggers, environmental exposures, risk factors; breadth of symptomology; spectrum of severity, establishing foundation to develop disease grading metric and instrumentation; exertional and cognitive provocation/PEM triggers; duration, fluctuation, progression, remission/recovery, relapse; comorbidities and overlapping syndromes (e.g. POTS, EDS, FM, MCAS, SFN, endocrine dysfunction, SIBO, MCS); functional and mobility impairment, disability.
- Assess and rectify age, sex, race, socioeconomic biases in diagnostic capture and prevalence estimates
- Overcome the sex, race, socioeconomic, age biases in existing data and research cohorts; account for males, minorities, poor, youth (underrepresented and underdiagnosed)
- Support appropriate community-based epidemiological strategies to help medical practitioners in underserved areas recognize ME in their patient populations
- Include ME-targeted components in existing broad epidemiological initiatives like the All of Us Research Program and the Environmental Influences on Child Health Outcomes Program
- Establish a large data and biorepository for comprehensive study of disease landscape, implementing exceptional rigor in data collection, construction, and design; and incorporate other large cohorts (e.g. UK Biobank, Klimas, Stanford) into the DMCC
- Fund establishment of a patient registry portal for data capture

- Fund targeted data aggregation efforts
- Fund retrospective analyses utilizing pooled existing cohort data and clinical histories
- Fund/initiate prospective longitudinal studies

ARTIFICIAL COHORT HETERO/HOMOGENEITY

Barriers:

- Lack of standardized research case definition, or agreement on core features required in all ME research cohorts
- Lack of validated, standardized objective measure(s) and/or biomarker(s) for cohort selection
- Lack of clarity, consensus, and transparency in defining and reporting cohort selection methods
- Deficiencies in disease-specific instrumentation, methods and guidelines to fully characterize and report disease features
- Lack of representation of severely ill in many studies
- Sex, race, age, socioeconomic, biases in existing data and research cohorts (males, minorities, youth, poor underrepresented)

Strategies:

- Encourage research selection criteria requiring PEM during grant application/review process
- Encourage transparency in reporting cohort composition metrics, including: definition(s) met and how this was determined; debility (KPS); severity definition and scale (by future disease-specific scale); duration; onset type; age; and sex
- Reach consensus on core inclusion/exclusion criteria and methods used for all ME research cohort selection to facilitate cross-study comparability and reproducibility
- Reconvene a methodological working group to identify deficiencies in CDE guidelines, further standardize assessment methods and measures, and recommend areas of need for development of novel tools
- Issue RFA for development and validation of disease-specific instrumentation and methodological practices to enable consistency in cohort selection, descriptive cohort reporting, comprehensive disease characterization, phenotype subgroup stratification, and sensitive capture of change in disease status, including: severity instrument, scale and standardized terminology; PEM instrument; fatigue instrument; sleep instrument; orthostatic intolerance instrument; pain instrument
- Review and refine CDE recommendations to include: require cohort reporting and data stratification by PEM status; PEM instrument; severity instrument, scale and standardized terminology; disease-specific fatigue, sleep, OI, pain instruments
- Develop and disseminate strategies for engaging severely ill and very severely ill in studies
- Overcome the sex, race, age, socioeconomic biases in existing data and research cohorts; account for males, minorities, youth, poor underrepresented (and underdiagnosed)

INTRINSIC BIOLOGICAL HETEROGENEITY

Barriers:

- Complex disease, multisystem involvement
- Multiple triggers/etiologies
- Disease provocation, spontaneous fluctuation
- Disease progression, remission, relapse
- Diversity of severity
- Diversity of symptomology
- Confounding comorbidities, overlapping syndromes
- Lack of validated, standardized objective measure(s) and/or biomarker(s) for cohort selection
- Deficiencies in disease-specific instrumentation, methods and guidelines to fully characterize and report disease features

Strategies:

- Issue FOA with set-aside funding for diagnostic tests
- Develop and disseminate strategies for engaging severely ill and very severely ill in studies
- Develop and disseminate strategies, methods and ethical guidelines for capturing baseline versus provoked states
- Encourage longitudinal data capture
- Large data and biorepository for comprehensive study of disease landscape
- Encourage and support identification of subjective-objective correlates
- Encourage and support subgroup stratification analyses:
    - Define prominent clinical phenotypes by: leveraging existing (and imminently expiring) clinical expertise, conducting large-scale data analysis in a comprehensive database
    - Encourage researcher data stratification analyses and reporting by: definition, severity, debility, onset type, exposure/trigger, duration, progression, recovery/remission, symptoms, age, sex
- Encourage transparency in reporting cohort composition metrics, including: definition(s) met and how this was determined, debility (KPS), severity (by future disease-specific scale), duration, onset type, age, sex
- Reconvene a methodological working group to identify deficiencies in CDE guidelines, further standardize assessment methods and measures, and recommend areas of need for development of novel tools
- Issue RFA for development and validation of disease-specific instrumentation and methodological practices to enable consistency in cohort selection, descriptive cohort reporting, comprehensive disease characterization, phenotype subgroup stratification, and sensitive capture of change in disease status, including: severity instrument, scale and standardized terminology; PEM instrument; fatigue instrument; sleep instrument; orthostatic intolerance instrument; pain instrument

