PATIENT-LED RESEARCH COLLABORATIVE

Response to Request for Information NOT-AI-25-007: Researching COVID to Enhance Recovery – Treating Long COVID (RECOVER-TLC)

Submitted by the
Patient-Led Research Collaborative
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Patient-Led Research Collaborative (PLRC) is pleased to respond to NOT-AI-25-007, which seeks input on RECOVER-TLC. PLRC is a group of patients with Long COVID and other infection-associated chronic conditions that conducts its own research on these conditions, consults on research, advances frameworks for patient-led research models, and advocates for better policies for the patient population. We have been grateful for our participation in the RECOVER-TLC workshop and in our partnership with NIAID to date. The below summarizes some of our key recommendations for clinical trials and structure for RECOVER-TLC, many of which were covered in the workshop. If you have any questions on any of these, please reach out to us at team@patientledresearch.com.

1. Trial Design and Therapeutics to Trial. There is a clear need for both larger platform trials and smaller experimental/proof-of-concept trials. We recommend starting with smaller signal finding trials (e.g. with 100 participants per arm) to explore a broad space of potential mechanisms of action, followed by larger validation trials that could generate sufficient evidence to drive adoption. Platform trials offer broad, generalizable data, while smaller trials enable deeper biological probing, phenotyping, and hypothesis testing that can inform larger trials. Use trial types like decentralized, adaptive, platform, and basket. The RECOVER network can play a key role in validating smaller trial results within larger studies, facilitating a more robust understanding of disease mechanisms and therapeutic approaches.

Trials targeting curative interventions should be the top priority. It's crucial that tested therapies be made accessible to all patients— starting with, if a treatment that is trialed is found to be effective, it should be offered to participants who were in the control group, and later ensuring treatment is scalable and affordable beyond study participants. Both new drug development and the repurposing of existing treatments are needed and should be pursued simultaneously. Trials looking at readily available or over-the-counter treatments should not be prioritized. Trial design and budget allocation should consider that combination therapies may be required to achieve substantial improvement in quality of life.

The duration of illness is one of the most important things to track and analyze. Trials should ideally be on patients who have been ill for over a year, as recovery in earlier stages sometimes happens naturally. However, recovery rates after the first year are low; several studies show only 7–9% are fully recovered at two years[1,2]. Additionally, Long COVID has different stages to its illness, and immune, inflammatory, and other markers change in the first years compared to

later years and these groups must be analyzed separately. Certain treatments are likely to only work for early-stage Long COVID, and vice versa.

Post-exertional malaise (PEM) must be addressed in trial design; it must be measured and embedded in clinical trial design accordingly. PEM is a physiological state that can change the results of various tests, and the presence or absence of it during measurement must also be identified (not just whether or not a patient ever experiences it as a symptom). It is crucial that all RECOVER investigators understand that any aspect of participating in a research study can increase PEM; study design must carefully balance requests of participants with study needs. For example this can include only requesting that participants provide data there are concrete analysis plans for, enabling at-home participation by sending study staff to housebound participants whenever possible, and offering accommodations such as a low sensory space to rest following data collection that can only be done in person, such as MRIs.

Consider tracking other clinical interventions patients are on, specifically medication, supplements and actions like pacing. Different Long COVID phenotypes have different likelihoods of improvement and recovery, and these must be tracked (including ME/CFS, POTS, gastro-Long COVID, neuro-Long COVID, respiratory-Long COVID). Comorbidities (e.g., connective tissue disorders, reproductive health) must be tracked as well. Whenever feasible, comparator groups such as ME/CFS, post-Lyme, and POTS should be added in order to maximize the efficiency of studies and target a full-range of infection-associated chronic conditions. Account for factors that affect symptoms and severity, such as illness duration, seasonal changes, menstruation and menopause, PEM triggers, medications, and viral reactivations.

