RECOVER-TLC Trial Design Challenges: Endpoints

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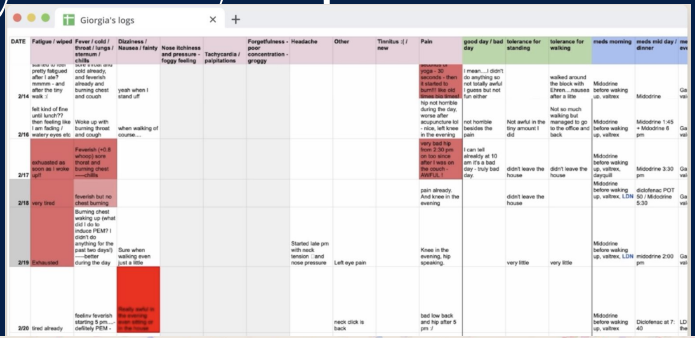
PATIENT-LED RESEARCH COLLABORATIVE

Long COVID's panoply of symptoms



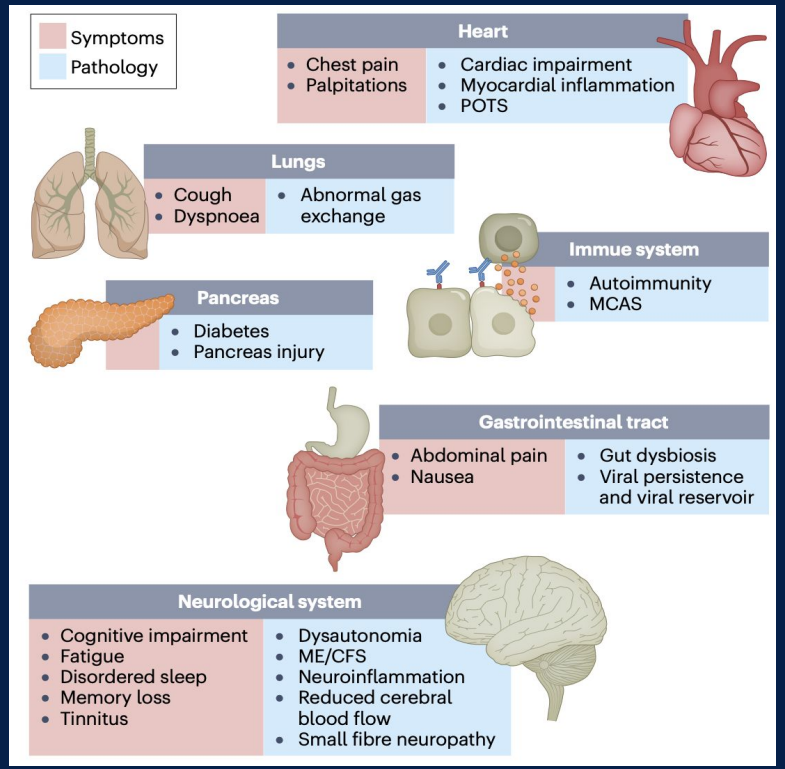
Excerpts from Giorgia Lupi's (2023) NYT op-ed: https://www.nytimes.com/interactive/2023/12/14/opinion/my-life-with-long-covid.html

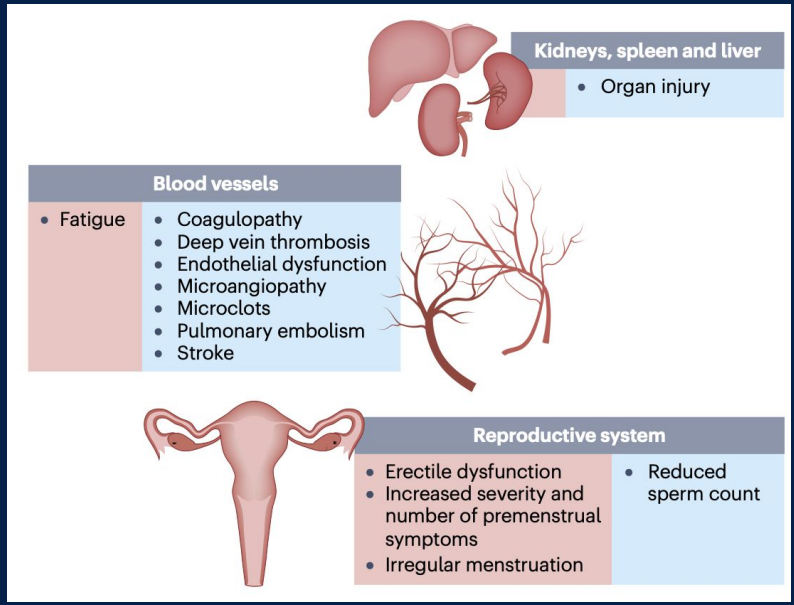
Outcomes that are meaningful to patients

Ms. Lupi asked members of her long Covid community to share their hopes, given the prompt: "I hope I will be able to _____ again." Hundreds of people responded.