- Review and refine CDE recommendations to include: require cohort reporting and data stratification by PEM status; PEM instrument; severity instrument, scale and standardized terminology; disease-specific fatigue, sleep, OI, pain instruments

BIOMARKER(S) DISCOVERY and VALIDATION

Barriers:

- Heterogeneous cohort even when properly characterized with case definitions that require core features of the disease such as PEM
- Lack of study reproducibility, incongruous findings across cohorts due to: intrinsic biologic heterogeneity, definition/selection criteria, specimen handling, laboratory methods
- Lack of replication studies of prior findings in larger cohorts
- Lack of comprehensive study of disease landscape to support subgroup analyses
- Specimen handling issues (e.g. culture of tissues without donor serum)

Strategies:

- Issue FOA with set-aside funding for biomarker discovery and validation
- Large data and biorepository for comprehensive study of disease landscape
- Expand cohort sizes and define selection criteria for replication of prior findings
- Deploy systems biology approaches for aggregate dataset analysis
- Support unbiased omics approaches with subgroup stratification analyses
- Fund large GWAS to identify risk variants, candidate pathways perturbed
- Encourage targeted subgroup stratification analyses defined by clinical phenotype, severity, comorbidities, symptom profiles
- Define, disseminate and incorporate into grant review feedback disease-specific specimen handling specifications and encourage adequate methods reporting

PATHOBIOLOGY DISCOVERY

Barriers:

- Artificially heterogeneous cohorts due to variable research case definitions not requiring PEM
- Lack of validated, standardized objective measure(s) or biomarker(s) for cohort selection
- Intrinsically heterogeneous cohorts due to biologic disease variability (diversity of severity, diversity of symptomology, potential diversity of triggers/etiology, confounding comorbidities, overlapping syndromes, multisystem involvement, fluctuation, progression/remission)
- Lack of dedicated disease-specific research funding opportunities
- Lack of *in vitro*/*in vivo* model systems, reliance on primary biospecimens for all experiments
- Dearth of clinical research resources: very few expert clinicians to support biospecimen pipeline; limits to properly diagnosed and characterized patients engaged with medical care (due to stigma, misperception, psychosomatic narrative, absence in medical education, few expert clinician); lack of centralized registry to channel patients toward qualifying research studies

- Paucity of aware, interested, capable, disease-informed researchers
- Lack of/failed study replication efforts across multiple/larger cohorts
- Spontaneously fluctuating and provoked disease state
- Need for appropriate control and illness comparison groups to support specificity
- Narrow focus of recent infectious acute-onset intramural study

Strategies:

- Issue FOA with set-aside funding for exploratory etiology investigations
- Issue FOA to develop *in vitro* and *in vivo* models (e.g. serum transfer studies)
- Expand cohort sizes and define selection criteria for replication of prior findings
- Encourage mitigation of artificial cohort heterogeneity by requiring PEM for all study participants
- Clarify methodological definition reporting standards to support study reproducibility
- Encourage use of sample sizes adequate to perform subgroup analyses on heterogeneous cohorts
- Encourage all researchers to conduct subgroup analyses within their datasets, supply suggested stratification variables (e.g. definition +/- PEM, clinical phenotype, symptomology, severity, comorbidities), and establish reporting expectations
- Solicit and fund “phase 0” exploratory trials in stringently-selected, enriched cohorts with the goal of pursuing exploratory outcomes, responder/non-responder and subgroup analyses rather than proving efficacy
- Encourage systems biology approaches, aggregate dataset analysis
- Utilize unbiased exploratory omics approaches with subgroup stratification analysis
- Support large GWAS to identify risk variants, candidate pathways perturbed
- Encourage accounting for baseline vs. provoked state with provocation studies
- Account for spontaneous fluctuation with longitudinal data capture, utilize time interval assessments to capture fluctuations, do not assume static even when unprovoked
- Survey and account for use of off-label pharmaceuticals, supplements
- Define and utilize appropriate control populations/illness comparison groups (i.e. activity-matched, fatigued, inflamed groups); ensure healthy controls are free of ME symptoms; standardize methods for determining control appropriateness
- Large data and biorepository for comprehensive study of disease landscape
- Establish disease-specific autopsy tissue biobank
- Support multi-disciplinary research studies that look at multi-system interactions
- Funding mechanism to support writing up case reports and comparison group studies
- Accelerate intramural infectious onset study; see multiple participants in parallel
- Initiate design process of comprehensive intramural studies on other subgroups (e.g. long duration, severely ill)

NIH ADMINISTRATIVE STRUCTURE, GRANT SUBMISSION AND REVIEW

Barrier:

- No formal institute home, administrative ownership, institutional accountability
- ME not listed on NINDS website list of diseases
- No dedicated full-time program officer(s) focusing solely on this disease

