RECOVER-Treating Long COVID (TLC) 3rd Annual Workshop

Applying Emerging Science to Clinical Trials Design

Community priorities regarding outcome selection and disease duration

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PATIENT-LED RESEARCH COLLABORATIVE

Outcome selection in Long COVID

- Very few outcome measures specifically designed and validated for Long COVID, clinical trial design and outcome selection process in will be imperfect

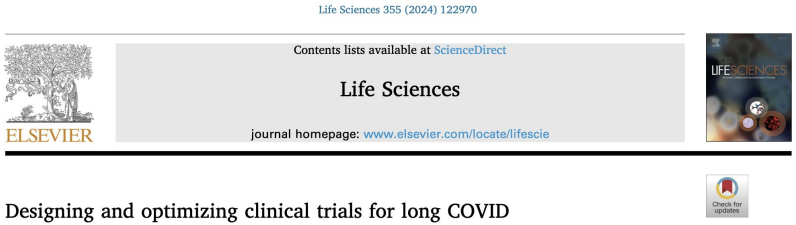


Personal View

Recommended long COVID outcome measures and their implications for clinical trial design, with a focus on post-exertional malaise

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Life Sciences 355 (2024) 122970

Contents lists available at ScienceDirect

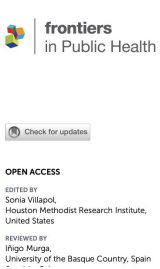
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journal homepage: www.elsevier.com/locate/lifescie

Designing and optimizing clinical trials for long COVID

Julia Moore Vogel [a,b,*], Beth Pollack [b,c], Ezra Spier [b], Lisa McCorkell [b], Toni Wall Jaudon [b,d], Megan Fitzgerald [b], Hannah Davis [b], Alison K. Cohen [b,e]

TYPE Review
PUBLISHED 19 October 2026
DOI 10.3389/fpubh.2026.1972605



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OPEN ACCESS

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Outcome measures in long COVID clinical trials: a review

Femke C. C. van Rhijn-Brouwer[1]*, Chloé de Canson[2], Joanneke E. L. VanDerNagel[3], Xandra Westerhuis[4], Susanne Y. Young[5], Sander M. J. van Kuijk[6], Laura V. de Vries[7], Jon-Ruben van Rhijn[8] and Merel Hellemons[9]

Post-exertional malaise

- PEM has the most substantive impact on clinical trial design and on the capability to include severe patients.
- **PEM prevention at the forefront** of clinical trial design: balancing choice of outcome measures, site visits, biospecimen collection, etc.
- PEM is a **pathophysiological state**: it may affect outcome measures and must be monitored and controlled for in the analyses.
  - ➤ monitoring PEM events throughout the trial - challenges: not validated, multiple ways to assess it
- Assessing PEM as an outcome measure
  - ➤ Current challenge in the field, no instrument that is 100% adequate.

Post-exertional malaise

- 2-day CPET: only objective measure for PEM, **not accessible to severe patients;**
  - pwME take an average 13 days to recover from a 2-day CPET vs. 2 days compared to healthy controls (Moore et al 2023) – careful assessment of benefit/risk ratio.
  - A **major research priority** is a non-invasive **direct measure for PEM**
- DSQ-PEM, DSQ-PEM-SF: determines if participant's phenotypes includes PEM, good for baseline characterization, cannot assess ongoing PEM, not designed for longitudinal assessment.
  - To assess ongoing PEM, recommend direct question. Soares et al 2026
- FUNCAP: assesses functional capacity while accounting for PEM
  - Does not assess PEM directly, needs validation in the context of Long COVID.

Disease duration

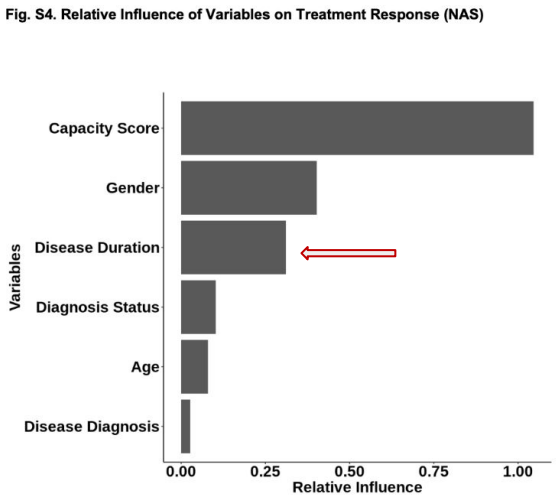
- Most recovery happens between 3 and 12 months of illness; recovery is uncommon after 12 months of illness.
  - 15.8% recovery at a median recovery time of ~8 months (Szewczyk et al 2024)
  - 5-9% at 2-3 years (Van Wambeke et al 2023, Mateu et al 2023, Gottlieb et al 2025)
- In the context of LC, clinical trials may fail due to high rates of remission in treatment and placebo arms that are unrelated to the intervention. Recovery observed in the placebo arm may mask efficacy when it's present. This is most likely to happen when:
  - Recruitment of pwLC sick for less than than 12 mo
  - Unbalanced and/or no stratification for illness duration

➤ Careful consideration of disease duration when designing inclusion criteria and participant stratification

➤ Recruit participants sick for 12 months or longer

Disease duration

- Evidence from Long COVID and ME/CFS that treatment efficacy may be associated with illness duration





[Eckey et al 2025]

Disease duration

- Long COVID changes over time; the illness at year 6 is not the same as the illness at year 1 and patients care about that being measured.