Excerpt from Giorgia Lupi's (2023) NYT op-ed: https://www.nytimes.com/interactive/2023/12/14/opinion/my-life-with-long-covid.html

Diversity of symptoms & endpoints





Davis, McCorkell, Vogel, & Topol, 2023

Example endpoints to consider

- Functional capacity
  - Self-report: FUNCAP (not yet validated), time use survey
  - Wearable: step count
- Post-exertional malaise
  - Self-report: DSQ-PEM
  - Biological marker: 2-day CPET (risk of decreasing participants' baseline)
- Autonomic symptoms
  - Self-report: COMPASS-31
  - Biological marker: cerebral blood flow
- Specific types of cognitive impairment
  - processing speed
- Viral persistence
  - Biological marker: levels of reactivated viruses (e.g., EBV) in blood
  - Biological marker: gut biopsy

Diverse outcomes used in clinical trials so far

- Primary outcomes
  - Core Symptoms Severity Scale Score
  - DSQ-PEM
  - PROMIS-cognitive 8a
  - Orthostatic Hypotension Questionnaire (OHQ)
  - PROMIS-29 Physical Health Summary Score

- Secondary outcomes
  - Relief of ≥1 core symptom for 2 weeks
  - Overall alleviation of a core symptom
  - Severity of most bothersome symptom
  - Time to relief of 6 core symptoms
  - **PROMIS subscores (physical function, fatigue, dyspnea-severity, cognitive function abilities)**
  - Orthostatic vitals (seated vs. standing BP)
  - 1-minute sit-to-stand test
  - **Patient Global Impression of Severity scale score**
  - **Patient Global Impression of Change scale score**
  - Endurance shuttle walk test (ESWT)
  - Active stand test
  - Neurocognitive battery
  - Modified GSQ-30
  - COVID Core Outcome Measure for Recovery
  - Euro-Qol EQ-5D-5L (USA version)
  - Functional Assessment of Chronic Illness Therapy Item GP5
  - Healthcare utilization
  - Symptom assessment
  - Death

UCSF

Whose Long COVID symptoms are measured?

- Remote trials allow for participation of greater spectrum of patients with Long COVID, including patients who are bedbound or homebound
- Many patients with Long COVID will only participate in trials that take COVID precautions (e.g., masking, air purification/ventilation, testing, remote)
  - Taking COVID precautions will increase spectrum of patients who are able to participate

Being strategic with in-person data collection

- People with more severe symptoms may systematically opt out of trials with longer in-person data collection visits (e.g., 2+ hours)
  - Be as selective as possible with what data needs to be collected in any in-person visit
  - Make it as easy as possible to get to in-person visit site to help conserve patients' energy
- In-person data collection could trigger post-exertional malaise
  - Consider measuring this in follow-up

Goal: endpoints that are measurable, meaningful to patients, and support regulatory decisions

- Key issues to consider
  - Strengths and limitations of different data collection approaches
  - Time horizons for endpoint measurement
    - Urgency of evidence for Long COVID treatments
  - Identify potential common data elements across studies
  - Deep patient engagement in study, including identification of endpoints