- Insufficient trans-institute coordination, institute participation, inconsistent funding commitments
- Insufficient commitment across NIH to making tangible progress on this disease
- In being handled exclusively by a Trans-NIH WG process, ME is not prioritized within any one institute; unclear how Trans-NIH WG recommendations translate into institute-specific strategies, goals, resource commitments, and actions
- Lack of transparency and stakeholder engagement with the Trans-NIH Working Group
- Ad hoc nature of Special Emphasis Panel not sufficient to ensure consistency in application review
- Dearth of qualified, informed grant reviewers, confounded by COI as collaborators in small research community
- Multidisciplinary representation required for each SEP review
- Not every ME application is captured and channeled through SEP
- Clinical trials applications not supported/reviewed by disease-informed reviewers across institutes
- Lack of disease-specific FOA to entice new researchers, support career focus
- Lack of ME researcher knowledge of availability of relevant RFAs in various institutes
- Lack of meritorious applications (rigor, novelty, significance)

Strategy:

- Develop a comprehensive outcomes-focused strategic plan that has the necessary funding, coordination, cross-institute commitment, stakeholder engagement, and NIH political leadership to aggressively address the challenges and barriers and truly "accelerate ME research". This plan must leverage the numerous opportunities to deliver patient-focused outcomes while simultaneously building up foundational knowledge about ME.
- Establish an Office of ME Research within the Division of Program Coordination, Planning, and Strategic Initiatives of the Office of the Director staffed with:
    - 1) A director responsible for developing and coordinating a long term fully-funded strategic plan, integrating ME initiatives into every Institute and Center (including leading/liaising with the Trans-NIH WG), who functions as a trans-institute "czar" (as recommended by CFSAC) driving progress across institutes; and
    - 2) At least one staff member responsible for outreach and coordination across all research priorities in each of the extramural and intramural grant programs, working with Program Officers in various institutes to facilitate informed review committees and ensure ample support to applicants during grant preparation.
- Increase Trans-NIH Working Group transparency and stakeholder engagement
- Hire multiple full-time Program Officers within ME's formal home institute focused exclusively on ME to support grant applicants, career development, study section composition
- Periodically re-evaluate Special Emphasis Panel effectiveness, composition, reviewer knowledge of disease-specific issues
- Bolster disease-specific grant writing support from Program Officers (e.g. regular grant assistance call-in "office hours" with NINDS and NIAID POs, invite junior/senior

investigators as well as outside domain experts, listserv, website covering study design issues)
- Engage a Program Officer in each of the Trans-NIH institutes with ME in their portfolio who knows how to navigate their institute
- Issue FOAs including those with set-aside funding; RFA and/or Program Announcement would resolve uncertainty about where to send applications and streamline grant application process
- Make guidelines and process very explicit and transparent to grant applicants (who to contact and when in considering submitting an application, whom to contact at various institutes and on the SEP)
- Ensure grant applicants and reviewers are given disease-specific CDE guidelines, feedback, and guidance
- Ensure clinical trials applications are handled by staff knowledgeable of ME issues
- Overcome reviewer bias toward significance versus basic questions that are not necessarily novel but are essential for this field at this time; ensure field-informed reviewers know to defend the merit of addressing basic questions in this disease
- Ensure grant reviewers understand and acknowledge the value of unbiased exploratory approaches versus standard hypothesis-driven proposals in this disease at this time

RESEARCH FUNDING

Barriers:

- Lack of set-aside RFAs, program announcements, administrative supplements
- Lack of year-over-year growth trajectory funding
- Inconsistent, insufficient contributions from other institutes
- Insufficient commitment from Office of the Director
- Paucity of investigator-initiated applications, including those from senior researchers at major academic centers
- Lack of meritorious applications
- Lack of committed, multi-year funding disincentivizing researchers, especially senior researchers from risking their career and entering this field

Strategies:

- Issue disease-specific FOAs for investigator-initiated applications
- Issue multiple, multi-year, disease-specific RFAs to ensure stability for newcomers (senior and junior investigators) to the field and enable a secure dedicated career path
- Supply, at minimum, an initial $50MM infusion to fund RFAs that will accelerate the field. Thereafter, implement consistent year-over-year growth trajectory funding increases (minimum 40%), including commitments from all trans-NIH WG institutes and a substantial commitment (e.g. 10% of the total NIH ME funds) from the Director's Common Fund, until funding is commensurate with disease burden.
- Issue and advertise the availability of interdisciplinary administrative supplements enabling grant recipients to recruit outside expertise, prompting established investigators to find expert collaborators in overlapping fields and construct joint approaches
- Solicit and fund high-risk, low-data exploratory and hypothesis-driven R21 applications
- Increase the payline for all ME grant applications

- Engage in targeted outreach and solicitation of applications from senior investigators at major academic centers whose domain expertise is relevant to ME

CLINICAL EXPERTISE

Barrier:

- ALL ME research currently relies on primary patient-derived data and/or biosamples
- There are very few expert clinicians with substantial experience diagnosing, monitoring or treating this disease
- The pool of diagnosed patients and the pipeline of patient-derived research resources are severely limited by the paucity of expert clinicians
- These expert clinicians are overburdened with clinical care obligations and existing research efforts and do not have the bandwidth to participate in new research collaborations with newcomers to the field or young investigators
- This small group of clinicians are nearing retirement, which will further diminish research capacity
- The collective knowledge of this clinician group is not recorded or disseminated, which is a barrier to new and less experienced clinicians
- ME diagnostic and treatment protocols are not incorporated into medical education curricula
- Medicare only allows for a 15-minute meeting in ME, meaning this complex illness is financially impossible for clinicians to take on
- Lack of objective testing/biomarkers poses an uncomfortable challenge to physicians in making an ME diagnosis by exclusion of other diseases and subjective symptom report