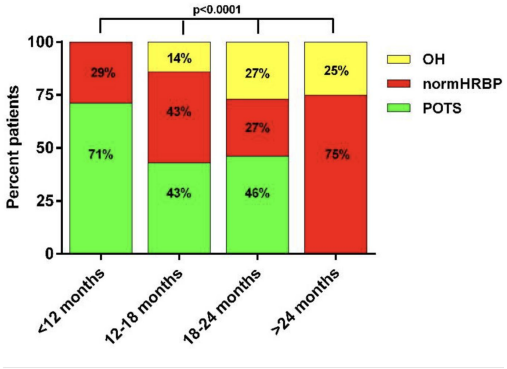
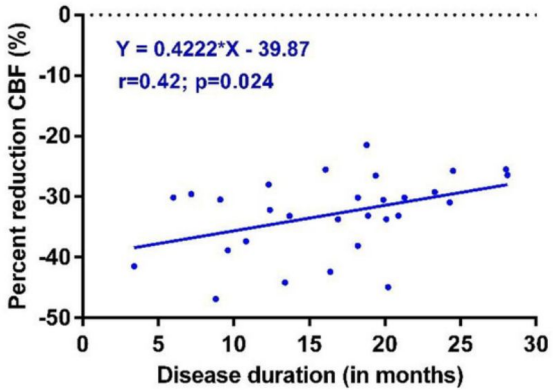


Figure 1. Frequencies of hemodynamic tilt test results in long-haul COVID-19 patients: relation with disease duration. OH: orthostatic hypotension; normHRBP: normal heart rate and blood pressure response; POTS: postural orthostatic tachycardia syndrome.



Van Campen and Visser 2022

- Autonomic dysfunction in LC less likely to be detected by tilt test over time

Disease duration

- Long COVID changes over time; the illness at year 6 is not the same as the illness at year 1 and patients care about that being measured.
    - Biological signatures that are different in short duration vs long duration illness, especially in ME/CFS: cytokines (Hornig et al 2015) and hyper inflammatory state vs immune-exhaustion state;

➤ Disease duration should be taken into account beyond the 3 mo cut-off for LC diagnostic criteria or the 6 mo cut-off targeting ME/CFS phenotypes

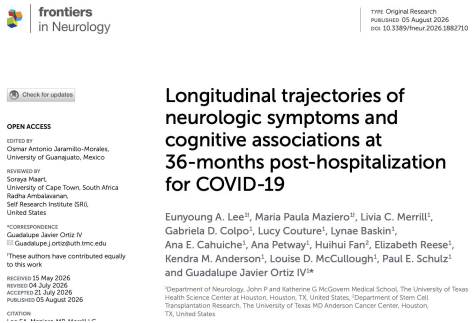
➤ **Hypothesis being tested** should **guide** considerations about disease duration when designing **inclusion criteria**, sample **stratification** and **subgrouping** for pre-specified analyses.

Disease duration and trajectories

- There's heterogeneity in Long COVID disease trajectories

➤ Consider longitudinal sampling

➤ Consider **stratification and analyses subgrouping** participants based on interactions of **disease duration and severity or functional capacity**



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TYPE Original Research
PUBLISHED 05 August 2026
DOI 10.3389/fneur.2026.1882710

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RECEIVED 15 May 2026
REVISED 04 July 2026
ACCEPTED 21 July 2026
PUBLISHED 05 August 2026

CITATION

Longitudinal trajectories of neurologic symptoms and cognitive associations at 36-months post-hospitalization for COVID-19

Eunyoung A. Lee[1†], Maria Paula Maziero[1†], Livia C. Merrill[1], Gabriela D. Colpo[1], Lucy Couture[1], Lynae Baskin[1], Ana E. Cahuiche[1], Ana Petway[1], Huihui Fan[2], Elizabeth Reese[1], Kendra M. Anderson[1], Louise D. McCullough[1], Paul E. Schulz[1] and Guadalupe Javier Ortiz IV[1]*

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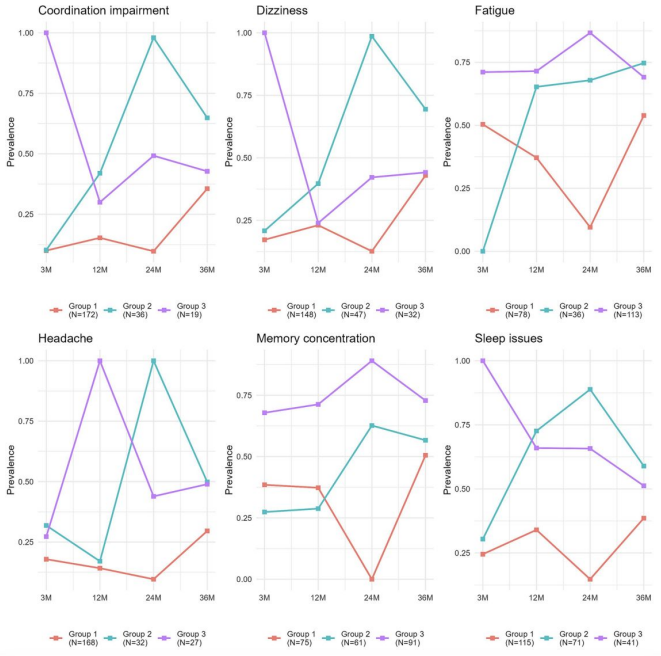


FIGURE 4
Distinct trajectory patterns of self-reported neurological symptoms identified through K-means clustering over 36 months. Three distinct groups were identified for each symptom. Clusters could represent meaningful patterns. Group 1: Stable trajectory; Group 2: Worsening trajectory; Group 3



THANK YOU!

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