The Myalgic Encephalomyelitis Action Network
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October 21, 2019

Dear Dr. Koroshetz,

We are writing to respond to the NANDS Council Working Group report on ME/CFS research. We thank NIH for commissioning the report and the Working Group members for their commitment and effort.

We acknowledge the positive aspects of this report: the recommendation for a strategic plan, the creation of an interagency group for stakeholder collaboration, and the recognition of the significant barriers that have impeded research. However, none of this is new; the two recommendations and the identified barriers have been repeatedly stated for decades in government reports and by CFSAC and the community. We acknowledge the short-term initiatives announced in the October 17 NIH call and the forthcoming PARs, but are concerned to hear that they lack set-aside funding.

Unfortunately, this is not enough. We see no indication that our urgent need will finally be met with the kind of comprehensive, proactive and ***funded*** response that is required to deliver outcomes to patients right now. Our community is in crisis and NIH's response again fails to address that crisis. Further, by failing to effectively address the most critical issues or dedicate the necessary resources, even the inadequate and incremental progress promised by the report is uncertain. Our specific concerns are outlined in Attachment 1. Our detailed list of concerns with the report and recommended solutions are listed in Attachment 2 table.

NIH must act now to allocate the resources and remove the critical barriers to research required to bring real change and hope to people with ME. In parallel with longer-term efforts, #MEAction is calling on the NIH to immediately:

1. Provide multiple, multi-year ME/CFS-specific program announcements, including those with set-aside funding, to fund researchers and accelerate research in both adult and pediatric populations. These must be consistently available year-over-year with growth-trajectory increases in order to effectively build up the field.
2. Effectively and rapidly address the critical barriers impeding research. In particular, NIH must fund and support a meeting of ME researchers and clinicians to reach consensus on patient selection methods and criteria for research.
3. Provide RFAs to accelerate identification and validation of biomarkers.

4. Fund establishment of a clinical trials network and clinical treatment trials, a recommendation broadly supported by the US ME/CFS Clinician Coalition.
5. Use NIH's political leadership and partnership with other federal agencies to proactively and boldly address the stigma and clinical crisis that are impeding progress in research.

For years, NIH has said that the patient community must do more to change the research landscape. But community funding and advocacy is already driving an active research program at Stanford along with the revamping of its clinical care center. Clinicians and researchers from Harvard have established a research center, and plan to establish a clinical care center. The Open Medicine Foundation has announced a $20M fundraising goal for 2020. Other institutions, such as the Institute for Neuroimmune Medicine at Nova are also leveraging private funds to progress research. This is being done with little support from NIH, while NIH-funded researchers, such as the collaborative research centers, state that the funding is inadequate.

It is long past time for NIH to truly "accelerate ME/CFS research" and mount a response to ME that is commensurate in scope, funding, and urgency with both the efforts of the ME community and the terrible disease burden and economic impact of ME. We appreciate that achieving these objectives will require strong leadership from Dr. Collins and commitment from multiple institutes. We encourage you to work with Dr. Collins to rapidly achieve the institute-wide commitment required to create real change and hope for people with ME.

Sincerely,

#MEAction

CC: Drs. Francis Collins, Vicky Whittemore, Joe Breen, Andrew Breeden, Robert Finkelstein

ATTACHMENT 1: Details on Key Concerns with the Report

Our key concerns with the report fall under the following four themes.

1. Lack of Urgency and Lack of Focus on Patient Outcomes

ME affects over one million Americans, can strike anyone at any time, and as Dr. Roberds acknowledged, causes more functional impairment and a lower quality of life than many other chronic diseases, a burden borne by patients with no treatments and dismissive, disbelieving medical providers. Further, the few clinical experts in practice are rapidly reaching the end of their careers, exacerbating the clinical crisis and placing the clinical knowledge base at risk.

Yet this report and the strategic planning approach described in the October 17 call lack the sense of urgency commensurate with the crisis the ME community faces. There are no timelines. There are no recommendations to fast-track initiatives to address critical gaps, such as lack of biomarkers and consensus on patient selection methods, well-known gaps that have hindered progress for decades. There are no plans to fast-track clinical treatment trials, which could relieve patient suffering in the shorter term while enriching efforts to understand disease mechanisms. There are no plans to address the clinical crisis, which is hobbling our ability to expand research. A lack of timelines and failure to pursue such opportunities in parallel are glaring omissions.

NIH's lack of urgency in its response is reinforced by how little in this report is new. While more detailed, the report reiterates the same problems that have been highlighted over decades, including in the 2011 State of Knowledge Report, the 2015 Pathways to Prevention Report, the 2015 National Academy of Medicine report, the 2018 Common Data Elements Initiative, numerous CFSAC recommendations issued from 2003-2018, those of the prior CFS Coordinating Committee, and in congressional appropriations reports going back to 1988 (as documented in the 2000 US Government Accountability Office report). We have spent years outlining the same issues and yet we find ourselves in much the same position as before: we see our problems restated again in a formal report with no concrete, comprehensive plans to tackle them. In fact, almost all of the strategies in this report explicitly defer to another process without a budget or timeline. At the Accelerating ME/CFS Research Conference in April, Dr. Collins said "we want to provide the kind of hope for ME/CFS that is attached to action." We do not see in this report the tangible, time-bound, outcomes-driven plans for action that warrant hope.

