Randomized Double-Blind Placebo-Controlled Trial EValuating Baricitinib on PERSistent NEurological and Cardiopulmonary symptoms of Long COVID

MPIs: Wes Ely, Vince Marconi, Priscilla Hsue

Co-Investigator: Carolyn Bramante

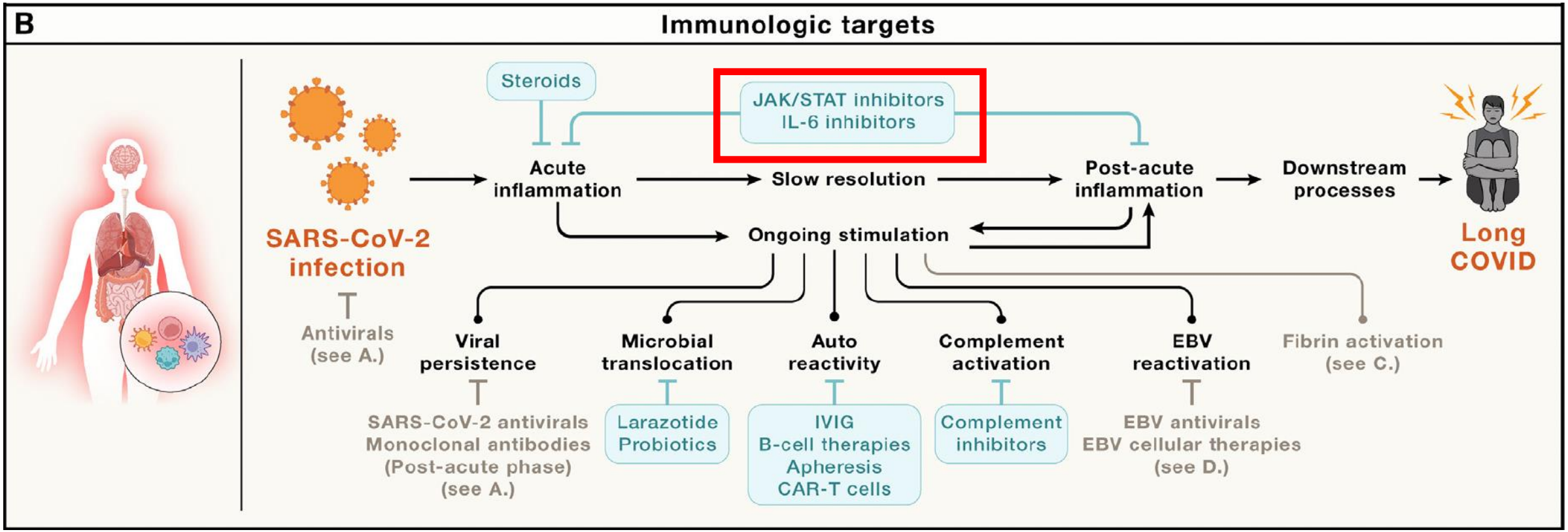
Funding / disclosures

- Will be talking about off-label use of baricitinib
- Funding:
  - R01AG085873
  - Study drug donated by Eli Lilly
  - Expansion sites: NIAID
- No financial disclosures

Mechanism of Action

- **Baricitinib:** oral janus kinase 1/ 2 inhibitor
- Jak 1/2 inhibition using Baricitinib in hospitalized COVID-19:
- **COV Barrier**
  - Hospitalized pts with COVID
    - Baricitinib had similar safety profile to SOC and was associated with reduced mortality among (Marconi V, Lancet Respir Med 2021)
  - Hospitalized pts not on mech ventilation
    - Bari + Remdesivir superior to remdesivir alone particularly among those getting high flow oxygen or noninvasive mech ventilation (Khalil AC NEJM 2021)
  - Patients receiving getting invasive mechanical ventilation or ECMO
    - Mortality benefit (Ely W, Lancet Respir Med 2022)

REVERSE-LC: Rationale



Peluso & Deeks, Cell Press

Impact of baricitinib on neurocognitive function and reservoir being evaluated in persons with HIV (Marconi, Gavegnano: NCT05849038)

Study Drug: Baricitinib

- FDA approved for use in moderate to severe RA (2018) and alopecia areata (2022)
- Oral med, daily dosing
- Good safety/side effect profile
- Safe in acute COVID-19
- Participant dosing based on current renal function

Participant eGFR	Baricitinib Dosage
≥ 90 mL/min/1.73m^2	4 mg/day
60 to < 90 mL/min/1.73 m^2	2 mg/day
30 to <60 mL/min/1.73 m^2	1 mg/day
eGFR< 30 mL/min/1.73 m^2	**Hold drug, recheck in 2 weeks.** If eGFR improves, resume dosing by eGFR as suggested in above rows. If eGFR remains stable or worsens, continue to hold drug and recheck approximately every 2 weeks. **Permanent discontinuation of drug if participant eGFR remains <30mL/min15 mL/min/1.73m^2 after an approximate 6-week period (approximately 3 checks).**

Subject Matter Experts with Lived Long COVID Experience who contributed to RVLC study planning

Hannah Davis (they/she)
Patient Led Research Collaborative

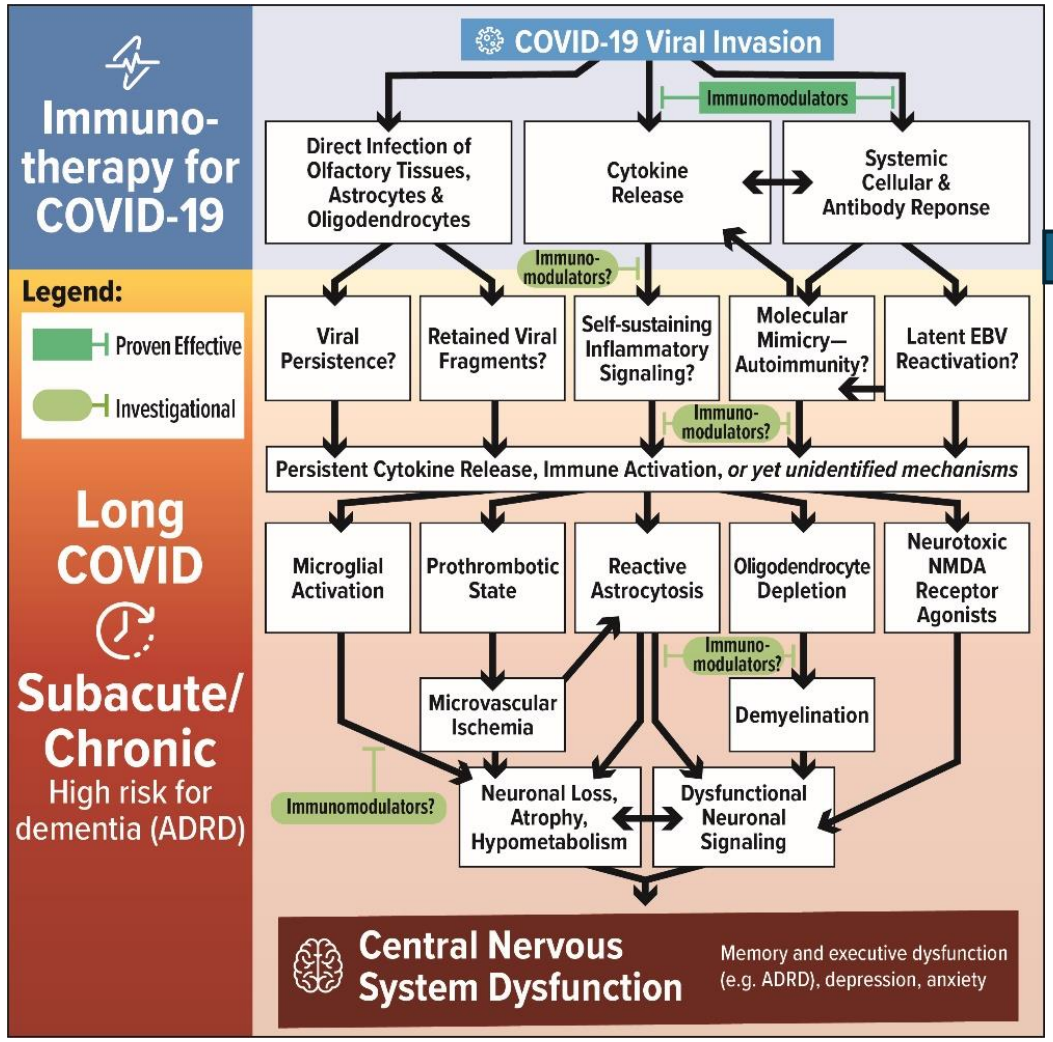
Lisa McCorkell (she/her)
Patient Led Research Collaborative