These are the sorts of insights that can emerge when patients are deeply and meaningfully engaged throughout the research process. We encourage deeper patient engagement than is currently happening with the patient and community representative engagement for the existing RECOVER trials, which have focused on brainstorming ideas for recruitment and have been startlingly insufficient (e.g., overwhelming recommendation to require masking and take other precautions to reduce the risk of reinfection, with no change by RECOVER). We encourage using PLRC's Patient-Led Research Scorecards[3] which help evaluate meaningful engagement of patients in research to guide this work.

2. Endpoints and Biomarkers. There is a need to validate patient-reported outcomes (PROs) and continue study and development of objective biomarkers (viral persistence, microclots, retinal markers, neuropathy biopsies, new imaging like ImmunoPET and 7T MRI, and others). However, this must be in parallel to working with what we have now (for example, see the endpoints used in: REVERSE-LC, Putrino's Truvada & maraviroc trial, Peluso's outSMART LC) as well as doing exploratory analyses (hormone, immune assays, tissue biopsies). This work must use disability-justice principles and trauma-informed practices. It is critically important that selected PROs are sensitive to changes in patient symptoms and functional capacity, as well as being robust to the many strategies patients use to moderate symptoms and avoid flares (e.g., pacing, limiting activity, using assistive devices). Simply asking if patients experience fatigue or

other symptoms is unlikely to reveal changes in patients' baseline capacity as a result of an intervention. Patient groups such as ours have thought carefully about these measures and should be consulted about their use at every stage of trial design.

Certain outcomes change over the course of Long COVID's progression, including tilt table tests and inflammatory markers. Others, like cerebral blood flow, are able to show abnormalities for greater durations of the disease.

It is important to include validated outcome measures, and to support this, there needs to be significant financial investment to support research aimed at developing and validating outcome measures for Long COVID.

Post-exertional malaise is one of the most important things to measure in every trial - not just whether or not patients experience it, but if they are experiencing it at the moment of test taking. It is more of a pathophysiological state over a symptom itself, which includes metabolic and microbiome changes, neuroinflammation, tissue damage, microclots, and amyloid plaques in tissue. Thus the presence or absence of PEM can impact test results. However, there are limitations to tools available to measure PEM, and there are no validated PROs available to detect the presence/absence of PEM as the patient experiences it. The primary two tools that are validated to measure PEM are a scale called DSQ-PEM[4,5] and 2-day CPET. Where DSQ-PEM[4,5] is helpful to determine if a patient experiences PEM at any given point (i.e. whether PEM is part of the patient's phenotype), it does not pick up on the nuances of PEM or capture patterns over time, and is not meant to be a primary outcome. Similarly, while 2-day CPET[6,7] is a validated biological marker for PEM, it is an intense test that risks decreasing participant's baseline and requires measurement on the second day when participants are most likely crashed; it is also not a feasible option for severe patients, thus its usage should be considered with care. We do recommend trying to study patients during PEM episodes specifically, which necessarily requires patients to be in a crash, but they need to know the risks and explicitly opt-in. 2-day CPET results should always be returned to patients, as they can help in applications for disability aid. When 2-day CPET is not possible or PEM is not explicitly being studied, we recommend using DSQ-PEM (including its short-form and DSQ pediatric version) overall, but also to include a binary question of whether or not physical PEM and cognitive PEM are happening each day the study is in progress, and to tie those results to any other test done.

All tests of all types should be considered that they may induce PEM, and methods to care for patients in the aftermath should be implemented, including compensation for time off work to recover.

For autonomic dysfunction, cerebral blood flow alongside standard autonomic function testing (AFT) should be the priority wherever possible. AFT includes a) a 10 minute unmedicated tilt test with beat to beat blood pressure and continuous heart rate monitoring (tilted to 70 degrees), b) Valsava maneuver, c) Heart Rate Response to Deep Breathing, and d) Quantitative Sudomotor Axon Reflex Testing (QSART). However, please note that tilt table testing may be less able to capture abnormalities in patients sick over one year, where doppler cerebral blood

flow tools retain the ability to capture abnormalities[8]. Also note that tilt table tests may make patients faint and induce PEM, so it's important to implement a protocol to care for patients in the immediate aftermath of the test.