Yes, important steps have been taken recently, as evidenced by the collaborative research centers and the intramural study, and additional steps are planned, as described during the call on October 17. But those steps are ***not nearly enough***. NIH continues to fail to provide the political leadership, institutional commitments, research funding, and relentless focus on urgently producing outcomes for patients in parallel with resolving the key barriers that have left the field in a quagmire. Without this, the field will stumble along for many more years - years of terrible debility and suffering endured by people with ME.

NIH is the only institution with the scope, resources, and influence necessary to resolve these complex, interconnected, field-wide barriers and rapidly drive meaningful change. Waiting for these problems to resolve organically within the research community has not worked for decades and is not an acceptable strategy. This passive approach will keep us going in

circles and unable to make progress. NIH must do more - bigger, bolder, faster - for people with ME.

In parallel with longer-term efforts to understand disease mechanism, NIH must implement an aggressive, milestone-driven response focused on rapidly addressing critical barriers to research and producing meaningful outcomes for people with ME.

2. Insufficient Institute and Funding Commitment

As with earlier reports, this report reiterates the lack of research, the lack of researchers applying for NIH grants, the stigma within the research and clinical communities, the inadequacy of basic research infrastructure and methods, the lack of clinicians to fill their essential role as research partners, and the substantial lack of research funding by NIH. As Dr. Roberds stated in his NANDS Council presentation, there are very few unique investigators and funding is less than that seen in many rare diseases. Certainly, NIH funding is far below what would be expected given the disease burden and is not much higher in real dollars than at its earlier peak in 1995.

This disease is trapped in a vicious cycle where these interdependent problems - stigma, lack of knowledge, lack of biomarkers, the small community of researchers and the vanishing pool of clinicians, challenges with the SEP grant review process, inadequate research infrastructure and methods, and especially the lack of accessible funding - are impeding progress. This situation is, in large part, the predictable result of decades of neglect and historical misdirection by NIH.

NIH's strategy is to bring new researchers to the field. But at the 2019 Stanford, InvestInME, and NIH ME/CFS conferences, researchers already studying ME emphasized that they struggle to access funding, which is impairing their ability to progress their research. Multiple, disease-specific funding opportunities, including those with sufficient set-aide funding, are needed now according to our researchers and clinicians, not in five or ten years. In addition to funding for basic research, of particular importance are funding opportunities to advance and validate biomarkers; to standardize patient selection methods and support clinical treatment trials; to expand both the number and level of funding for the collaborative research centers; and to find ways to creatively address stigma and the clinical crisis.

Therefore, it is stunning that this report made no recommendations for NIH to issue multiple, multi-year ME/CFS-specific funding announcements, particularly those with set-aside funding, to overcome these barriers and jump-start disease progress. Dr. Whittemore announced that PARs would be issued but failed to state which problems these will tackle and which will remain unaddressed. More problematic is the lack of set-aside funding in these PARs, which are unlikely to galvanize a field that has been starved and stigmatized for decades. This is particularly troubling given that Congress has repeatedly recommended such action in its yearly appropriations report and in congressional letters to NIH.

The NANDS Council Chair reiterated what NIH has said repeatedly: that NIH "shies away" from disease-specific funding, except where congressionally mandated. However, as noted in the NANDS Council discussion, exceptions can be made to this policy. ME is a situation that warrants such an exception because NIH, through its neglect and misdirection, holds significant responsibility for the magnitude of dysfunction in the ME/CFS research ecosystem.

NIH cannot wait for a sick and impoverished community to obtain a congressional mandate to fix what is so clearly broken.

Issuing such disease-specific funding opportunities will require NIH to leverage Director Collins' leadership to address the apparent unwillingness of NIH institutes to commit the level of funding needed for ME research, as evidenced by the anemic funding commitments made by the individual institutes to the ME/CFS CRC RFA. Unless the individual institutes make ME a strategic priority within their institutes, the Trans-NIH ME/CFS Working Group is going to continue to struggle to achieve the needed outcomes.

NIH's response to ME must include a robust program of multiple, multi-year, ME/CFS-specific funding opportunities, including those with a substantial commitment of set-aside funding from across the institutes, to advance the field and rapidly address the critical gaps and challenges that have stymied progress for the last 30 years.

3. Critical Issues Inadequately Addressed

Multiple critical gaps were inadequately addressed and the recommended strategies are too weak to be timely and effective.

For example, the report fails to adequately address the crisis in clinical care and the **lack of expert clinicians,** critical bottlenecks to research progress and growth of the field. NIH has stated that clinical issues are outside its remit. However, acquiring enough research subjects is already one of the most fundamental barriers to ME research, despite the tragic fact that ME is twice as common as MS. Without knowledgeable clinicians to help design studies, properly diagnose ME and identify study participants, research cannot move forward. This issue is exacerbated by the impending retirement of the few existing expert clinicians, especially given the lack of current consensus on patient selection criteria and methods. NIH and their federal partners must provide the leadership, political capital and resources necessary to resolve this issue and capture expert clinicians' collective knowledge now before the remaining few leave their practices.