Scripps Research
Science Changing Life

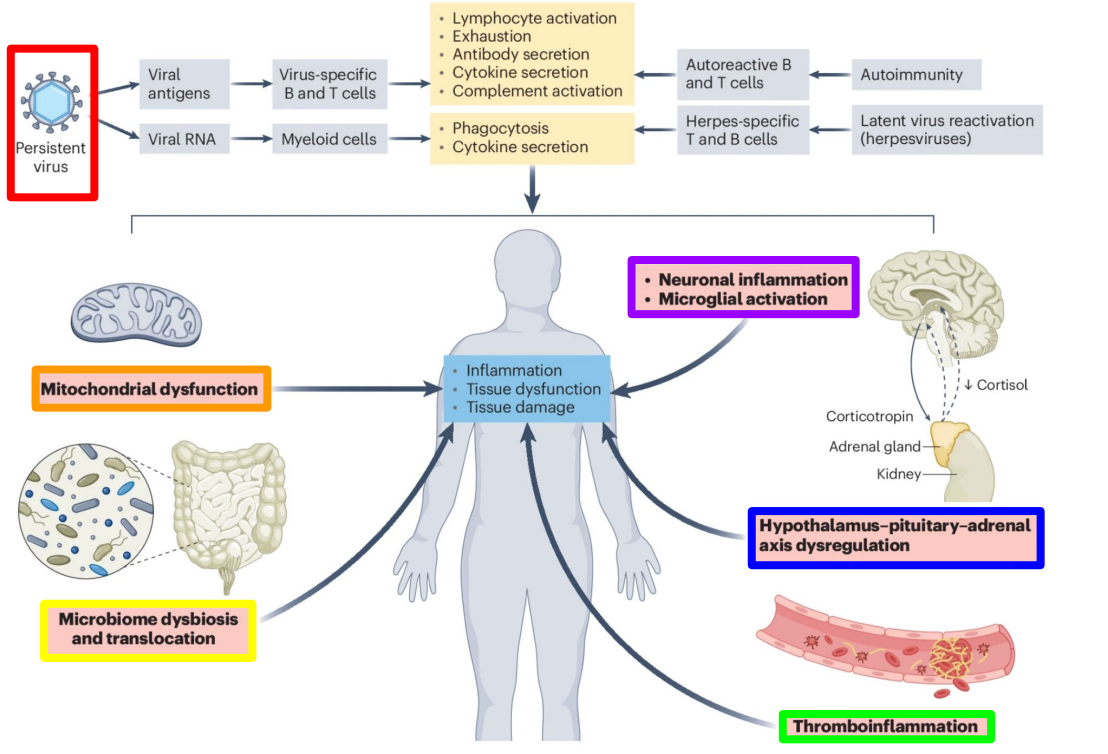
Selecting & Prioritizing Interventions: Current Landscape

Julia Moore Vogel, PhD, MBA
(views my own)

What can we (reasonably) expect to accomplish?

Scripps Research
Science Changing Life

Mechanisms of Long COVID to address



Over 200 symptoms in virtually any combination

Al-Aly et al, 2024
https://pubmed.ncbi.nlm.nih.gov/39122965/

Davis et al, 2021
https://pubmed.ncbi.nlm.nih.gov/34308300/

Number of interventions to test

- If we have enough funding to include 3,000 participants and each box is 100 participants, we could trial 2 to 30 (combinations of) interventions

Strategy 1: 2 interventions
Minimum detectable effect size:
~10 percentage points (pp)