Jaime Seltzer (she)
Scientific Director, #MEAction

Gina Assaf (she)
Patient Led Research Collaborative

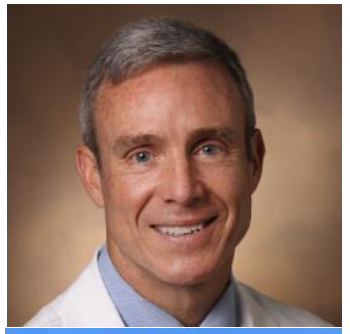
Kelly Sealey (she)
NAM Long COVID Testifier

RVLC: Evaluation of immunotherapy from acute covid to long covid

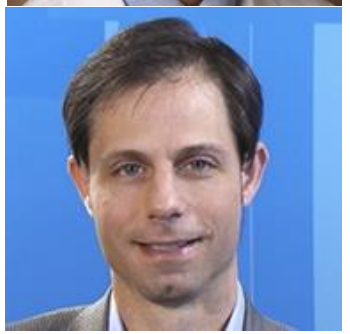


REVERSE LC:
Randomized placebo controlled study of baricitinib 4mg oral once daily for 6 months, N=550, 4 sites

Funded by NIA



Wes Ely
Vanderbilt

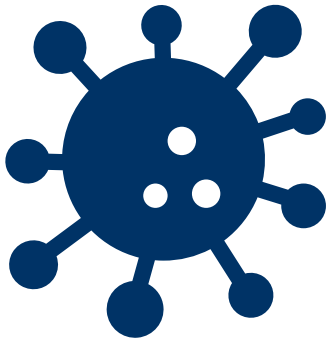


Vince Marconi
Emory

Priscilla Hsue
UCLA

Key Inclusion Criteria

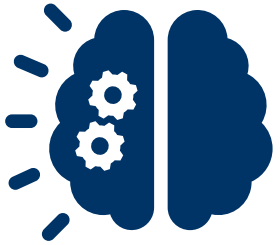
- COVID infection at least 6 months prior to enrollment.
  a. Cohort 1 (n=500): Documented SARS-CoV-2 infection 6 or more months prior using an Antigen or PCR test
  b. Cohort 2 (n=50): Suspected COVID infection, compelling history yet no positive COVID test (e.g., first wave COVID-19 prior to test availability)



- Clinical Evidence of Long COVID defined by all points below.
  a. At least one Long COVID symptom that is new or worsened since the time of SARS-CoV-2 infection
  b. Symptoms must have been present for at least 6 months prior to screening.
  c. Symptoms must be reported to be at least somewhat bothersome and to have an impact on quality of life and/or everyday functioning.
  d. Symptoms cannot be explained by an alternative diagnosis.
  e. Cognitive impairment present defined by having at least 20% positive items on the 39-item ECog questionnaire.

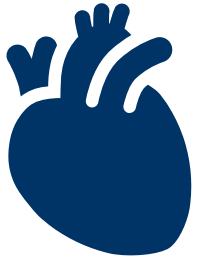
Study Objectives

Primary objective: To determine the safety and efficacy of baricitinib versus placebo on objective neuropsychological outcomes at 6-month follow-up in participants with neurocognitive LC.



Secondary objectives: To determine the effect of baricitinib versus placebo on:

- additional neurocognitive objective domains
- participant-reported cognitive dysfunction
- exercise capacity (peak VO2) using cardiopulmonary exercise testing (CPET)
- Brain MRI findings
- other participant-reported outcomes
- quality of life at 6- and 12-month follow-up
- and the global cognition index at 12-month follow



Exploratory objective: To evaluate the effect of baricitinib versus placebo on

- plasma and cerebrospinal fluid (CSF) biomarkers
- autonomic function, and neuroimaging at 6- and 12-month follow-up in
- identify inflammatory mediators of neuropsychological outcomes.

Primary Objective Measure

- CNS-VS: Cognitive testing battery comprised of validated and psychometrically robust neuropsychological tests.
- At n=500, we're 90% powered to detect a true mean difference of 5 or more points in the neurocognitive index between the drug and placebo groups.
- Cognitive Domains for RVLC:
  - Verbal and Visual Memory
  - Finger Tapping Tests (fine motor control)
  - Symbol Digit Coding (processing speed)
  - Stroop Test (reaction time)
  - Shifting Attention Test (executive function)
  - Continuous Performance Test (attention over time)
  - Digit Span (working memory)

Secondary Objectives Measures

- Cardiopulmonary Exercise Testing (CPET): measures cardiorespiratory fitness or exercise capacity (peak VO_2)during maximal effort exercise
- 6-Minute Walking Test (6MWT): sub-maximal exercise test that assesses aerobic capacity and endurance by measuring a distance walked over 6 minutes
- Questionnaires: subjective measurements from participants on multiple areas of interest
  - Quality of Life (EuroQoL-5D-5L)
  - Post Exertional Malaise (DSQ-PEM)
  - Symptom Burden (SBQ-LC)
  - General wellbeing (PROMIS-29)
  - Subjective cognition (PROMIS-CF-SF8a)
  - Mental Health (DASS-21)
  - Orthostatic Intolerance (OIQ)
  - Autonomic Dysfunction (COMPASS-31)