This report also makes no recommendations regarding **clinical treatment trials** or even the establishment of a clinical trials network. In the October 17 NIH call, the statement was made that we lack the knowledge of disease pathophysiology needed to support "rational drug design." But in the meantime, the US ME/CFS Clinician Coalition has recommended proceeding with clinical treatment trials based on the experience of expert clinicians with successfully repurposing existing drugs to improve patients' quality of life and reduce disease burden. As studies in Norway are demonstrating, conducting such trials is an excellent way to better understand disease mechanisms, identify subgroups, establish outcome measures, and establish best practices for performing clinical trials in ME, all while simultaneously finding ways to improve the lives of patients. NIH must take the steps to quickly establish a clinical trials network and progress clinical treatment trials.

Further, while the issue of a lack of consensus on **case definition** was highlighted in the report, the strategies listed fail to tackle the issue. Instead, the report calls for NIH to "encourage" researchers to report the case definition and ascertainment methods used, a solution that does not address the fundamental problem. This is not a new problem: NIH's 2011 State of Knowledge report stated that the failure to address this issue was threatening

the “entire scientific enterprise.” Yet eight years later, NIH still has not made progress on this front. Given the variability of definitions and diagnostic tools and their effects on the research landscape, continuing to skirt this issue is not acceptable. This is not an issue of the natural heterogeneity of a complex disease but of the *artificial* heterogeneity introduced by varied practices and case definitions that do not require the core features of the disease. Without clarity and consistency in how the umbrella ME disease population is defined, it will be impossible to decipher differences and arrive at consensus on various relevant subgroups. To address these issues, NIH must urgently bring together researchers and clinicians to reach consensus on case criteria and methods for cohort selection in ME research.

As noted in the report and the call, underpinning the artificial heterogeneity introduced by variability in diagnostic and cohort selection methods is the lack of an objective, sensitive and specific disease biomarker or subgroup-specific **biomarkers**. This critical missing element is at the foundation of progress in nearly every other aspect of the field, from stigma and lack of professional interest, diagnostic and prognostic clinical care, basic and clinical research selection methods, to trial outcome measures. Failure of NIH to propose aggressive strategies to facilitate biomarker identification undermines advancement in nearly every other domain. “Encouragement” of research toward biomarker identification is an insufficient response to such a cornerstone problem; substantial and immediate financial investment specifically toward this goal is absolutely essential.

The report addresses the need for linked **data repositories**, however current NIH efforts focus only on the Collaborative Research Centers, omitting volumes of valuable data from other research centers and institutions. No indication is made in the report that NIH intends to leverage all available sources to produce the type of aggregate datasets that are needed for powerful, large-scale analyses. Additionally, strategic investments are needed to standardize instrumentation and research methods across the field to ensure critical variables are consistently captured and may be synchronized in aggregate datasets. This effort must begin with funding the required research on the gaps in data collection standards and instrumentation that was identified during the ME/CFS Common Data Elements initiative.

Finally, while this report acknowledges the impact of **stigma** among both researchers and clinicians, the proposed strategies to address stigma are vague and relatively passive. Dr. Collins, his office, and relevant NIH institutes must implement concrete, proactive strategies, such as those used for HIV/AIDS or lung cancer and those outlined in the National Academy of Medicine’s report on combating stigma, to rapidly reverse the stigma and misinformation in the research and medical communities towards ME. Stigma and bias do not disappear in the light of new knowledge: it requires leadership, explicit acknowledgement, and direct action.

Collectively, these issues continue to throttle progress. Yet, the strategies recommended in the NANDS report to address these issues are weak and incapable of effectively creating the change that is needed. NIH’s passive approach to such critical problems is unacceptable.

NIH must immediately address critical issues that are holding the disease back with particular focus on the following:

- *Fund and support a meeting of ME researchers and clinicians to reach consensus on patient selection methods and criteria*
- *Provide one or more RFAs to accelerate identification and validation of biomarkers*

- *Implement a plan to fund clinical treatment trials starting with a clinical trials network.*
- *Take concrete, nontraditional steps to rapidly address the stigma and the lack of clinicians*

4. Lack of Engagement in the Trans-NIH ME/CFS Workgroup

The report recommended the establishment of a community engagement working group, but implementation of report recommendations falls to the Trans-NIH working group, an entity which entirely lacks community engagement and transparency. Dr. Roberds championed the patient community as the identifiers of relevant research priorities, however currently, there is no mechanism within the Trans-NIH working group process for incorporating this supposedly vital input. In the meantime, we are very concerned that the Trans-NIH Working Group is already making decisions without patient voices on priorities and next steps that will set the direction of ME/CFS research for years to come.

The Community Engagement Working Group must be implemented as quickly as possible, along with a mechanism for that group to give input and feedback to the Trans-NIH ME/CFS Working Group on short and long-term priorities. This input is essential to determining the research priorities that generate meaningful impact.