Strategy:

- Fund, convene and maintain a clinical network leveraging medical and scientific expertise
- Document, operationalize and encourage dissemination of clinical expert knowledge to researchers and the medical and patient communities
- Leverage Director Collins' political capital to draw attention to the clinical care crisis and pressure other federal agencies and medical societies to resolve barriers in expert clinician workforce growth, medical education, medicare funding, and accessibility to clinical care
- Provide leadership for a cross-agency structure to identify and tackle critical bottlenecks in clinical care and the clinical research pipeline
- Utilize existing NIH programs and work with other federal and state agencies to incentivize clinical specialization and research via loan forgiveness programs
- Pair researchers/clinicians with patients/advocates as mentors to help people new to the field learn how pervasively ME impacts lives and why work in this field is important

CLINICAL INTERVENTION TRIALS

Barrier:

- Paucity of clinical expertise, expert knowledge not widely accessible, limited bandwidth, nearing retirement, few sites that are remote for most patients
- Clinical subtypes undefined
- Variable selection criteria, lack of objective biomarker

- Cohort heterogeneity and complexity of presentation, comorbidities, concomitant medications
- Lack of standardized objective and subjective measures, undefined safety and efficacy outcome measures
- Historic failed grant applications are a deterrent to reapplication
- NIH's stated position that the field is not ready for clinical treatment trials
- Complexity of assessing response to intervention(s) (e.g. long term relapsing/remitting pattern, short term fluctuation, potentially high or low placebo effect, comorbidities, concomitant medications)
- Disease modifying versus symptomatic treatment approaches
- Lack of FDA engagement
- Population highly vulnerable to iatrogenic harm (especially severely and very severely ill)
- Lack of/failed study replication efforts across multiple/larger cohorts
- Spontaneously fluctuating and provoked disease state
- Need for appropriate control and illness comparison groups

Strategies:

- Fund, convene and maintain a clinical trials network leveraging clinical and scientific expertise
- Operationalize clinical expert knowledge
- Support standardization of research case definition, terminology, methods, and instrumentation
- Solicit and fund phase 1/2/3 efficacy trials in stringently selected, enriched cohorts, i.e. therapies that are already being used in clinical practice to decrease symptom burden, address comorbidities, and improve quality of life; therapies which have demonstrated efficacy in subsets of patients in small preliminary studies; and potentially promising novel interventions implicated in disease-specific and overlapping domain research. Examples of these therapies include: antivirals, immune modulators, drugs for pain, orthostatic intolerance, sleep, and comorbidities such as MCAS that are already being successfully used off-label in expert clinical practice to decrease symptoms and improve quality of life.
- Given the absence of understanding of underlying disease mechanism or *in vivo* models, solicit and fund "phase 0" exploratory clinical trials in stringently-selected, enriched human patient cohorts with the goal of pursuing exploratory biologic and subjective outcomes and utilizing comprehensive responder/non-responder and subgroup analyses rather than targeting efficacy outcomes in order to generate disease knowledge, parse cohort heterogeneity, and produce enrichment strategies and outcome measures for subsequent efficacy trials
- Support development of enrichment strategies:
    - Clinical subgrouping (e.g. symptoms, comorbidities, severity, duration, sex, medication use)
    - Objective selection criteria (e.g. 2-day CPET, PEM instrument, nano-needle impedance, cytokines, orthostatic intolerance measures)

- Define and utilize appropriate control populations/illness comparison groups (i.e. activity-matched, fatigued, inflamed groups); ensure healthy controls are free of ME symptoms; standardize methods for determining control appropriateness
- Define/develop and validate objective and subjective disease-specific measures of disease status for use as outcome measures/endpoints (e.g. CPET, activity meters, hours of upright activity ('feet on the floor'), heart rate variability, symptom assessment instrumentation, disease severity instrument, cognitive measures, and QoL measures)
- Include physical and cognitive provocations to measure PEM at baseline and endpoints in study protocols
- Account for disease fluctuation, appropriate longitudinal timecourse and data capture
- Survey use of off-label pharmaceuticals, supplements
- Develop methods for and ensure appropriate study design accounting for complexity of assessing response to intervention(s) (e.g. long term relapsing/remitting pattern, short term fluctuation, potentially high or low placebo effect, comorbidities, concomitant medications)
- Large data and biorepository for comprehensive study of disease landscape
- Support large-scale, high-throughput profiling studies to identify molecular targets/pathways
- Support large-scale, *in vitro* drug screening to identify candidate repurposed drugs
- Facilitate FDA engagement
- Engage the severely ill through encouraging studies to budget for e.g. home visits and mobile phlebotomists and engage very severely ill in studies through caregivers
- Develop instrumentation to capture a change in disease severity (as well as severity scale, standardized terminology, definitions), ensure usage during trials to capture potential harms due to participation/intervention, ensure vigilant harms assessments and reporting

WORKFORCE DEVELOPMENT

Barrier:

- Ignorance about ME in academic community
- Stigma/lack of disease validity in academic, medical community
- Lack of senior mentorship support to young investigators, discouragement to enter field
- Lack of evident funding stream to entice outside expertise, sustain a dedicated young investigator's career
- Lack of accessible bioresources (lack of large biorepository, patient registry, paucity of clinical expertise)
- Lack of *in vitro*/*in vivo* models to entice outside expertise, sustain a dedicated young investigator's career
- High threshold of disease knowledge for entry into the field
- Paucity of review materials in literature
- Publications often relegated to niche/low impact journals
- Psychosomatic narrative continues to pollute literature

Strategies:

- Heavily leverage NIH intramural and extramural networks to actively promote disease awareness and scientific intrigue; actively bait interest in disease mystery, novel opportunities for discovery
- Leverage Director Collins's and Koroshetz's megaphones, utilize every NIH media opportunity available to make the untapped scientific opportunities and plight of patients known within academia and industry
- Engage a concerted campaign to rectify medical and scientific stigma
- Sponsor NIH conferences annually to endorse validity, disseminate findings, facilitate collaborations; include dedicated day(s) and poster sessions for young investigators
- Require publication of whitepapers out of NIH-sponsored events
- Disseminate recorded materials out of NIH-sponsored events
- Facilitate representation at society conferences, encourage block symposium to elevate disease profile, invite high-profile scientists to leverage star power
- Exhaustively publicize new disease findings, CRC results
- Targeted outreach soliciting proposals from relevant intramural and extramural domain experts (senior PIs)
- Compile and disseminate a disease primer/educational videos for new investigators of biologic knowns, clinical resources, crash-course on disease-specific issues
- Facilitate matchmaking between domain experts and clinical expertise/bioresources
- POs perform matchmaking between applicants and outside domain experts during grant submission/revision
- Issue dedicated disease-specific RFA to entice outside expertise, demonstrate capacity to sustain a dedicated young investigator's career
- Improve perception of limited funds by e.g. broadcasting existing funding availability and SEP support across various institutes, via NIH communiques, Director's office
- Issue administrative supplements to support interdisciplinary involvement of senior newcomers
- Establish career training and mentorship program for young investigators
- Develop and disseminate documentation encouraging young investigators to enter the field, ensure a viable career path
- Further support a network of young investigators through the following initiatives: annual NIH young investigators conference; website; Program Officer availability for career growth; grant application support; proactive notification of applicable funding/fellowship opportunities, facilitation of collaboration and mentorship matchmaking dispersal of information on available bioresources; quarterly email updates on new resources/research findings targeted education on applicable funding opportunities; supplement awards to enable young investigator collaborations with established PIs/CRCs; encouragement and sponsorship for society conference attendance; encouraging young investigators to evangelize about ME to their colleagues; and providing materials summarizing research knowns, needs and opportunities
- Create a large data and biorepository for comprehensive study of disease landscape
- Create a patient registry to support study recruitment and data/sample procurement
- Support resolution of clinical expertise bottleneck to facilitate patient/data/sample access

- Fund development of *in vitro*/*in vivo* disease models
- Fund epidemiologic studies
- Fund biomarker discovery, disease-specific instrumentation and methods studies
- Utilize existing NIH programs and work with other federal and state agencies to incentivize specialization and research via loan forgiveness programs
- Pair researchers with patients/advocates as mentors to help people new to the field learn how pervasively ME impacts lives and why work in this field is important
- For conferences, working group meetings, e.g., include presentations by patients/advocates (live, video conferencing) about real life with ME (school, work, SSDI, encounters with HCP, housing, food access, social) to help them better understand the range of difficulties encountered by people with ME and as a reminder of why the work they are doing is so important

INTERDISCIPLINARY COLLABORATIVE APPROACHES

Barriers:

- Investigators with expertise in overlapping domains are ignorant about ME
- ME research is currently being conducted in silos
- Need mechanisms to link clinicians and researchers
- Role of comorbidities, overlapping syndromes understudied
- Clinical subtypes undefined

Strategies:

- Targeted outreach soliciting proposals from relevant domain experts (senior PIs) (e.g. energy metabolism, neuroinflammation, autonomic dysfunction, mechanisms of central/peripheral asthenia)
- Issue FOAs for collaborative projects to facilitate engagement of outside expertise with established ME researchers
- Issue FOA for collaborative supplements to existing projects (i.e. NIGMS Supplements for Collaborative Science (SCS))
- Issue FOA for interdisciplinary collaborative project proposals (i.e. NIGMS Glue Grants)
- Sponsor NIH conferences annually to disseminate findings, facilitate collaborations
- Facilitate representation at society conferences, encourage block symposium to elevate disease profile, invite high-profile scientists to leverage star power
- Engage in targeted outreach soliciting proposals from relevant intramural and extramural domain experts (senior PIs)
- Facilitate matchmaking between domain experts and clinical expertise/bioresources
- Compile and disseminate a disease primer/educational video(s) for new investigators of biologic knowns, clinical resources, crash-course on disease-specific issues
- Program Officers perform matchmaking between applicants and outside domain experts during grant submission/revision
- Issue dedicated disease-specific RFA to entice researchers and clinicians with outside expertise