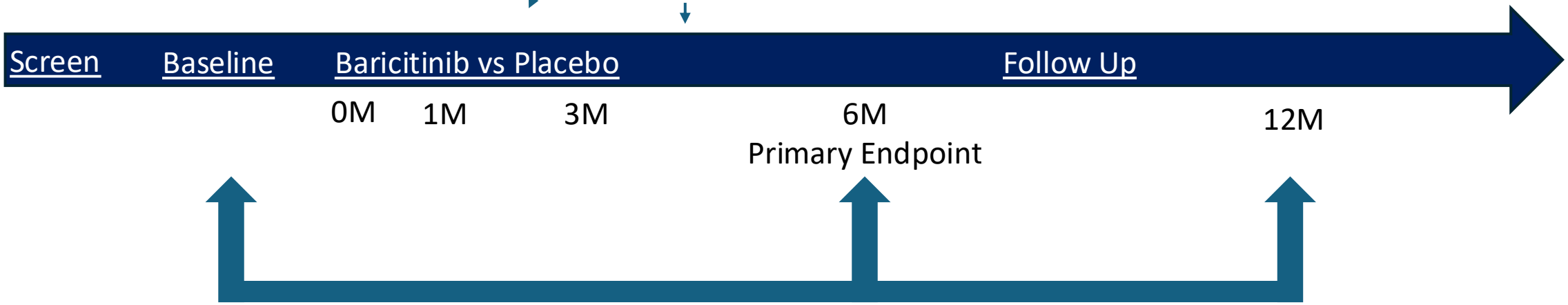
Exploratory Objectives Measures

- Biospecimens: plasma, PBMCs, and CSF collected at multiple timepoints will be used to investigate inflammatory markers/changes
  - Biospecimen analysis to be guided by the BnB committee
- Neuroimaging: brain structure and measure of atrophy via MRI
- Autonomic Dysfunction: at certain sites, Tilt Table/Autonomic Function Testing will be available to investigate AD

Administrative supplement for gut biopsy and microbiome assays submitted

Flow through study: informed by patient partners

Multiple safety lab rechecks between months 1-5 due to eGFR changes and lipid changes



Assessments

Patient Reported Outcomes including PEM

CNS-Vital Signs

CPET (opt-out)

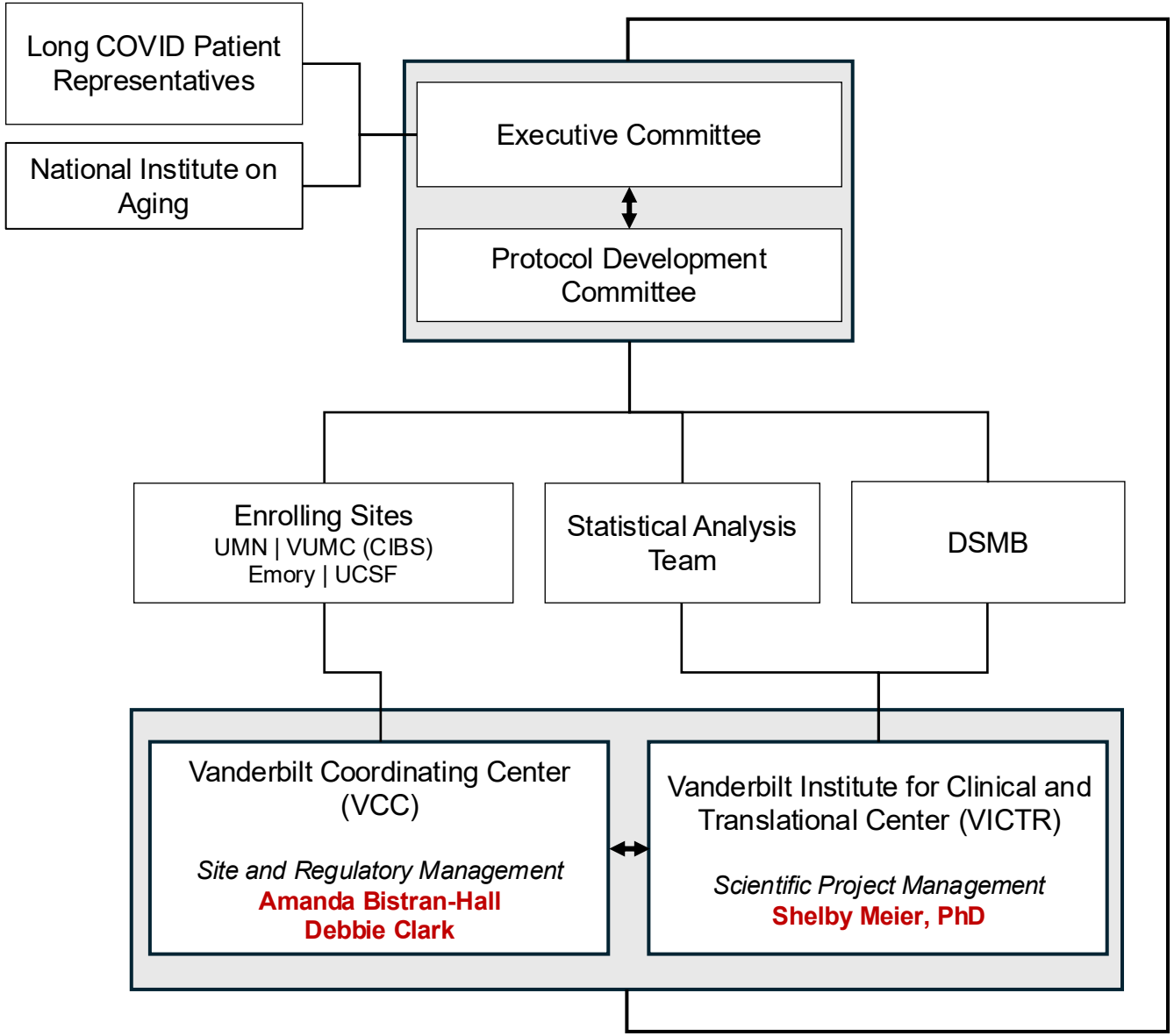
LP (opt-in)

MRI (opt-in)

Tilt table (opt-in)

Additional (gut biopsy)

REVERSE LC
Organizational Chart



REVERSE-LC is a **highly collaborative** study, not just between institutions but also within the VUMC infrastructure as well.

The Reverse-LC Study's

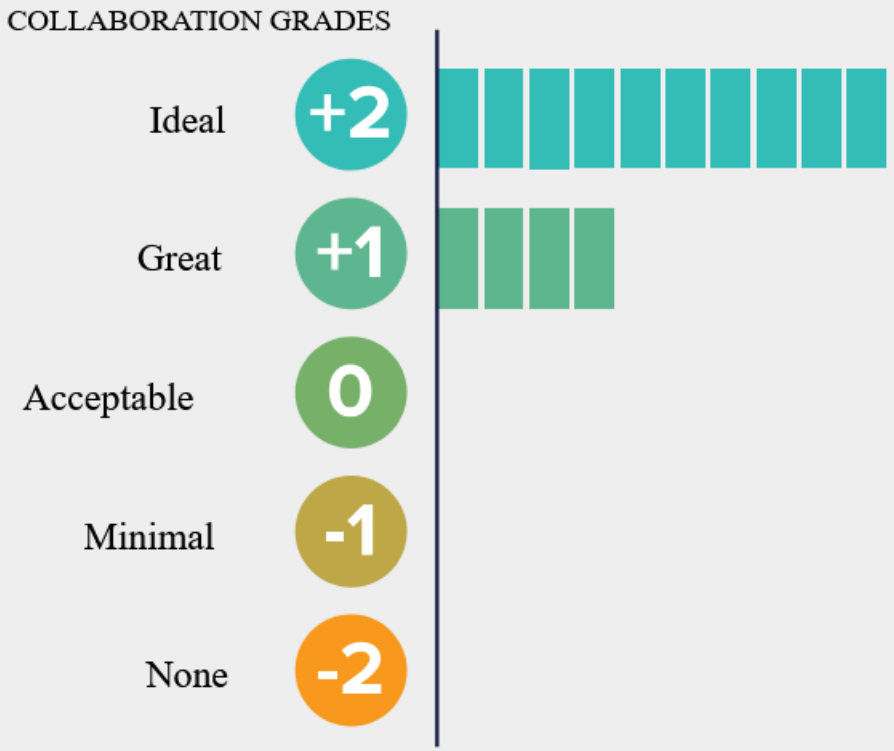
Patient-Led Research Scorecard

Our trial was graded by leaders at the Patient-Led Research Collaborative (PLRC) (Hannah Davis, Gina Assaf), ME-Action (Jaime Seltzer), and National Academy of Medicine Long COVID testifier (Kelly Sealey).