TABLE: #MEAction Detailed Response to NANDS Report on ME/CFS Research
The following table outlines our critiques of the proposed strategies and recommended solutions for each gap identified in the report.

GAP	STRATEGY	INADEQUACY	IDEAL SOLUTION
Devising an overarching research strategy to address the complex nature of ME/CFS	The Trans-NIH ME/CFS Working Group should coordinate a research prioritization and strategic planning process to create an overarching roadmap for ME/CFS research. The process should identify key research priorities across relevant scientific areas. Scientists and clinicians with relevant outside expertise should be included in the process, as well as other stakeholders such as individuals with ME/CFS, advocates, and caregivers. (Detail in Appendix L)	▪ Process timeline not stated, likely to take far too long ▪ Conducted by Trans-NIH ME/CFS Working Group without accountability to senior leadership and pan-institutional prioritization ▪ No formal institute home, administrative ownership, institutional prioritization and accountability ▪ Conducted by Trans-NIH WG without stakeholder representation or process transparency ▪ Unclear whether process will include full cross-institute and inter-agency collaboration ▪ Unclear specifically how various community stakeholders will be involved in the development process ▪ Not stated where funds will come from or whether the process will be constrained by a budget ▪ Not stated how, when, and by who the strategic plan will be implemented or whether it should include short and long-term milestones ▪ Unclear how Trans-NIH WG recommendations translate into institute-specific strategies, goals, resource commitments, and actions ▪ Unclear what the scope of content the strategic plan should encompass (i.e. prioritization of patient-focused outcomes; specifically which "relevant scientific areas"; needs for instrumentation, methods and tools; critical issues such as case definition, lack of clinicians to support a robust research subject pipeline; prevalent disease stigma; structural issues at NIH such as grant review and institute-specific strategies)	▪ Accelerated timeline for development and release ▪ Sufficient budget to fully address the scope of needs ▪ Clear structures for stakeholder engagement and transparency ▪ Accountability to senior NIH leadership with authority to implement bold action and full committment of NIH institutional resources ▪ Full cross-insitute and inter-agency coordination and committment ▪ Focus and prioritization of patient-focused outcomes as quickly as possible in parallel with understanding disease mechanism ▪ Formally house within NINDS and publicize ME/CFS information via NINDS venues
Enhancing cooperation among federal agencies and other interested stakeholders	NIH should create a group that includes members from federal agencies involved in ME/CFS research, nonprofit foundations supporting ME/CFS research, and other interested stakeholders. The group should promote increased collaboration toward common research goals, monitor progress of the overall ME/CFS research field, share information on ME/CFS research activities, highlight advances, and discuss research gaps and opportunities. (Detail in Appendix M)	▪ Does not include individual stakeholders not associated with nonprofit organizations ▪ Does not include scientific centers that are not 501c3 nonprofits ▪ Does not include pharmaceutical industry representatives ▪ Biannual meeting frequency is far too slow ▪ Limited set of passive goals that focus on assessment and communication, but fail to explicitly initiate action to tackle difficult problems in the field ▪ Unclear what the work product of this group would be ▪ Unclear what the level of transparency around the group's activities would be	▪ Involvement of individuals with ME/advocates who are not associated with a nonprofit organization ▪ Involvement of scientific centers that are not 501c3 nonprofits (Stanford, Harvard, Nova Southeastern, Columbia, Cornell, Jackson Labs, etc.) ▪ Involvement of pharmaceutical industry representatives ▪ Increase meeting frequency in the near term to accelerate progress on critical issues in the field ▪ Include structured transparency in meeting agendas, minutes & work products ▪ Explicitly state goals which produce meaningful outcomes such as tackling key issues like case definition, clinical education, etc. ▪ Leverage Director Collins’s political capital to ask HHS to restore CFSAC