- Create a large data and biorepository for comprehensive study of disease landscape. Leverage the integration database created for the current Centers to store research from present and future ME-related projects. Make data integration a requirement for NIH-funded research on ME. This could include structured and unstructured data with all PII masked to safely protect patient data. Solicit data from other agencies to get a baseline sample set for research. Department of Veteran Affairs has a very large health database, for example.
- Exhaustively publicize new disease findings, CRC results
- Leverage Director Collins's and Koroshetz's megaphones, utilize every NIH media opportunity available to make the untapped scientific opportunities and plight of patients known within academia and industry
- Support development of *in vitro*/*in vivo* disease models

COLLABORATIVE RESEARCH CENTERS

Barrier:

- Not enough CRCs
- Existing CRCs are underspending
- Ongoing and renewal funding for existing CRCs not secure
- Lack of clinical capacity within CRCs, dependent upon sparse, busy, distant outside clinical expertise
- Not enough scientific and clinical outreach, lack of clinical education component
- Narrow focus of CRC studies (primarily blood omics)
- Not enough collaboration, data sharing

Strategy:

- Fund existing CRCs adequately; encourage rapid CRC funding utilization by leveraging follow-up RO1 availability to build upon promising findings; and issue renewal funds at expiry
- Issue administrative supplements to support educational outreach to the research and medical communities
- Issue administrative supplements to facilitate engagement of outside/overlapping domain expertise in CRC projects
- Issue FOA to fund a minimum of three more CRCs with expanded domains of focus
- Support new CRCs with a diversity of research domains, for example: characterize functional/exertional features (i.e. Cook, Stevens, Keller, Systrom), neurologic aspects (i.e. Younger, VanElzakker, structural, neurocognitive).
- Enforce requirements for collaboration, data sharing between CRCs
- Accelerate DMCC construction, analyses, and make CRC/DMCC data publicly available to the scientific community
- Heavily publicize CRC existence, publications, study recruitment

STAKEHOLDER ENGAGEMENT

Barriers:

1. Dissolution of CFSAC has left the ME community with no channel through which to communicate needs to NIH or other federal agencies
2. No specific venue within NIH for community engagement
3. Lack of transparency and community engagement with the Trans-NIH Working Group
4. Sparse disease-specific information and resources available online
5. Lack of venues for researcher engagement with patient/caregivers to understand disease features
6. Level of patient physical and cognitive impairment, disability and lack of financial resources
7. Not enough CRCs
8. Lack of clinical capacity within CRCs, dependent upon sparse, busy, distant outside clinical expertise
9. Not enough scientific and clinical outreach, lack of clinical education component
10. Not enough collaboration, data sharing

Strategies:

- Leverage Director Collins's political capital to ask HHS to restore CFSAC
- Develop a structured, NIH-led venue focused on advancing research that engages: ME patient, caregiver, and advocate communities; clinical communities; research communities; relevant NIH institutes; other federal agencies; academic institutions; medical and scientific societies; and the pharmaceutical industry in order to:
    - >> undertake a holistic approach to the wide-ranging problems impacting ME research
    - >> engage cross-agency collaboration in resolving interrelated and interdependent bottlenecks in growing the field
    - >> provide leadership and structure for a venue which facilitates movement on key issues that fall outside NIH's remit (e.g. HHS, Department of Education, SSA, VA) but impact the community and ultimately the capacity for growth in NIH-led research (such as diagnosis, clinical care, medical education, school accomodations, social security disability, and medicare).
- Establish Trans-NIH Working Group transparency and stakeholder engagement
- Proactively leverage Director Collins's and NIH Institutes' political capital and networks to increase disease awareness and active engagement among medical and scientific societies, academic institutions, and federal agencies
- Leverage NIH intramural and extramural networks to promote disease awareness and scientific intrigue; actively bait interest in disease mystery, novel opportunities for discovery
- Initiate a concerted academic awareness campaign to bait scientific interest
- Leverage Director Collins's and Koroshetz's digital megaphones, utilize every NIH media opportunity available to make the untapped scientific opportunities and plight of patients known within academia and industry
- Initiate a concerted public awareness campaign to rectify medical and scientific stigma
- Fund additional CRCs
- Encourage/require and support CRC education, clinical training, outreach efforts

- Sponsor NIH conferences annually to endorse validity, disseminate findings, and facilitate collaborations; include dedicated day(s) and poster sessions for young investigators, and invite the patient and advocacy communities to attend and participate
- Disseminate recorded materials out of NIH-sponsored events
- Require publication of whitepapers out of NIH-sponsored events
- Facilitate representation at society conferences, encourage block symposium to elevate disease profile, invite high profile scientists to leverage star power
- Exhaustively publicize new disease findings, CRC results
- Compile and disseminate a disease primer/educational video(s) for new investigators of biologic knowns, clinical resources, crash-course on disease-specific issues
- Facilitate matchmaking between domain experts and clinical expertise/bioresources
- Initiate and host digital roundtable events between researchers and patients/caregivers to facilitate discussion and brainstorming around key issues in ME research (e.g. barriers to study participation, what PEM feels like, triggers of PEM or long-term relapse)
- Include ME in the list of diseases on the NINDS website
- Expand the NIH digital space addressing ME research to include recorded materials (conference presentations, links to CDC resources), disease-specific educational materials for researchers and newcomers to the field, links to patient registries and available data/biorepositories, links patient support/advocacy organizations
- Disseminate new research findings, funding opportunities, study recruitment opportunities, event notifications via listserv
- Support a patient registry to facilitate study recruitment and data/sample procurement
- Establish and maintain NIH-funded centralized data and biospecimen repositories, which can store anonymized clinical and research data including imaging data, and biospecimens collected from well-characterized patients in past, current, and future research studies, including existing repositories. Make accessible to outside researchers.
- Fund epidemiologic studies
- Support resolution of clinical expertise bottleneck to facilitate patient/data/sample access
- Fund, convene and maintain a clinical network leveraging clinical and scientific expertise
- Document, operationalize and encourage dissemination of clinical expert knowledge to researchers and the medical and patient communities