As a secondary endpoint, three 3mm skin punch biopsies from the lateral leg to assess intraepidermal (sensory) and sudomotor (autonomic) small fibers would be done as well; these help determine if small fiber neuropathy is associated with diabetic/metabolic issues (length dependent, worse at the toes) or autoimmune/immune-modulated issues (non-length dependent, worse at the thighs)[9,10]. Around 3 out of 5 Long COVID patients have neuropathy, and this test can help validate other findings[11]. These should be combined with validated PROs (e.g. Orthostatic Grading Scale[12], Malmö POTS symptom score[13]) and others with objective measures of cerebral blood flow[14,15].

Secondary endpoints are crucial in the Long COVID landscape, and are helpful to explore hypotheses as well as results that may only be true in a subset of patients (i.e. viral persistence markers). Viral persistence tests (which can include different components of viral biology (RNA forms, viral proteins, imagining in tissue, viral transcriptome) should also be included wherever possible[16]. Other new but promising biomarkers to include are microclot testing, retinal biomarkers (include microcirculation)[17], and whole-body positron emission tomography imaging using [18F]F-AraG tracer for tissue-based T-cell activation[18], ultra-high field (7T) quantitative susceptibility mapping to detect neuroanatomical changes[19], and TSPO PET imaging for microglial activation[20] should also be included wherever possible and suitable.

While new endpoints for Long COVID are being validated, potential outcome measures should involve significant relief, meaning more than 20% improvement in frequency and severity, of most disabling symptom(s).

Mental health outcomes should never be used as primary endpoints–psychiatric symptoms affect only a subset of patients[21], except when the intervention specifically targets new onset neuropsychiatric conditions after COVID-19[22]. When mental health conditions are tracked as secondary outcomes, instruments that include somatic symptoms should never be used[21,22].

3. Inclusivity and equity. Clinical trials must serve the entire community of people with Long COVID, meeting people where they are, including those who are severe or very severe, transgender and gender diverse, Black, Indigenous, and people of color, low socioeconomic status, rural populations, and those without documentation of a positive test. Doing so will require financial investment to support intentional outreach to marginalized communities, including leveraging community engagement programs within and external to ongoing RECOVER activities, such as CEAL. We must also consider potential generalizability to children, older adults, pregnant people, incarcerated individuals, and those outside the US; these could be important populations for follow-up trials. Trial design must ensure safety (e.g., masking, ventilation), digital equity, compensation, and gender- and culturally competent care. Patient navigators can help ensure access and support.

The trials should consider diverse populations, including marginalized groups and those with socioeconomic and geographic barriers, and prioritize safety measures, digital equity, and culturally competent care. Trials must offer a treatment waitlist for control groups and expanded access, which is especially important while we figure out the right endpoints and phenotypes in order to identify a signal.

Severe bedbound patients are often unable to participate in any studies, and RECOVER-TLC should plan either a trial on severe patients alone, or to commit to making a percentage of each study severe bedbound patients. This would require meaningful infrastructure, likely including the need for home visits, and careful planning of non-exacerbating outcomes.

4. Patient Engagement. Meaningful and equitable patient engagement is crucial throughout the research process, with diverse patient and caregiver representation. We must learn from past experiences and other infection-associated chronic conditions. Include us as real partners on committees and as reviewers, from the very beginning of conceptualizing the trial to the reporting and dissemination of its results. Continuous patient involvement in trial committees and as reviewers is crucial to ensure that trials reflect real patient needs, helping to solve the challenges posed by Long COVID collectively. Patient engagement also ensures consensus decisions that prioritize what is important to patients. Safety thresholds can have different meanings to patients versus researchers. For example, preclinical and clinical efficacy data can have different levels of quality and meaningfulness to patients. Patients will be less likely to enroll in trials of interventions that are harmful or irrelevant (e.g. is it testing exercise or a video game). The design of patient engagement strategies should refer to the document "Meaningful Involvement of Patient Advocates (MIPA) in RECOVER: Summary of Structural Proposal", submitted by Body Politic and the Patient-Led Research Collaborative in November 2021.