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Promoting increased awareness in the medical and scientific community	▪ NIH should offer information and feedback to stakeholders who are engaged in outreach and medical education. ▪ When appropriate for its mission, NIH should partner with other federal agencies, such as CDC, and professional organizations to disseminate information about research on ME/CFS.	▪ Passive approach ▪ Unclear what information would be propagated or who would select this content ▪ Fails to acknowledge how critical a bottleneck to research growth the lack of expert clinicians is ▪ ME/CFS not listed on NINDS website list of diseases	▪ A broad scientific awareness campaign aggressively leveraging all NIH media platforms and high-profile voices with frequent and consistent broadcast ▪ Active outreach to scientific and medical societies to solicit their efforts to build awareness, spark interest and dispel misperceptions among their members ▪ Call on federal partners to partner with recognized disease experts to aggressively conduct clinical education and outreach to grow the ranks of clinical expertise needed to support research ▪ Formally house within NINDS and publicize ME/CFS information via NINDS venues
Reducing disease stigma by promoting the importance and value of research on ME/CFS	▪ NIH should leverage events to publicize information about ME/CFS. ▪ NIH should continue to publicize its ME/CFS research efforts, such as the NIH ME/CFS intramural study and the ME/CFS Research Network. ▪ NIH should provide materials about ME/CFS, including information from the CDC, at exhibit booths during professional conferences.	▪ Passive approach ▪ Unclear what information would be propagated or who would select this content ▪ ME/CFS not listed on NINDS website list of diseases	▪ A broad scientific awareness campaign aggressively leveraging all NIH media platforms and high-profile voices with frequent and consistent broadcast ▪ Active outreach to scientific and medical societies to solicit their efforts to build awareness, spark interest and dispel misperceptions among their members ▪ Formally house within NINDS and publicize ME/CFS information via NINDS venues ▪ The National Academy of Medicine's 2013 report on combating stigma contains important strategies used in other diseases that should be considered
Increasing the number of ME/CFS research grant applications submitted to NIH	▪ NIH should solicit ME/CFS proposals through targeted outreach to investigators in relevant scientific and medical fields identified by the Trans-NIH ME/CFS Working Group to be relevant to ME/CFS, regardless of whether those investigators have previously studied ME/CFS. ▪ As part of its outreach efforts, the Trans-NIH ME/CFS Working Group should develop a resource guide for investigators, which should include information from Institute/Center websites related to grant and training opportunities. ▪ NIH should actively encourage investigators to contact program staff with questions related to their grant applications, including identifying appropriate Funding Opportunity Announcements (FOA) for their basic, translational and clinical research studies.	▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research to incentivize researchers ▪ Lack of community input and transparency in development of a research advisory resource by the Trans-NIH ME/CFS Working Group ▪ Does not include additional and expansion of existing Collaborative Research Centers	▪ Issue multiple, multi-year FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases ▪ A broad scientific awareness campaign aggressively leveraging all NIH media platforms and high-profile voices with frequent and consistent broadcast ▪ Develop the research advisory document with full community engagement and transparency ▪ Issue another U award to fund several more CRCs and fully fund existing centers
Promoting a more multidisciplinary and collaborative approach to the study of ME/CFS	▪ NIH should continue to encourage multidisciplinary approaches in grant proposals. ▪ NIH should increase awareness among the researcher community about current multi-PI funding opportunities that encourage investigators with diverse skills and expertise to work together on projects.	▪ Does not include issuance of specific funding mechanisms to encourage and support multidisciplinary ME/CFS research (such as the Glue Grants) ▪ Does not include additional and expansion of existing Collaborative Research Centers	▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases ▪ Issue FOAs with sufficient set-aside funds for ME/CFS to support multidisciplinary collaborative projects ▪ A broad scientific awareness campaign aggressively leveraging all NIH media platforms and high-profile voices with frequent and consistent broadcast ▪ Issue another U award to fund several more CRCs and fully fund existing centers ▪ Issue administrative supplements to facilitate engagement of outside/overlapping domain expertise in CRC projects

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Expanding the number of new researchers entering the ME/CFS field	▪ NIH should solicit ME/CFS proposals through targeted outreach to investigators in relevant scientific and medical fields identified by the Trans-NIH ME/CFS Working Group to be relevant to ME/CFS, regardless of whether those investigators have previously studied ME/CFS. ▪ NIH should facilitate wider availability of ME/CFS biospecimens, as detailed below. Access to biospecimens will help reduce barriers to new and early career investigators entering the ME/CFS field. ▪ As part of a strategic planning process, the NIH should include scientists with relevant outside expertise. ▪ NIH should continue to hold ME/CFS conferences on a regular basis. ▪ NIH should continue to provide information on both the NIH ME/CFS website as well as on the ME/CFS Network website about ongoing research efforts. ▪ NIH should continue to issue press releases when significant NIH-funded ME/CFS research is published.	▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research to incentivize researchers ▪ Lack of transparency and stakeholder input in Trans-NIH ME/CFS Working Group's targeted outreach activities ▪ No stated timeline for Trans-NIH ME/CFS Working Group's outreach efforts ▪ Biospecimen availability is dependent upon limited supply of clinicians ▪ No specific timeframe stated for conferences on a "regular basis" ▪ Posting information on little-known websites is not an adequate level of outreach to attract researchers to the field ▪ Infrequent press opportunities for published NIH-funded work is not an adequate level of outreach to attract researchers to the field ▪ Does not include additional and expansion of existing Collaborative Research Centers	▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases ▪ A broad scientific awareness campaign aggressively leveraging all NIH media platforms and high-profile voices with frequent and consistent broadcast ▪ Host and publicize annual ME/CFS conferences ▪ Sponsor workshops with researchers from adjacent fields to discuss overlaps and identify opportunities ▪ Issue FOAs focused on researching overlaps with key fields (e.g. POTS, hEDS, Lyme, GWI) ▪ Issue another U award to fund several more CRCs and fully fund existing centers ▪ Issue administrative supplements to facilitate engagement of outside/overlapping domain expertise in CRC projects ▪ Partner with other federal agencies and the medical community to aggressively address the shrinking pool of clinicians
Expanding the number of early career investigators entering the ME/CFS field	▪ NIH should partner with nonprofit research organizations to create training resources for early career investigators interested in becoming ME/CFS researchers. ▪ NIH should continue to hold events geared towards early career investigators to provide guidance on how to apply for NIH research support and navigate the peer review process. ▪ NIH should continue to actively participate in efforts to support early career investigators such as the “Thinking the Future: Early Career Network (Invest in ME).” ▪ NIH should provide a list of currently funded ME/CFS research, including the Principal Investigator(s) for each grant award to enable trainees to identify potential mentors.	▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research to incentivize researchers ▪ No stated timeline for hosting events ▪ Without effective strategies to attract established senior researchers to the field it will be difficult for early career investigators to succeed ▪ Does not include additional and expansion of existing Collaborative Research Centers	▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases ▪ Combat stigma and misinformation in academic centers and the research community with a broad scientific awareness campaign aggressively leveraging all NIH media platforms and high-profile voices with frequent and consistent broadcast ▪ Host and publicize annual events ▪ Issue another U award to fund several more CRCs and fully fund existing centers
Enabling access to bioresources for ME/CFS research	▪ NIH should continue to support expansion of ME/CFS biorepositories that also include detailed clinical data about the study participants. ▪ NIH should encourage funded research projects to provide biospecimens to existing biobanks for sharing with qualified investigators. ▪ NIH should partner with stakeholders to develop a registry through which potential study participants can be identified. ▪ NIH should work with funded investigators to ensure that steps are taken to enable future data sharing and biobanking. Examples include writing consent forms to allow for biobanking and wider data sharing, as well as the use of Globally Unique Identifiers (GUIDs) to track research subjects who are participants in multiple studies.	▪ Biospecimen availability is dependent upon a limited supply of clinicians ▪ Deflects critical work to other parties ▪ Fails to leverage NIH institutional resources ▪ Approach is too slow to supply the resources needed to rapidly grow the field	▪ A broad scientific awareness campaign aggressively leveraging all NIH media platforms and high-profile voices with frequent and consistent broadcast ▪ Active outreach to scientific and medical societies to solicit their efforts to build awareness, spark interest and dispel misperceptions among their members ▪ Lead an effort to rapidly synthesize existing data/specimen repositories ▪ Partner with other federal agencies and the medical community to aggressively address the shrinking pool of clinicians

