



February 28, 2023

Dr. Eldrin Lewis
Co-chair
RECOVER Clinical Trials Steering Committee

Dear Dr. Lewis,

We are deeply concerned by the RECOVER initiative's choice of **exercise therapy** as one of the few clinical treatment trials it is pursuing for people with Long COVID. We support Long COVID advocates' calls for this trial to be halted and for RECOVER to [fund strategic therapeutic research](#).

If RECOVER intends to proceed with this trial, it must first publicly address and satisfy the **serious concerns over its safety and efficacy**. We call for an **immediate release of the study protocol**, with a period for public review and comment, before the study is allowed to proceed.

Why are we so alarmed? Exercise treatments may be appropriate in some people with non-syndromic Long COVID (e.g. acute kidney injury, pulmonary fibrosis, cardiac pathology). However, exercise interventions can **worsen symptoms and cause harm** to those with syndromes such as myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) and those with post-exertional malaise (PEM), a worsening of symptoms and function following exercise, for which **exercise is contraindicated**.

Research has demonstrated that exercise causes an abnormal physiological response in people with PEM, including [cardiac preload failure](#), [impaired systemic oxygen extraction](#), [metabolic dysregulation](#) and abnormal immunological and neurological changes. Patients with PEM have repeatedly [reported harm](#) after undergoing exercise at the recommendation of their clinicians. This is of particular relevance for RECOVER since the [majority of Long COVID patient population reports experiencing PEM](#).

RECOVER cannot claim that no Long COVID participants will be harmed by this exercise study unless it **excludes all Long COVID patients for whom exertion causes a worsening of symptoms**.

People with ME/CFS are concerned because we have a long [history](#) of being harmed by recommendations for exercise therapy. The largest trial used to justify these recommendations was scientifically and methodologically [flawed](#) and eventually [debunked](#) by the research community. RECOVER has a duty not to harm those Long COVID patients who experience PEM by repeating these well-documented mistakes.

#MEAction has identified [numerous flaws](#) in the design of previous exercise trials for ME/CFS. Below we raise key concerns about the safety and efficacy of the design of RECOVER's exercise clinical trial:

1. What are the study's assumptions and rationale for the use of exercise to improve symptoms and functioning for people with Long COVID who experience PEM?

- a. What prior research on PEM is cited to support this hypothesis?
- b. What does this research say about the risk of harm from exercise in these patients? What assumptions does the trial make about this risk of harm?

2. Will the study include participants with any level of severity of PEM, whose symptoms and functioning can worsen after exertion?

- a. If so, how are patients with PEM being identified? What tools, methods, and thresholds (e.g. severity, frequency, last occurrence) are being used? Is there a clinical evaluation to confirm?

3. What is the exact nature of the exercise intervention?

- a. Does this include a graded exercise protocol? How is the baseline level of exercise and the frequency and magnitude of each increase in exercise determined? An impaired aerobic metabolism has been reported in those who experience PEM and approaches used for healthy people can overestimate exercise capacity.
- b. How many times per week and how many weeks overall?
- c. What is the length of followup post exercise intervention? Is it sufficient to determine whether the effect endures and whether adverse effects arise?

4. If the study includes participants with and without PEM, how will the study evaluate safety and efficacy?

- a. What specific outcome measures are being used to assess efficacy? Do they include objective measures as well as patient reported outcomes? Are they appropriate for both people who experience PEM and those who do not?
- b. Is the study treating these two groups (+PEM and -PEM) as separate subgroups, given potentially significant differences in response to exercise? Failure to do so could result in overly generalized conclusions that are potentially harmful to those who experience PEM.
- c. What specific methods are being used to monitor for, identify, analyze, and report on PEM as an adverse response to exercise?
- d. Will these methods be used to collect any potential adverse reactions following every bout of exercise? Will safety monitoring continue for at least two weeks following the end of the intervention? These processes are important even in those who do not experience PEM at study onset because they could develop PEM during the trial.
- e. Presuming positive effects in a non-PEM subgroup with Long COVID, how will these results be reported to the public? Will the results be reported separately by subgroup? What steps will be taken to ensure that the research will accurately convey the results and the population to whom they do or do not apply?

5. Are patients fully informed about the risk of harm to those who experience PEM at trial onset or who could develop PEM over the course of the trial?

6. What guidance will the study provide to participants in how to recover from PEM when they do experience it?

The RECOVER exercise clinical treatment trial cannot be allowed to proceed before these concerns over its safety and efficacy are fully addressed, which includes making the study protocol publicly available and providing an adequate period for public review and comment on areas of concern.

Sincerely,

Ben HsuBorger
U.S. Advocacy Director
#MEAction

CC:

RECOVER Clinical Science Core,
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