Q3: Potential research resources, tools, and/or materials that could help advance ME/CFS research or enable early career investigators and senior investigators new to the ME/CFS field to more easily conduct research.

Q4: Relevant considerations and strategies for clinical ME/CFS research, including the development and validation of data standards and outcome measures.

CLINICAL EXPERTISE
CLINICAL INTERVENTION TRIALS
ARTIFICIAL COHORT HETEROGENEITY
INTRINSIC BIOLOGICAL HETEROGENEITY
BIOMARKERS
STAKEHOLDER ENGAGEMENT

Q5: Overcoming challenges or barriers to establishing a career in ME/CFS research for early career investigators and those new to the field.

WORKFORCE DEVELOPMENT
NIH ADMINISTRATIVE STRUCTURE, GRANT SUBMISSION AND REVIEW
RESEARCH FUNDING
CLINICAL EXPERTISE
PATHOBIOLOGY DISCOVERY
BIOMARKER
ARTIFICIAL COHORT HETEROGENEITY
INTRINSIC BIOLOGICAL HETEROGENEITY
EPIDEMIOLOGIC KNOWLEDGE
INTERDISCIPLINARY COLLABORATION

Q6: Approaches to strengthen research and career training for ME/CFS investigators.

WORKFORCE DEVELOPMENT

Q7: Identifying related scientific areas that may be relevant to ME/CFS and strategies for establishing collaborations with experts in those areas to help advance ME/CFS research.

Scientific Areas:

Neuroimaging
Neuroinflammation
Autonomic Nervous System
Orthostatic, vascular dysfunction
Neurovirology
Neuroendocrine
Hematology
Immunology
Rheumatology
Metabolomics
Microbiome
Exercise intolerance
Fatigue, cancer fatigue
Sleep dysfunction
Emergency Medicine
Integrative Medicine
Nutrition

Diseases:

Mitochondrial disorders
Connective Tissue Diseases (EDS)
Small-fiber neuropathy
Fibromyalgia
Dysautonomia (POTS, NMH)
Neurologic trauma
Neuroinfections, viral encephalitis
Neurostructural disorders (spinal stenosis, CII, cranial hypertension, Chiari malformation, CSF leak, cranial hypoperfusion)
Neurocognitive, neurodegenerative disorders (Parkinson's, Alzheimer's, Huntington's, vascular dementia, frontotemporal degeneration, Lewy body disease, prion disease, normal pressure hydrocephalus, dementia due to HIV infection)
Neurologic autoimmunities (MS, MG)
Humoral autoimmunities (Hashimoto's thyroiditis, Sjogren's, SLE)
Autoinflammatory disorders (MCAS, PFAPA/FMF, APS, sarcoidosis)
Immunodeficiencies (hypogammaglobulinemia)
Endocrine disorders (hypothyroidism, pituitary tumor, Hashimoto's)
Brain, pituitary tumors
Migraine

Paralysis, Bell's palsy, seizure disorders, myoclonus, ankylosing spondylitis
Hematologic malignancies, splenomegaly (NHL)
Multiple chemical sensitivity, tinnitus
Dysbiosis, IBD, SIBO
TMJ
Adenitis, sinusitis, pharyngitis, blepharitis, optic neuritis
Pernicious anemia, hemophagocytic lymphohistiocytosis
Unexplained infertility, endometriosis, vulvodynia

INTERDISCIPLINARY COLLABORATIVE APPROACHES
COLLABORATIVE RESEARCH CENTERS
WORKFORCE DEVELOPMENT

Q8: Approaches to reduce barriers that prevent individuals with ME/CFS from participating in research. For example, these might be logistical challenges, such as difficulty traveling to a study site, or might be because of an unwillingness to undergo certain types of research protocols.