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Continuing and strengthening the NIH ME/CFS Special Emphasis Panel (SEP)	▪ NIH should continue to ensure that the ME/CFS SEP includes reviewers with relevant ME/CFS expertise. Reviewers with other relevant subject matter expertise, including experts in tools and methodologies being proposed, should also be included. ▪ NIH should consider study section formats that provide for productive interactions between members of the review panel, for example face-to-face or video conference meetings. ▪ NIH should consider inviting members of the SEP to be reviewers in multiple grant cycles to build a sense of community within the SEP.	▪ Dearth of qualified, informed grant reviewers, confounded by COI with collaborators in small research community ▪ Not every ME/CFS application is captured and channeled through SEP	▪ Should have a Program Officer in each of the trans-NIH institutes with ME/CFS in their portfolio who knows how to navigate their institute
Using case definitions that facilitate broader research utility and data sharing	▪ NIH should encourage all NIH grant applications on ME/CFS to clearly state which case definition is being used and what data collection instruments will be used to obtain the data needed to apply that case definition. ▪ NIH should encourage applications proposing to use one particular case definition to also obtain sufficient clinical data so that the subjects can be categorized according to any of the primary case definitions of ME/CFS.	▪ Passive approach ▪ Fails to address the known issue with lack of consensus on patient selection methods that has confounded research for years ▪ Does not include recommendation for update/revision of the CDE guidelines	▪ Immediately fund and convene a group of disease experts to reach consensus on the criteria and assessment methods to select patients for ME/CFS research ▪ Encourage mitigation of artificial cohort heterogeneity by requiring PEM for all study participants
Building consensus on inclusion/exclusion criteria for control groups in ME/CFS research	▪ NIH should encourage ME/CFS studies to assess the health status of control groups using valid data collection instruments, such as those recommended in the ME/CFS CDE guidelines and the NIH toolbox. ▪ NIH should encourage studies to formally assess physical activity levels of all cases and controls, using validated and standardized instruments. Justification for using fit controls (e.g. comparison to model systems) should be provided when appropriate. ▪ NIH should encourage studies to rigorously assess and control for confounding factors in all studies of ME/CFS that may influence the results and comparisons between those with ME/CFS and the chosen controls. Physical fitness and the presence of other diseases are common potential confounding factors.	▪ Passive approach, fails to actually address the longstanding issue ▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research ▪ Does not include recommendation for update/revision of the CDE guidelines	▪ Immediately fund and convene a group of disease experts to capture existing knowledge ▪ Actively partner with disease experts and CDC to undertake properly designed epidemiologic studies
Achieving consistent data collection, analysis, and reporting	▪ NIH should urge investigators to use the ME/CFS CDEs, to both characterize comorbid conditions and details of the disease. ▪ NIH should work with the CDC and other stakeholders to identify additional required data elements and instruments that will facilitate more detailed ME/CFS phenotyping and improve data sharing. ▪ NIH should support development and validation of new instruments where needed to measure disease features of importance to people with ME/CFS (e.g., PEM).	▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research ▪ Does not include recommendation for update/revision of the CDE guidelines	▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases
Increasing understanding of different stages of ME/CFS	▪ Investigators should be encouraged to take into account the onset and length of disease in all ME/CFS studies.	▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research ▪ Does not include recommendation for update/revision of the CDE guidelines	▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases ▪ Immediately fund and convene a group of disease experts to capture existing knowledge ▪ Actively partner with disease experts and CDC to undertake properly designed epidemiologic studies