This scorecard was created by Patient-Led Research Collaborative.

The figure shows the high degree of collaboration between the physician-scientists and patient-researchers with not only lived experience of the illness, but also experience with the research process, participatory design, patient engagement, and study design.

We are grateful for the input from so many who shared their wisdom and advice to make this NIH-funded trial the best it can be. Reverse-LC is a campaign of human service and scientific discovery.



Hannah Davis

Gina Assaf

Jaime Seltzer

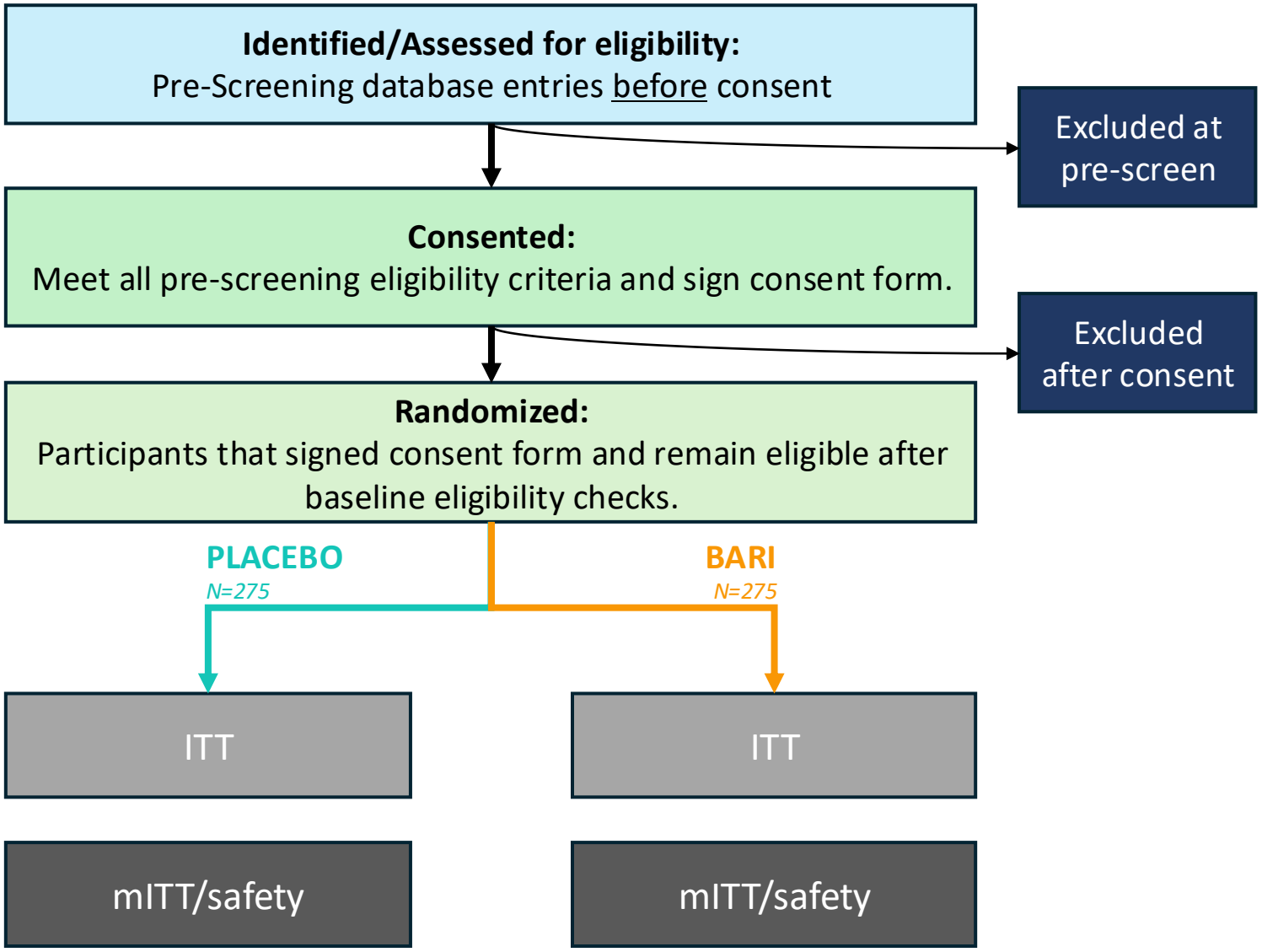
Kelly Sealey

Kick-Off Meeting

- In-person in Nashville
- Site PI's and lead coordinator
- Subject matter experts with lived Long COVID Experience
- Family Members of individuals with lived Long COVID experience

CONSORT Flow

Potential participants are considered enrolled after they have been RANDOMIZED.



ITT = any participant that was randomized, including participants that don't take any drug/placebo

mITT/safety = any participant that received at least a single dose of drug/placebo

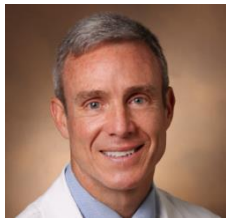
Design: Minimize Burden on Participants

- Sending the consent for them to read on their timeline
- Conducting consent remotely to minimize in-person time
- Confirming as much about the eligibility criteria as possible remotely, before having potential participants come in person for screening labs

Design: Remote data collection

- **Questionnaires obtained remotely via an app**
  - Symptom Tracker- 5-10 min
  - SQB-LC Circulation 5 min
  - PROMIS-29 8-10 min
  - PROMIS-CF-SF8a 5 min

Enrolling Sites



Vanderbilt
(Ely)

Emory
(Marconi)

UCSF
(Peluso)

U of Minnesota
(Bramante)

Key Collaborating Labs

Yale
(Iwasaki)

Stanford
(Levy)

UCSF
(Henrich)

Abbott
Labs

REVERSE LC Schedule of Activities

Screening/Baseline
Day -29 to 0

Visit 1: Screening
These items are completed first to ensure participant eligibility before burdensome activities.

Order	Activity
1	**Informed Consent**
2	**Cognitive Test** • ECOG
3	**Documentation of COVID Infection** • Cohort 1 only (n=500)
4	**Interview** • Medical History/Charlson • Medication Review • AE review
5	**Physical Exam** *Including vitals, height, weight*
6	**Blood Draw (eligibility)** • eGFR • CBC with differential • CMP • CPK • Lipid panel • Coagulation tests • QuantiFERON-TB Gold • Hep B • Hep C • HIV • EBV • VZV • HSV • CMV
7	**Pregnancy Test**
8	**Nasal Swab**

All items above the red line should be completed before an in-person visit is scheduled.

Visit 2: Baseline
These items are completed after participant eligibility is confirmed.