- Currently, most participants in ME research are patients of the dozen or so expert clinicians, most of whom don't take insurance. This greatly limits the diversity of patients being studied. To increase diversity, train doctors in underserved areas to diagnose people with ME and refer patients to studies. This can also help with the clinical care crisis.
- Very severely ill and severely ill patients are rarely involved in research because they are completely or mostly unable to leave the house. Most studies are self-selecting for minor and minor-moderate patients. Perform in-home blood draws or other assessments whenever studying severe and very severe patients or patients during a crash.
- It may also be possible to tap biorepositories of well-characterized patients to utilize samples that have already been collected or may be collected in the future.
- Arrange for cabulance or taxi/rideshare transport to/from study site to reduce financial and cognitive burden to mild/moderate patients.
- Consider satellite sites for larger studies to minimize travel. This need can be leveraged as an opportunity to partner with universities and larger medical centers and engage them in ME research.
- Participating in research can be challenging for patients at all levels of severity since both physical and mental expenditures can lead to negative health effects. Make sure to allow for as much rest as possible between tests whenever doing so wouldn't affect research results. Wherever the study design allows, ask the person with ME whether they prefer to make one, intensive trip or several, shorter trips spaced out over a manageable period of time.
- Minimize filling out of forms and/or allow participants to fill out forms at home days before or after the research.
- Whenever possible, researchers should provide test results to patients' clinicians.
- Provide flexibility in scheduling visit times would both make it easier for patients with delayed sleep schedules to participate and improve baseline data collection, as early start times can create extra physical stress by drastically reducing sleep.
- Provide an environment equipped with ample comfortable upright and recumbent seating opportunities (chairs with stools, recliners, beds) and continually communicate with patients about their availability. Supply wheelchairs and escorts to transit patients between locations, including meeting them at the door for dropoff/pickup. Limit the number of steps required between location changes as much as possible, providing seating opportunities along the way and time between tests for stopping to rest.
- Make efforts to limit the sensory stimuli within research environments (light, sounds, smells), including: dimming lights, supplying dark glasses; reducing ambient noise, adjusting machine volumes, asking staff persons to speak quietly and limit

communication to minimum necessary if patients are experiencing sensory overload, and supply noise muffling ear muffs; asking staff persons to refrain from wearing fragrances, limiting odorous chemical uses in cleaning the research environment. Before inviting patients to a study site, have staff transit the required route being especially attentive to visual, auditory and olfactory stimuli, and remedy any exposures wherever possible. Throughout study visits, be especially attentive to patients' body language and expressions, and ask patients often if anything can be done to make them more comfortable. They may be experiencing extreme sensory overwhelm but are unlikely to voluntarily communicate the fact, or may be so overloaded that they are unable to verbalize, but could nod if asked.

- Offer nutritious snacks free of common allergens and hydration during study visits, especially before and following blood draws and exertion/postural challenges.
- Administer post-procedure supportive measures such as IV saline to make stress testing less dangerous/frightening and aid in comfortably making the trip home to bed and in limiting the severity of PEM.
- Many patients are intolerant to loss of even minimal amounts of blood. Limit blood draw volumes to the absolute minimum necessary. Provide extra fluids before and after draws. Perform blood draws while the patient is reclining or lying down. Be prepared for loss of consciousness, breathing or arrhythmia/arrest. Offer rehabilitating IV saline to mitigate crashes after blood loss.
- Researchers may get very short responses before, during, after testing because of difficulty focusing, pain, or exhaustion from testing. Patients may be more able to respond if they can lie down or recline, and may become more responsive after being given time to recover.
- Account for and accommodate a caregiver's essential role before, during and after studies.
- Many research protocols involve exercise testing which can lead to long-term and even permanent worsening of symptoms for people with ME. Focus on finding ways to measure impairment without requiring multi-day exercise testing.
- Ensure provocation studies incorporate disease-specific training and staffing of clinical support personnel present at all study visits in order to mitigate and navigate PEM subsequent to exertional or cognitive challenge (e.g. advance hydration, post-challenge IV saline, postural support, control of environmental stimuli, transport, cardiac resuscitation, seizure support, ER transfer, and post-visit follow up)
- Develop standardized disease-specific informed consent protocols for use in provocation studies that adequately inform patients of potential long term iatrogenic harms and risks of undergoing CPET or other major exertional challenge. Recognize that rather than being unwilling, people with ME may be unable to perform certain activities without high risk of harm.
- Support study designs which incorporate tiers of exertional risk in order to supply study participants with a choice in undergoing mild/moderate/extreme challenges rather than forcing an all-or-nothing decision. Participants may be uncomfortable with one extreme option, but eager to participate at a lower threshold.

- Many patients face financial constraints due to their inability to work. Whenever possible, provide coverage for travel expenses to/from study site. Consider appropriate monetary compensation given the potentially deleterious physical effects on participants.
- Overcome the sex, race, socioeconomic, age biases in existing data and research cohorts; account for males, minorities, poor, youth underrepresented (and underdiagnosed). Take steps to ensure that diversity is considered for researchers, clinicians and support staff participating in studies by liaising with the NIH's National Institute on Minority Health & Health Disparities Office.
- Aim for study populations large enough to be able to support subgroup analysis and identification.
- Ensure that findings determined in narrowly defined cohorts are then replicated in populations that are more typical of the diversity of the disease seen in clinical care with its varied presentation, demographics, comorbidities, and concomitant medications.
- Maintain a centralized website where enrolling studies funded by the NIH are listed, in which keeping content and contact information up to date is a required task for grant recipients

Q9: Strategies for increasing ME/CFS research collaboration and communication between relevant stakeholders.

STAKEHOLDER ENGAGEMENT
INTERDISCIPLINARY COLLABORATIVE APPROACHES
COLLABORATIVE RESEARCH CENTERS
WORKFORCE DEVELOPMENT

Q10: Other approaches that may improve the overall field of ME/CFS research.