5. Leveraging lessons from other clinical trial networks. Long COVID clinical trials should mirror the urgency and collaboration of ACTIV and the meaningful patient engagement of HIV/AIDS Clinical Trials Network. Engage and coordinate with ongoing clinical trials outside of the RECOVER network, including experts with decades of experience in researching infection-associated chronic illnesses, such as ME/CFS and persistent Lyme disease.

6. Structure and management.
To support these efforts, adequate funding mechanisms are essential, and we encourage large investments over a shorter timeline to respond to the urgency of Long COVID. Additionally, a coordinator is needed to manage logistics and ensure integration of findings.

There should be a full-time point person for RECOVER-TLC within the NIAID Director's office. The process of selection of interventions to be trialed must be transparent, with established mechanisms for feedback before trials are implemented. Trial selection criteria must be transparent and developed with patient feedback. The panel reviewing and selecting interventions must include patients, with equal say in the decision making-process. The panel should include experts outside of RECOVER, particularly those currently running high-reward, potentially curative Long COVID clinical trials (e.g. David Putrino, Wes Ely) and those running

drug trials in other IACCs. Commit to not including behavioral interventions in your considerations for what to trial. We also would like to see mechanisms to speed up and diversify the NIH grant awarding process, leveraging lessons from NSF (e.g. RAPID, EAGER, RCN). Trials must be addressed with urgency, following emergency-response models (e.g. acute COVID-19) for funding and implementing trials.

7. Accessibility considerations for future RECOVER-TLC meetings.
We have recommendations for accessibility of any future in-person workshops for RECOVER-TLC. Please require masking for any future events, using N95 or KN95 respirators. This is crucial due to the potential for reinfection to cause further reduction in quality of life for people with Long COVID, and to prevent Long COVID[23]. Designating a separate room for unmasked people to watch the event on simulcast could be a way to technically be in compliance with the federal rule that cannot require masking. Consider providing antigen tests to all in person attendees to use every day. Require proof of a negative test each day to enter the main room.

Ensure the meeting follows the ADA mobility guidelines for meetings and events. People with energy and/or mobility limitations should be proactively offered advanced visitor passes and those with disabled parking passes should be offered parking passes that allow them to park very close to the meeting. Ensure the NIH shuttle has a working wheel-chair lift. Consider holding meetings in a hotel so participants can rest in a private space when needed. Rest between meeting and travel days can help decrease the high health cost of attending the meeting to participants with Long COVID. This is an accommodation that can be supported by the Americans With Disabilities Act. An eight hour meeting duration is way more than most people with energy-limiting diseases like Long COVID can handle; consider a 12pm - 5pm Eastern time to also accommodate west coast participants.

Improve accessibility to enable people with Long COVID to participate in Q&A sessions. This includes ensuring that participants attending the event can access the microphone, and questions asked by participants online are presented and attributed to the asker. Prioritize questions by those with lived experience. Create an online portal to submit questions. Consider offering compensation for patients who may need to use paid time off to attend and participate.

Implement accommodations that enable participation of severe patients such as high quality live captioning, and summaries of presentations shared prior to the event, and summaries of Q&As and roundtables released within 24 hrs. Ensure that participants online can watch, listen, and engage in the meeting by planning for IT issues beforehand.

Provide networking options for remote participants, the majority being patients and disabled people. This could include enabling the chat function in zoom to allow peer-to-peer conversation, provide scheduled times for online breakout groups or other opportunities for the online and in-person attendees to have conversations.

Additional Resources:
Slides from Lisa McCorkell's summary presentation at the RECOVER-TLC Workshop: https://patientresearchcovid19.com/wp-content/uploads/2024/09/RECOVER-TLC_McCorkell.pdf

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