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GAP	STRATEGY	INADEQUACY	IDEAL SOLUTION
Addressing the heterogeneous and multifactorial nature of ME/CFS	▪ NIH should encourage ME/CFS research that evaluates the interactions between multiple biological systems that, individually, have been found to have abnormalities within the same cohort of people with ME/CFS.	▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research ▪ Does not include recommendation for update/revision of the CDE guidelines	▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases ▪ Immediately fund and convene a group of disease experts to capture existing knowledge ▪ Actively partner with disease experts and CDC to undertake properly designed epidemiologic studies
Addressing heterogeneity within individuals with ME/CFS	▪ NIH should encourage clinical characterizations of study participants that better inform the scope of the disease and the changes in symptoms over time. ▪ NIH should encourage investigators to measure symptoms from multiple perspectives (e.g. assessing current, peak, and typical symptom levels; and/or assessing different timeframes and situational frames) to gather a more complete picture of the symptom complex of people with ME/CFS.	▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research ▪ Does not include recommendation for update/revision of the CDE guidelines	▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases ▪ Immediately fund and convene a group of disease experts to capture existing knowledge
Increasing knowledge about disease subtypes	▪ NIH should encourage research to identify and validate ME/CFS subtypes. Researchers examining subtypes should be encouraged to consider relevant clinical information including (but not limited to) onset triggers, disease severity, stage of disease, and symptom presentation, as well as combinations of clinical and biological data. ▪ A strategic planning process should include discussions, informed by knowledge from clinicians and people with ME/CFS, about clinical phenotypes and studies that may reveal ME/CFS subtypes. This should be coordinated with efforts at the CDC.	▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research ▪ Does not include recommendation for update/revision of the CDE guidelines ▪ Defers real action to a protracted strategic planning process	▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases ▪ Immediately fund and convene a group of disease experts to capture existing knowledge ▪ Issue a funding mechansim that provides support for formation of a clinical trials network to convene clincial experts ▪ Actively partner with disease experts and CDC to undertake properly designed epidemiologic studies
Increase understanding of overlapping syndromes and comorbid conditions related to ME/CFS	▪ NIH should encourage multidisciplinary ME/CFS studies to examine and report on comorbid conditions utilizing the appropriate ME/CFS CDEs. ▪ If CDEs for the comorbid conditions do not exist in the ME/CFS CDEs, they should be co-opted from other disease CDEs. ▪ NIH should inform ME/CFS investigators when relevant NIH Funding Opportunity Announcements are available in related fields and conditions (such as chronic pain, etc.). ▪ NIH should explore ways to coordinate ME/CFS research efforts with ongoing activities in overlapping syndromes.	▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research ▪ Does not include recommendation for update/revision of the CDE guidelines	▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases ▪ Immediately fund and convene a group of disease experts to capture existing knowledge ▪ Issue a funding mechansim that provides support for formation of a clinical trials network to convene clincial experts ▪ Identify mechanisms to support clinical treatment trials ▪ Actively partner with disease experts and CDC to undertake properly designed epidemiologic studies
Clarifying the specificity of research findings	▪ When scientifically appropriate, NIH should encourage investigators to include disease comparison groups with other fatiguing illnesses (e.g., multiple sclerosis, systemic lupus erythematosus, major depression, Sjogren's syndrome) as well as healthy control subjects.	▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research ▪ Does not include recommendation for update/revision of the CDE guidelines	▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases

TABLE: #MEAction Detailed Response to NANDS Report on ME/CFS Research
The following table outlines our critiques of the proposed strategies and recommended solutions for each gap identified in the report.

