January 14, 2022

Identifying and tracking ME/CFS cases in Long COVID Research

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Dr. Walter Koroshetz, Director, National Institute of Neurological Disorders and Stroke (NINDS)
Dr. Anthony Fauci, Director, National Institute of Allergy and Infectious Diseases (NHLBI)
Dr. Amy Patterson, Deputy Director, NHLBI
Dr. Clinton Wright, Associate Director, NINDS
Dr. Andrea Lerner, Medical Officer, NIAID
Dr. Stuart Katz, RECOVER Initiative Clinical Science Core Principal Investigator, New York University (NYU) Langone Health
Dr. Leora Horowitz, RECOVER Co-Principal Investigator, NYU Langone Health

CC: Dr. Lawrence A. Tabak, Acting Director, National Institutes of Health (NIH)
Dr. Lenora Johnson, Director, Office of Science Policy, Engagement, Education, and Communications, NIH

Dear Drs. Gibbons, Koroshetz, Fauci, Patterson, Wright, Lerner, Katz, and Horowitz:

One of the key scientific aims of the entire RECOVER Initiative is the sub-phenotyping of post-acute sequelae of SARS-CoV-2 infection (PASC or Long COVID). A sizable fraction of people with Long COVID/PASC have symptoms consistent with myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS), and many will go on to acquire an ME/CFS diagnosis. However, we are deeply concerned that the **NIH RECOVER Initiative lacks a clear plan for how to accurately identify and consistently track cases of ME/CFS** onset in PASC patients.

To achieve this goal, there needs to be agreement on which ME/CFS case definitions will be used and how case-defining symptoms will be assessed. It is critical that the RECOVER Initiative take the following immediate actions to ensure data can be effectively harmonized across research sites and sub-phenotyping of PASC-ME/CFS is clearly defined:

AREAS FOR IMMEDIATE ACTION

1. The research criteria (inclusion/exclusion) for ME/CFS diagnosis must be specified in the RECOVER research protocols. Selected **ME/CFS case definitions must require the hallmark symptom of post-exertional malaise (PEM)** as it is defined in the NINDS ME/CFS Common Data Elements (CDEs).[1] Older chronic fatigue syndrome criteria such as Fukuda (1994) do not require PEM; these must not be used, as they can capture a very different cohort of patients not in line with the way ME/CFS is characterized today.

2. One of the key requirements of a reliable case definition is the use of standardized procedures for assessing symptoms. In addition, the thresholds or scoring methods for

evaluating the presence or absence of each of the case-defining ME/CFS symptoms must be applied consistently. At a minimum, **the DePaul Symptom Questionnaire (DSQ) should be required in all RECOVER research protocols**. The DSQ is designated as a "core" tool of the NINDS ME/CFS CDE Initiative and has been recommended for use across all ME/CFS studies. Furthermore, its scoring algorithm determines which of the case definitions a patient's responses meet.[2,3]

Failure to tackle these definitional and methodological issues have significantly hampered ME/CFS research to date. With the huge number of study participants to be involved in the NIH RECOVER Initiative, this is a singular opportunity to validate previous post-viral illness research findings and establish meaningful clinical subgroups of chronic post-acute COVID illnesses, including ME/CFS. Inaction on these issues will only waste taxpayer dollars and further impede research progress, resulting in a series of cascading negative impacts. These include:

1. Introducing investigator-initiated heterogeneity into the characterization of PASC phenotypes;
2. Impeding establishment of ME/CFS as a meaningful, distinct, and replicable PASC phenotypic subgroup;
3. Preventing meaningful associations of ME/CFS sub-phenotypes with observed biological changes in RECOVER cohorts that could be amenable to therapeutic intervention;
4. Making it difficult to accurately enroll homogeneous subgroups of PASC-ME/CFS cohorts in clinical treatment trials, and
5. Impeding generalizability and accurate application of RECOVER findings to future studies of ME/CFS patients without a prior SARS-CoV-2 infection.

Inaction would delay answers and treatments for millions of people. NIH officials have repeatedly assured the ME/CFS community that the $1.15 billion Long COVID/PASC research initiatives, such as RECOVER, represent a unique "research opportunity" that offers "hope" of scientific breakthroughs for people living with ME/CFS. But hope is not a course of action. **There is no basis for "hope" if the NIH does not take strategic and specific steps to make this outcome possible.**

We want the RECOVER Initiative to be as successful and impactful as possible, without leaving significant PASC sub-phenotypes under-characterized or left behind.

Respectfully
Ben HsuBorger
U.S. Advocacy Director
#MEAction

[1] ME/CFS diagnostic criteria that require the hallmark symptom of post-exertional malaise (PEM) include: Canadian Consensus Criteria (CCC) (2003), ME International Consensus Criteria (ICC) (2011), and National Academy of Medicine (NAM) (2015).

[2] The alternative CDC “ME/CFS Symptom Inventory/Checklist" tool should not be used in place of the DSQ, as its scoring algorithm pertains only to the Fukuda diagnostic criteria for chronic fatigue syndrome.

[3] Importantly, individuals with other chronic illnesses may experience some version of PEM, but their exertion-induced symptoms are primarily within the fatigue domain, whereas those with ME/CFS have post-exertion symptoms that involve multiple domains. In addition, the onset (sometimes delayed) and duration (frequently over 24 h) of a person’s post-exertion symptoms can vary, which is also not typical of other chronic illnesses. The DSQ captures these essential features of PEM as it relates to ME/CFS diagnosis. As PEM has also been reported by many Long COVID patients and is not well-understood, it is essential that we accurately capture and characterize its presence.