Viral persistence intervention 1

Mitochondrial dysfunction intervention 1

Control

Strategy 2: 27 interventions

Minimum detectable effect size: ~20pp

Viral persistence interventions 1-4

Mitochondrial dysfunction interventions 1-5

Microbiome interventions 1-4

Thrombo-inflammation interventions 1-5

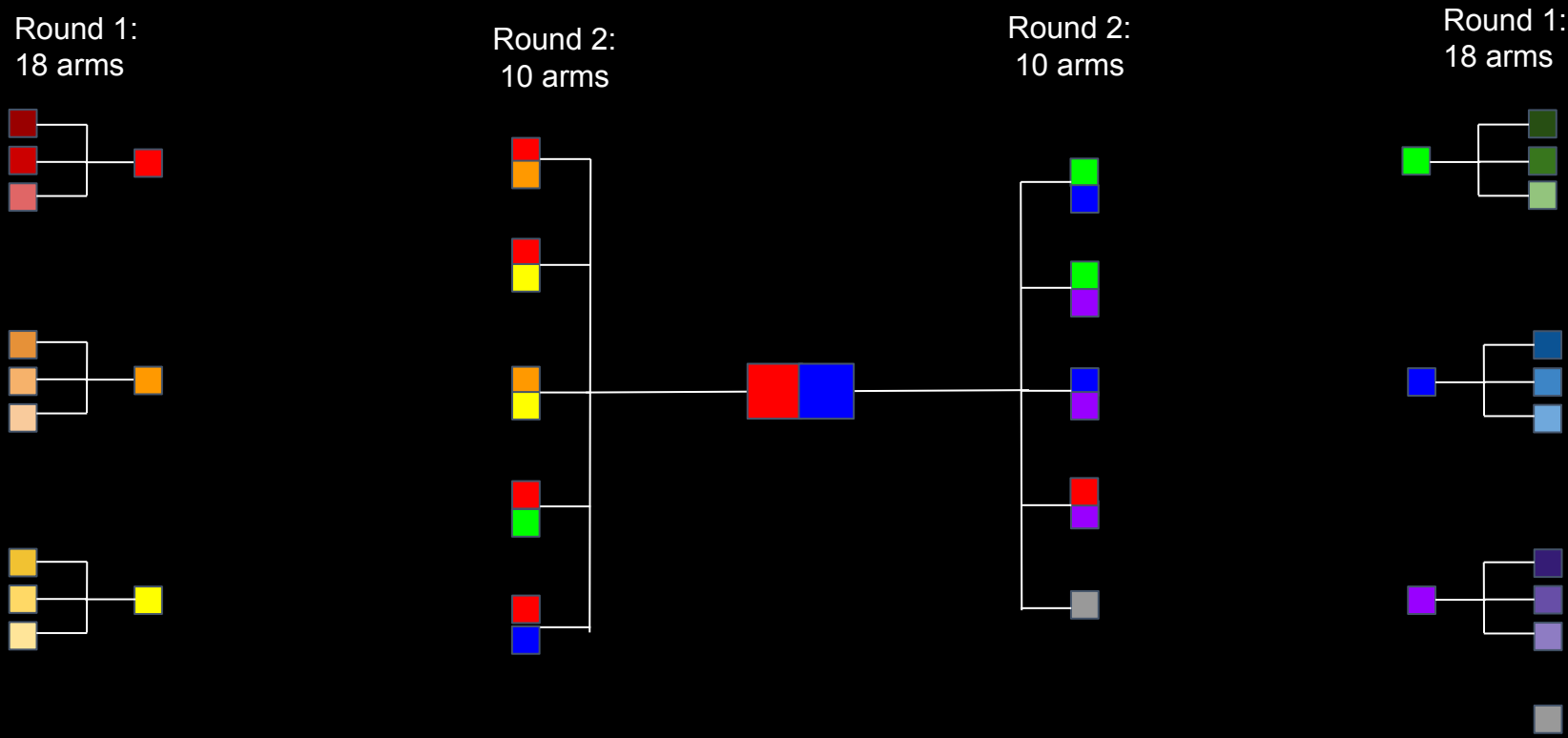
Adrenal, etc. interventions 1-4

Neuronal & microglial interventions 1-5

Controls (delivery methods) 1-3

Testing combinations: platform trial playoffs model

Could also allow for adjusting round 2 based on new literature



Priorities based on (my) lived experience

1. Curing >> managing
   a. “If you set a[n]…ambitious goal and miss it, you’ll still achieve something remarkable.” Larry Page

2. Balance risk/reward
   a. Let participants make informed choices
   b. Doing nothing is doing harm: move quickly & don’t let the perfect be the enemy of the good
   c. Trials must take COVID precautions to avoid (re)infecting participants

3. New drug development in addition to repurposing
   a. After decades of attempting to treat IACCs, there are no blockbusters
   b. Lower priority on over the counter options, unless they are in combinations

Intervention Options (1 of 3)

Viral persistence (and reactivation)

1. Remdesivir
2. Monoclonal antibodies
3. Valcyte/Valganciclovir
4. Famvir
5. Valtrex/Valacyclovir
6. Artemisinin
7. EBV vaccine
8. CAR-T cell therapy
9. Glutathione
10. Maraviroc & Truvada

Mitochondrial dysfunction

1. Rapamycin
2. Mestinon
3. Ubiquinone
4. Acetyl-L-Carnitine
5. Palmitoylethanolamide (PEA)
6. DRP-1 Inhibitors
7. Modafinil

Microbiome dysbiosis and translocation

1. Synbiotic preparation (SIM01)
2. Lactoferrin
3. Low histamine microbiome

Crowdsourced list - combinations may be required

Intervention Options (2 of 3)

Thromboinflammation

1. Nattokinase & serrapeptase
2. Pycnogenol
3. Sulodexide
4. Triple therapy (Clopidogrel, Aspirin, Apixiban, plus PPI)
5. Statins
6. Sildenafil

Hypothalamus-pituitary-adrenal axis

1. JAK-STAT inhibitors (especially JAK-1)
2. Cyclophosphamide
3. Inspiritol
4. Ampligen
5. Imunovir/Isoprinosine
6. FcRn inhibitors

Neuronal inflammation & microglial activation

1. GLP-1 inhibitors
2. Low Dose Aripiprazole
3. Intravenous immunoglobulin (IVIG)
4. Perispinal etanercept
5. Low Dose Naltrexone (recommend as combination)
6. Many others on Jared Younger's list

Crowdsourced list - combinations may be required

Intervention Options (3 of 3)

Comorbidity-specific & over the counter options could be used in combinations

POTS

- Beta blockers, Midodrine, Ivabradine, Colchicine, Spironolactone

Migraine

- Anti-CGRP and other standard of care

ME/CFS

- Table 4 here contains numerous pharmacological and nonpharmacological management options

Craniocervical instability

- Copper collagen peptide therapy

Misc over the counter

1. Antihistamines
2. Red light therapy
3.