Order	Activity
1	**Vital Signs**
2	**Nasal Swab**
4	**Cognitive Tests** • CNS-VS (1° outcome)
5	**Physical Tests** • 6MWT • CPET (opt-out)
6	**Blood Draw** • PAXgene • Biomarkers (50mL)
7	**Opt-In Procedures** • Autonomic Function (VUMC only) • MRI • LP • Tilt Table
8	**Questionnaires** • SBQ-LC Circulation • EuroQoL-5D-5L • DSQ-PEM • mMRC • PROMIS-29 • PROMIS-CF-SF8a • OIQ • COMPASS-31 *Note: These will be completed in MyCap but coordinators can encourage/help participants complete them while at the study visit.*

Randomization
Day 1

Order	Activity
1	**Pregnancy Test** *Note: Must be completed immediately before initiating medication to ensure no one starts the medication while pregnant.*
2	**Initiate Study Medication** *Note: Study drug/placebo should NOT be started until a participant has completed all baseline measures.*

1mo

3-month Follow-Up
Day 84 (+/-14 days)

Order	Activity
1	**Medication Review**
2	**Vital Signs**
3	**Nasal Swab**
4	**Pregnancy Test**
5	**Cognitive Test** • ECOG

6	**Blood Draw**
	• Safety Labs
	  • *eGFR*
	  • *CBC with differential*
	  • *CMP*
	  • *CPK*
	  • *Lipid panel*
	  • *Coagulation tests*
	• Biomarkers (20mL)

7	**Questionnaires** • SBQ-LC Circulation • EuroQoL-5D-5L • DSQ-PEM • mMRC • PROMIS-29 • PROMIS-CF-SF8a • COMPASS-31 • OIQ

1- Month Monitoring Visit

Blood Draw (Safety Labs)

Questionnaires
Completed at visit
- SBQ-LC Circulation
- PROMIS-29
- PROMIS-CF-SF8a

Note: Additional monthly visits for ONLY safety labs occur monthly while on drug/placebo.

6-Month Follow-Up
Day 168 (-28 days)

Order	Activity
1	**Vital Signs**
2	**Nasal Swab**
3	**Pregnancy Test**
4	**Cognitive Tests** • CNS-VS (1° outcome) • ECOG
5	**Physical Tests** • 6MWT • CPET (opt-out)
6	**Blood Draw** • eGFR • CBC with differential • CMP • CPK • Lipid panel • Coagulation tests • PAXgene • Biomarkers (50mL)
7	**Interview** • Medication Review • AE review
8	**Opt-In Procedures** • Autonomic Function (VUMC only) • MRI • LP • Tilt Table
9	**Questionnaires** • SBQ-LC Circulation • EuroQoL-5D-5L • DSQ-PEM • mMRC • PROMIS-29 • PROMIS-CF-SF8a • COMPASS-31 • OIQ

12-Month Follow-Up
Day 365 (-28/+56 days)

Order	Activity
1	**Vital Signs**
4	**Cognitive Tests** • CNS-VS (1° outcome) • ECOG
5	**Physical Tests** • 6MWT • CPET (opt-out)
6	**Blood Draw** • PAXgene • Biomarkers (50mL)
7	**Interview** • Medication Review • AE review
8	**Opt-In Procedures** • Autonomic Function (VUMC only) • MRI • LP • Tilt Table
9	**Questionnaires** • SBQ-LC Circulation • EuroQoL-5D-5L • DSQ-PEM • mMRC • PROMIS-29 • PROMIS-CF-SF8a • COMPASS-31 • OIQ

Remote Data Collection

Questionnaires
- SBQ-LC Circulation (7&9mo)
- PROMIS-29 (7&9mo)
- PROMIS-CF-SF8a (7&9mo)
- Symptom Tracker (monthly)

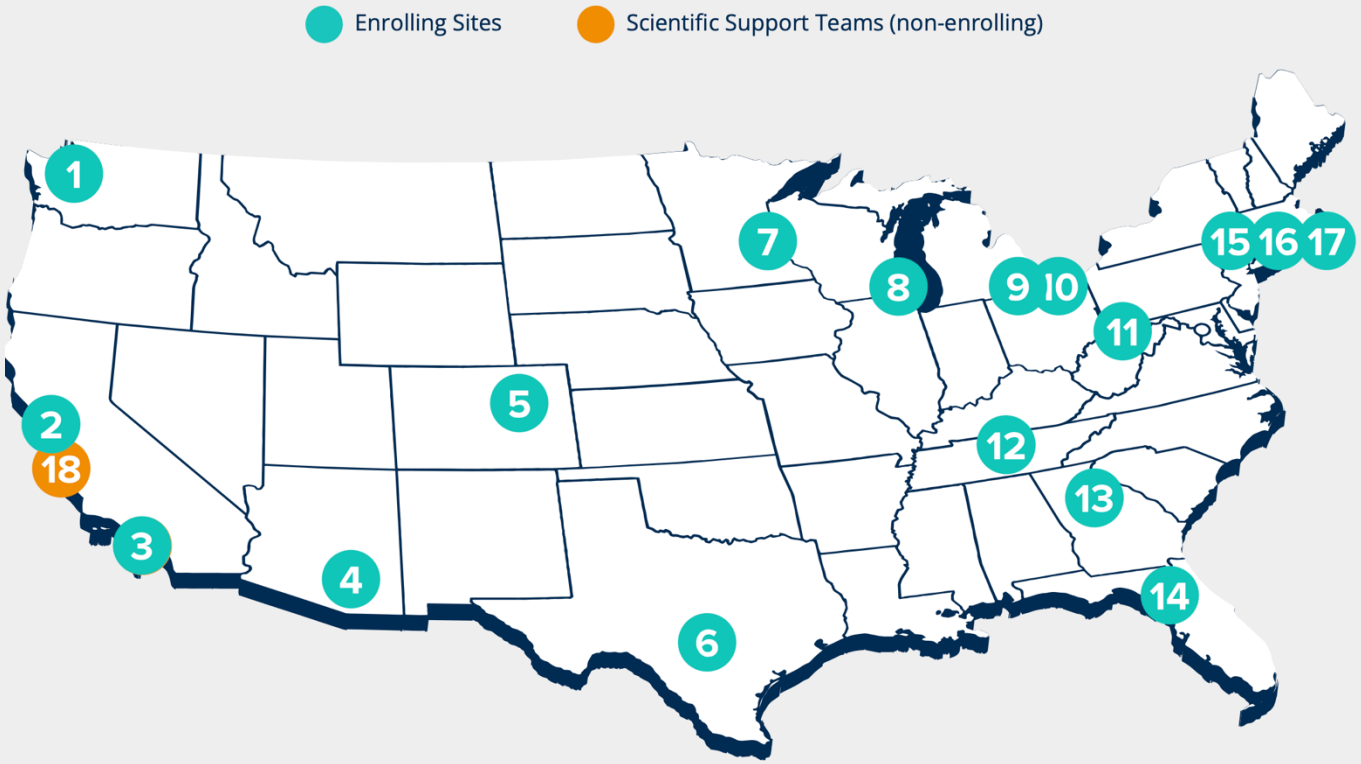
Collaborators and Investigators

Enrolling Sites

1. **Swedish Medical Center**
   Seattle, WA
2. **University of California, San Francisco**
   San Francisco, CA
3. **University of California, Los Angeles**
   Los Angeles, CA
4. **University of Arizona/Banner**
   Tucson, AZ
5. **University of Colorado-Anschutz**
   Aurora, CO
6. **University of Texas, San Antonio**
   San Antonio, TX
7. **University of Minnesota**
   Minneapolis, MN
8. **University of Illinois - Chicago**
   Chicago, IL
9. **MetroHealth Cleveland**
   Cleveland, OH