GAP	STRATEGY	INADEQUACY	IDEAL SOLUTION
Taking advantage of big data approaches to create widely shared large datasets	▪ NIH should urge investigators to use the ME/CFS CDEs. These instruments standardize the collection of data about symptoms, past medical history, family medical history, physical examination, and common laboratory test results. These instruments may also help to categorize patients into certain disease subtypes, and to identify comorbid diseases. Standardized data collection and reporting through the CDEs is critical to enable cross study comparison, aggregation, and replication. ▪ NIH should partner with nonprofit and private organizations to develop a platform for ME/CFS researchers to facilitate data sharing. ▪ NIH should work with funded investigators to ensure steps are taken to enable future data sharing and biobanking, as detailed above. ▪ Once a comprehensive database is created, NIH should encourage secondary data analysis of aggregated existing datasets.	▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research ▪ Does not recommend funding to support research to address the gaps identified by the CDE initiative, many of which directly impede big data approaches ▪ Does not explicitly enforce data sharing publicly and between Collaborative Research Centers ▪ Does not include accelleration of DMCC analyses	▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases ▪ Provide funding for initiatives to address the gaps identified by the CDE initiative, many of which have a direct impact on data sharing ▪ Make CRC/DMCC data sharing infrastructure available to all NIH-funded researchers
Addressing barriers to ME/CFS clinical trials	▪ A strategic planning process should consider clinical trial design, patient selection and enrichment strategies, outcome measures, and sources of heterogeneity across patients and within the same patient over time. ▪ The planning process should more rigorously assess the relative merits of different patient-reported outcome measures (such as alternative scales for determining fatigue severity, post-exertional malaise, or functional capacity). ▪ A strategic planning process should also discuss the scientific rationale for potential studies of off-label treatments used by clinicians. ▪ NIH should encourage research proposals to better understand the proposed mechanism of action of currently utilized therapeutics in either clinical research or mechanistic clinical trials. The primary outcome would be mechanistic information for further study and potentially larger separate clinical trial(s) designed for efficacy, etc. ▪ As indicated above, NIH should encourage research to identify and validate ME/CFS subtypes.	▪ Does not address proposals and funding mechanisms for efficacy trials ▪ Delaying action on clinical trials until after a strategic planning process is unacceptably slow ▪ Does not provide support for formation of a clinical trials network ▪ Defers real action to a protracted strategic planning process	▪ Issue clinical trial-specific FOAs to support ME/CFS trials of symptom relieving treatments ▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases ▪ Issue a funding mechansim that provides support for formation of a clinical trials network to convene experts
Addressing barriers to clinical research participation	▪ NIH should encourage the use of telemedicine or home visits for research on home- or bed-bound people with ME/CFS to include this group of individuals in research studies when feasible. ▪ NIH should encourage the use of validated wearable devices and/or apps for symptom tracking of individuals with ME/CFS outside the research lab/clinic setting. ▪ NIH should encourage measurement of symptom severity.	▪ Does not address the need for development of instruments and standardized scales to measure disease severity ▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research ▪ Does not provide support for formation of a clinical trials network	▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases ▪ Issue a funding mechansim that provides support for formation of a clinical trials network to convene experts ▪ Issue an FOA to support development of methods for the most severely ill and clarify levels of severity
Deciphering the underlying mechanisms specific to ME/CFS	▪ A strategic planning process should include discussions of the state of knowledge about the possible etiologies for ME/CFS and how to identify findings that are likely to be disease causes versus physiological responses (i.e. epiphenomena and thus not the underlying cause(s) of ME/CFS).	▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research ▪ Defers real action to a protracted strategic planning process	▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases ▪ Immediately fund and convene a group of disease experts to capture existing knowledge

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GAP	STRATEGY	INADEQUACY	IDEAL SOLUTION
Leveraging provocation study designs	▪ When scientifically appropriate, NIH should encourage provocation studies. These may help to reveal the underlying cause(s) of ME/CFS.	▪ Does not clarify ethical issues around provocation studies	▪ In conjunction with community stakeholders, develop and disseminate guidelines for researchers in working with vulnerable ME/CFS populations ▪ Ensure guidelines adequately address issues with informed consent, pre/post-challenge supportive practices, etc.
Developing ME/CFS biomarkers with diagnostic and prognostic utility	▪ NIH should encourage research leading to the identification of objective measures that can be utilized as biomarkers for diagnosis, disease progression, and response to treatment. ▪ NIH should encourage investigators to consider information provided by the FDA-NIH Biomarker Working Group.	▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research for dianostic/prognostic biomarkers	▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases ▪ Immediately fund and convene a group of disease experts to capture existing knowledge ▪ Issue a funding mechanism that provides support for formation of a clinical trials network to convene experts
Improving understanding of onset, triggers, etiology, and pathogenesis	▪ Where scientifically appropriate, NIH should encourage systematic clinical and epidemiological research to better characterize disease onset, triggers, etiology, and pathogenesis. ▪ NIH should encourage researchers to consider study designs, such as prospective and longitudinal studies, that may improve our understanding of ways in which ME/CFS develops.	▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research for clincial and epidemiologic studies ▪ Does not call on CDC to conduct a comprehensive epidemiologic study or partner with NIH in acheiving this work	▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases ▪ Actively partner with disease experts and CDC to undertake properly designed epidemiologic studies ▪ Immediately fund and convene a group of disease experts to capture existing knowledge
Development of preclinical models relevant to ME/CFS	▪ A strategic planning process should identify key issues related to the development and usage of in vitro and in vivo ME/CFS models. ▪ NIH should encourage research to develop in vitro and in vivo models of ME/CFS.	▪ Does not include issuance of specific funding mechanisms with set-aside funds for ME/CFS research ▪ Defers real action to a protracted strategic planning process	▪ Issue FOAs with set-aside funds for ME/CFS research consistently year-over-year with growth trajectory increases