Expansion Sites

10. **University Hospital Cleveland Case Western**
    Cleveland, OH
11. **West Virginia University**
    Morgantown, WV
12. **Vanderbilt University Medical Center**
    Nashville, TN
13. **Emory University**
    Atlanta, GA
14. **University of Florida**
    Gainesville, FL
15. **NYU Langone**
    New York, NY
16. **Yale University**
    New Haven, CT
17. **Brigham and Women's Hospital**
    Boston, MA



Continued Input from those with Lived Experience

- Duration of time between consent and randomization
  - Based on feedback from participants
- Monitoring labs done close to participants homes (as allowed per local regulations for each enrolling site)
- Careful enrollment pacing
  - Important to have space and scheduling flexibility for participants
  - Complete data for 6- and 12-month CPETs, AFT/TTs, MRIs, LPs

How can we be found?

- **reversinglongcovid.org**
- Each site has their own website
- ResearchMatch.org
- Clinicaltrials.gov

Operational Considerations for DCTs in Long COVID

SCT | 47TH ANNUAL MEETING

Yale

Disclosures

- This study was supported in part by Pfizer

The Study

Design:

- Phase II, Randomized, Double Blind, Placebo

Regulatory Oversight:

- FDA via IND Application

Intervention:

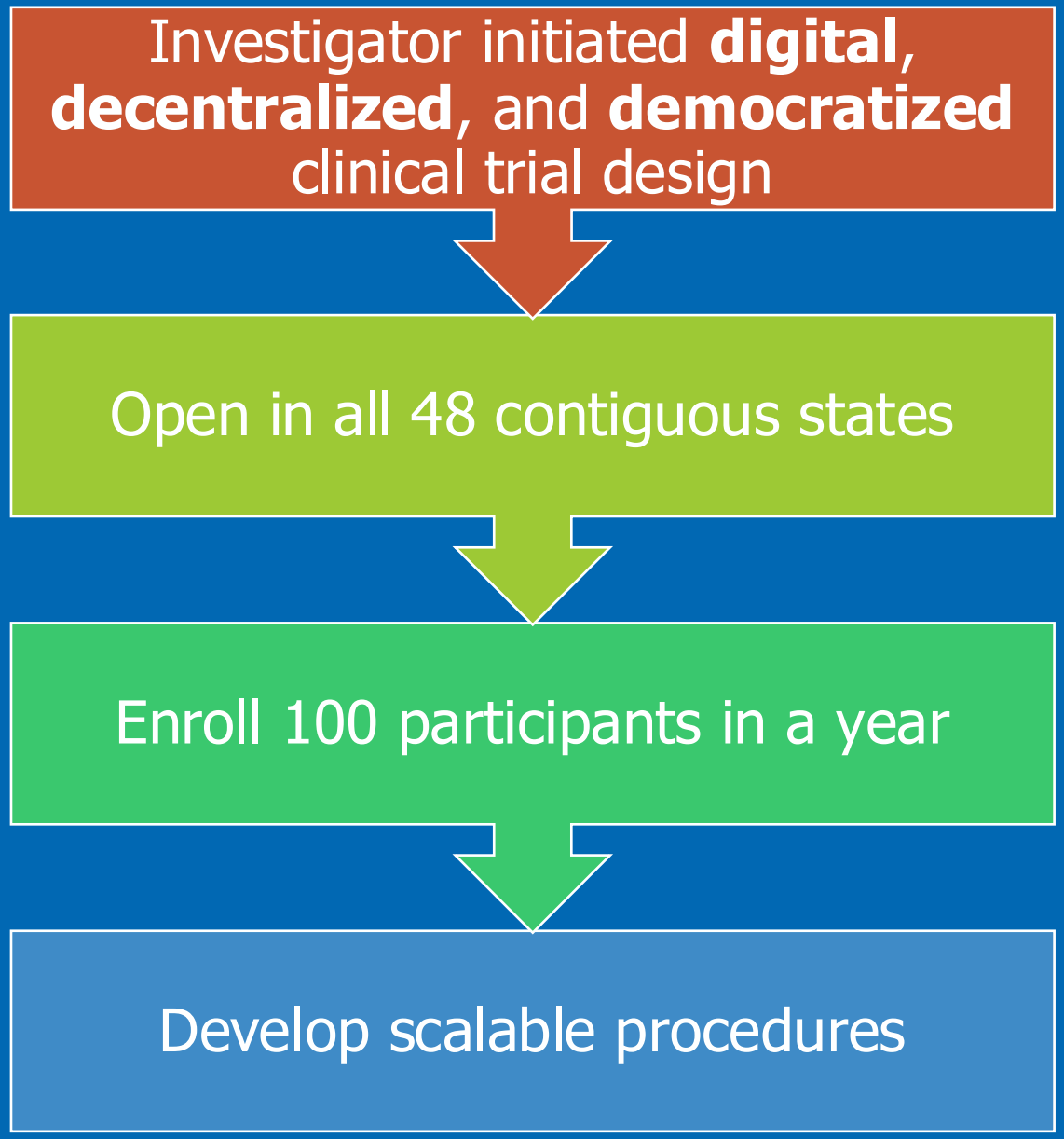
- Nirmatrelvir/ritonavir vs placebo/ritonavir (15 days)

Outcomes:

- Primary - PROMIS-29 Physical Health Summary Score (Baseline to Day 28)
- Secondary – PROS
- Exploratory - Immunophenotyping

Methods Paper Published in American Journal of Medicine

The Goal


Investigator initiated **digital**, **decentralized**, and **democratized** clinical trial design
Open in all 48 contiguous states
Enroll 100 participants in a year
Develop scalable procedures

Why a DCT for Long COVID?

Long COVID presented a unique opportunity …	Leveraging a decentralized design allowed us to …
• Patients have significant disease burden and disability making traditional research visits often incompatible • Many participants felt unheard and a sense of mistrust of providers who dismissed their symptoms • Large population of potential participates • Unknown cause and no treatment options → UNMET RESEARCH NEED	• Prioritize convenience and access by delivering research direct to the participant reducing participant burden • Tailor and control communications with central staff using consistent and compassionate approach • Access participant populations that would otherwise not be reached • Increase traditional timelines be faster to results

Regulatory

- Submission strategy and timing
- Legal considerations
    - IP Distribution, Prescribing Laws, Telemedicine
- External collaborators
    - Engagement and reliance determinations
- Local context considerations
- Scope and focus of IRB review
- Meeting FDA requirements in decentralized models
    - Monitoring

Operations

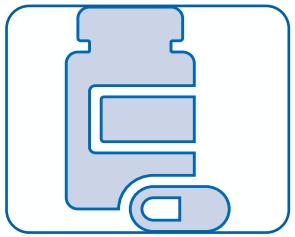
- Increased reliance on vendor partnerships & digitalization
- Operations need to consider the “site” processes
- Roles and responsibility considerations of study team
- Risk evaluation and mitigation
- Vendor complexity

Participant Interaction

- Participant Interaction
  - Providing participants with the quality service remotely
- Meet or exceed experience of traditional trial
- Trust building
- Communication methods
- Review of "real time" data

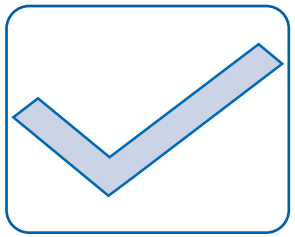
Results

Study results paper



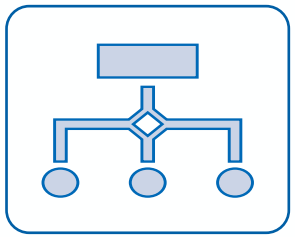
First Participant First Dose – Last Participant First Dose

- 8 months
  7/11/2023 – 3/12/2024



119 total consented

- 10.5 months
- 4/14/2023-2/26/2024



100 total randomized

- 89 at least 1 dose & completed baseline/day 28 PROs
- 86 took 15 days of treatment & completed baseline/day 28

How Patient Engagement Improves Clinical Trials:

Learnings from Long COVID and RECOVER-TLC

Justin Lin
Parent Caregiver
May 20, 2026

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Nothing to Disclose

About Serena and Justin

Serena's Story

From the 2nd Annual RECOVER-TLC Workshop
Sep. 9, 2025 in Bethesda, MD

Long COVID in Children and Teens

- As many as 6 million children in US impacted
- Often misunderstood or written off by medical providers, schools, etc.
- Disparate access to healthcare resources and educational supports
- Limited treatment options: pediatricans extremely reluctant to prescribe anything off-label to children

Kids are Overlooked in Research and Care

- 400-500+ clinical trials for Long COVID currently registered globally
- The Sick Times found 6 pediatric Long COVID clinical trials as of Feb 2026.
- Fewer than 20 pediatric Long COVID clinics nationwide: most states have zero. Long waitlists and travel distances.

Kids with Long COVID are Struggling

- Stigma: disability is often invisible and no "one size fits all" - different manifestations / phenotypes
- Looming adolescent mental health crisis
- Hopes and dreams derailed at such a pivotal time: real risk of a failure to launch into adulthood

BRAVE-LC: Low-dose Naltrexone Pediatric Clinical Trial

Goal: LDN label change for kids

- Anecdotal effectiveness widely reported across Long COVID community
- LDN is low-risk and readily obtained off-label by adults
- High-dose already prescribed to children for addiction, eating disorders
- If we can get one label change for kids, maybe more will follow

Gold-Standard Pivotal Trial

- **~1,300 participants, age 6-25**
- **~150 sites across the US**
- Phase 3, 2 parallel arms, double-blind, placebo-controlled

- **Primary Endpoint:** fatigue (physical + cognitive) - PedsQL-MFS
- **Secondary:** by age group, QoL, pain, neurocognitive function, safety
- **Exploratory:** PK in children, mental health, biomarkers, durability of effect, by sub-group (ME/CFS, Dysautonomia, POTS, MCAS, PEM)

BRAVE-LC: Positive Impact Regardless of Results

An Improved Standard of Care

The trial establishes a playbook that pediatricians can follow to diagnose Long COVID in children and teens, developed by top pediatric LC experts for the first time.

We are:

- Taking history and establishing an epi. (or test confirmed) link to COVID infection
- Confirming the child's illness essentially conforms to the NASEM definition for Long COVID.
- Ruling out other potential conditions (eg. thyroid, anemia, etc.) through lab tests and PI medical judgment.
- Measuring and documenting actual level of impairment (fatigue, cognitive, sleep, QoL) that the child is experiencing.
- Confirming and documenting phenotype of their illness (eg. tilt table test for POTS)

Essentially BRAVE-LC enables pop-up pediatric Long COVID clinics across the US for a limited time

The best second opinion a family can get

Best Practices and Future Trials

We are also:

- Demonstrating how e-diaries can be incorporated into a treatment regime that **improves doctor / family communication and recovery tracking.**
- Advocating best practices for visits and care touches that are as **inclusive and convenient** as possible
- Establishing protocols and endpoints that can be **re-used by future trials**
- **Sharing all raw data** to public: can inform future investigations into pathogenesis, biomarkers, etc.

Raising Awareness of Pediatric Long COVID

- Primary care providers
- Schools
- Press / Media
- Mobilize local patient advocacy groups

To the kids and families:

Stay BRAVE. You are not alone. We're fighting for you.

Rewind:
Background on RECOVER

RECOVER 1.0: Two Years Ago

The Sick Times

‘They bungled it:’ NIH documents reveal how $1.6 billion Long Covid initiative has failed so far to meet its goals

Written by **Betsy Ladyzhets** – May 31, 2024

The Washington Post

An exercise trial for long covid is being criticized by some patients

NIH’s RECOVER initiative plans to study exercise as a potential treatment for long covid. Some long-covid patients say exercise does them more harm than good.

May 22, 2023 More than **2 years ago**

PATIENT-LED RESEARCH COLLABORATIVE

Open Letter regarding the RECOVER initiative to study Long COVID

In order to do so, we must begin with two fundamental structural adjustments to the Initiative to support the truly meaningful engagement of people with Long COVID:

- **A comprehensive and adequately resourced patient engagement structure** must be rapidly created and sustained using existing best practices such as those in the NIAID HIV research structure that ensure empowered participation across all segments of RECOVER and include a collaborative of patients themselves. **A draft proposal can be found here.**
- **Post-viral illness experts**, including researchers, clinicians, and patient advocates with expertise in conditions seen in Long COVID (including ME/CFS, postural orthostatic tachycardia syndrome [POTS] and other dysautonomias, and mast cell activation syndrome [MCAS]) **must be integrated into the Initiative**, as well as supported as a collective advisory panel in the RECOVER structure, as noted in an open letter from Body Politic to the NIH in April 2021.

RECOVER-TLC: a fresh reset

- NIAID leadership
- Annual conference, regular webinars
- RECOVER-TLC Working Groups to evaluate submitted therapeutics
- 3 new clinical trials launching:
  - LDN (pediatric), GLP-1, stellate ganglion block
- Patient and community engagement at all levels

The Sick Times

"A good step": Long COVID advocates and researchers respond to the RECOVER-Treating Long COVID meeting

Written by **Betsy Ladyzhets** – October 1, 2024

Small Protocol Working Group

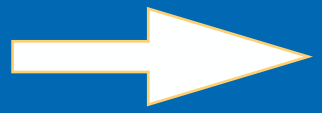
- 40+ meetings (1-2x / week) over Teams
- 5 SMEs from all over the country (incl. leading pediatric LC clinicians)
- 2 patient / community reps
- Medical officers from NIAID

- Also: data scientists / statisticians, pharmaceutics, safety, regulatory, RTI CRO team
- Special experts: neurocognitive, safety, etc.

Behind the Scenes:
Example Learnings

#1: Getting Inclusion Criteria Right

From: *professional* lab test required after 2023



To: at-home test acceptable OR
met clinical criteria + epi link to test-positive individual

2. History of SARS-CoV-2 infection as evidenced by: (1) a positive professional use or at home SARS-CoV-2 nucleic acid amplification test (NAAT) or antigen test[a], **OR** 2) met clinical criteria **AND** had epidemiologic link to an individual with a positive SARS-CoV-2 NAAT or antigen test[b,c].
   a. See the Schedule of Activities (SOA) for more information related to documentation required to confirm past SARS-CoV-2 infection.
   b. Clinical criteria is defined as either (1) acute onset of fever AND cough (influenza-like illness); OR (2) acute altered/loss of taste and/or smell plus one additional symptom including fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, nausea, diarrhea, or anorexia; OR (3) three or more symptoms, including fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, nausea, diarrhea, or anorexia.
   c. Epidemiologic link is defined as having contact (within 6 feet for at least 15 minutes) with a household member, another student, coworker, teammate, friend, or significant other while they were sick with SARS-CoV-2 test-positive COVID-19 illness.

Proposed criteria: Combination of approaches

- 2020 – present: Detection of SARS-CoV-2 lab result from CLIA-certified provider
  - *Detection was made of the following in a clinical specimen: SARS-CoV-2 nucleic acid using a diagnostic molecular test (e.g., NAAT) performed by a CLIA-certified provider, SARS-Co-V 2 RNA by genome sequencing, or SARS-CoV-2 specific antigen by diagnostic immunocytochemistry staining performed by a CLIA certified provider during or after 2025*
  - *Detection was made of SARS-CoV-2 specific antigen in a clinical specimen using a diagnostic test performed by a CLIA certified provider*
- *Before 2023: Detection of SARS-CoV-2 lab result without CLIA oversight if also accompanied by clinical symptoms and epi link to case(s) confirmed via CLIA-certified provider*
  - *Detection of nucleic acid or specific antigen using a test performed without CLIA oversight (e.g., at-home tests)*
  - *Detection of specific antigen by immunocytochemistry before 2025*

(Taken from previous adult Long COVID studies)

How many of you have professional lab tests for your kid's COVID infections?

Eventually did you even tell your pediatrician about your kid coming down with COVID?

Pediatricians have stopped bothering to record COVID test results in the EHR

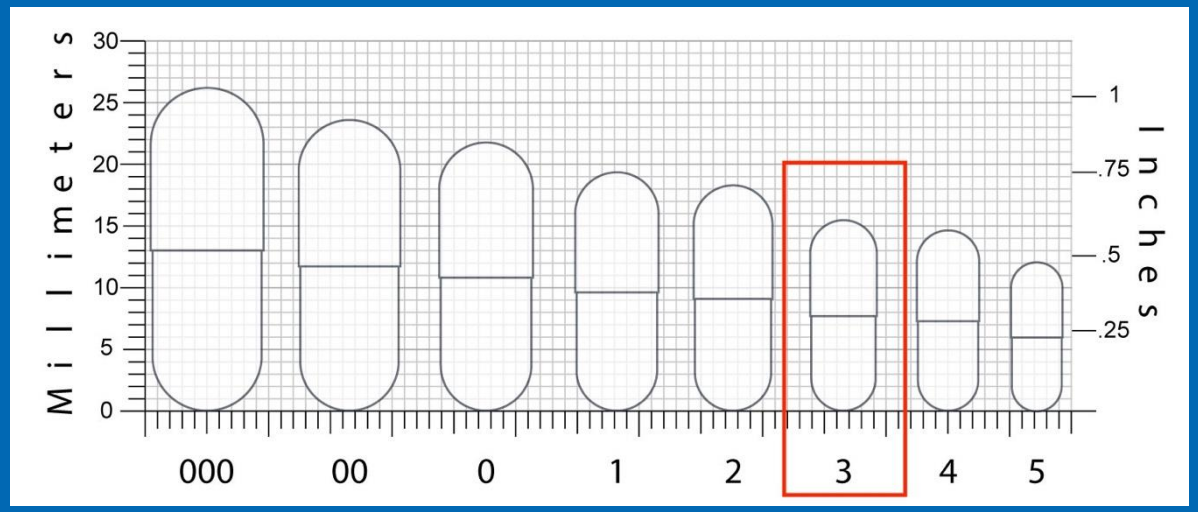
#2: Minimize Clinic Time w/ Telehealth

- Every clinic visit = missed day of school, missed day of work for parent, logistics for siblings. Not to mention potential long-distance travel.
- Went from 9 potential in-person visits —> just 3 (rest remotely)
- Initial enrollment: 2 full days in-person —> 1 day with initial screening and assessments instead done online, saving 6+ hours of clinic time
- After-hours and weekend appointments whenever possible

#3: Child-friendly ODT Melts vs. Pills

Dosage: requires swallowing three pills / day (3 x 1.5mg = 4.5mg total)

Size 3 capsules: over 1/2 inch long



Soliciting and Acting on Public Feedback

Public Comment Period

Outcome Assessment by Long COVID Subgroups

Respondents requested analyses for subgroups such as postural orthostatic tachycardia syndrome (POTS), dysautonomia, post-exertional malaise (PEM), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and mast cell activation syndrome (MCAS), and emphasized that not all participants have formal diagnoses.

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PWG Actions Taken

- Added planned subgroup analyses for POTS, dysautonomia, PEM, ME/CFS, and MCAS
- Ensured that the study will collect prior clinical diagnoses of the identified subgroups
- Added additional assessments: Composite Autonomic Symptom Score (COMPASS-31), the modified DePaul Symptom Questionnaire - Post-Exertional Malaise (mDSQ-PEM) assessment, and the Active Stand Test
- Implemented a comprehensive Long COVID symptom assessment

> *"Long COVID looks different for different people. It would be helpful to understand whether LDN works better for certain symptom groups."*

Participant and Family Support

Respondents emphasized reducing burden through flexible scheduling, telehealth, transportation support, multilingual materials, and clear communication.

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PWG Actions Taken

- Ensured that telehealth visits are supported whenever safe and feasible
- Encouraged flexible scheduling at sites
- Provided travel reimbursement
- Expanded translation and participant-facing resources

> *"Travel and in-person visits can be exhausting for Long COVID patients. Telehealth options make a big difference."*

Patient-Led Research Collaborative Scorecard

Scorecard measures:

- Patient / Partner Governance
- Integration into Research Process
- Patient Burden
- Research Organization Readiness

- Some general comments from the Round 1 Survey responders:
  - Clear communication about risks and rationale, leading to high levels of trust, responsiveness, and mutual respect.
  - Community representatives feel represented and respected, and their input meaningfully informs protocol design, burden mitigation strategies, and governance discussions.
  - Research team readiness for patient-engaged research was consistently rated as strong with shared decision making evident.
  - Qualitative feedback was optimistic that the protocols are participant-centered, and public concerns are being considered.

Learn More about the Patient-Led Research Collaborative Scorecard:

Next: expanded Community Advisory Board

Recap

- Patient engagement can create a better trial
- Trials can make a positive impact regardless of the results
- But most importantly…

Always remember who you're fighting for

From the 2nd Annual RECOVER-TLC Workshop
Sep. 9, 2025 in Bethesda, MD

Thank You

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Learn More about RECOVER-TLC:

Special thanks to:

RECOVER-TLC
Researching COVID to Enhance Recovery-Treating Long COVID

NIH
National Institute of Allergy and Infectious Diseases

FNIH
Foundation for the National Institutes of Health

RTI INTERNATIONAL

SCT | 47TH ANNUAL MEETING

Welcome

47TH Annual Meeting

PHOENIX

May 17-20, 2026

SCT

SOCIETY FOR CLINICAL TRIALS