Project Title: Randomized Study to Evaluate Strategies to Address Cognitive Fog in Long-COVID Patients

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Project Summary

The multi-disciplinary UPMC Post-COVID Recovery clinic serves the clinical needs of Long-COVID patients, those with persistent symptoms after initial infection recovery. Using an IRB-approved research registry collecting biomarkers, clinical data, imaging results and patient-reported outcomes (PROs), this group defines burden of long-COVID and guides personalized medicine strategies.

To date, phenotyping of 148 Long-COVID patients show 86% with new onset cognitive fog (using validated criteria) and 48% with depression (PHQ8 criteria). Cognitive fog was the most common complaint endorsed by patients during their clinic evaluations. ***Additionally, a subgroup of patients requesting a behavioral evaluation, who were in the prime of their adult productivity, reported that "cognitive fog" was the main symptom impacting their functioning, work performance, and life satisfaction; making it a critical domain to target clinically.*** The specific cognitive deficits reported as part of this "fog" varied across patients.

In a pilot study, we prescribed 90 of these depressed patients a coached digital cognitive behavioral therapy (dCBT) app developed by UPMC called RxWell, as part of care. Half of the patients (N = 45) downloaded the app and the 75% who completed techniques showed improvement in depression over 3 months (large effect size of change with PHQ8 (delta 6; p=0.001; Cohen's d=1.1; mean age 46)).

We posit rapid, accurate, and scalable assessment of cognitive impairment and implementation of the right interventions targeting specific deficits is a better fuller recovery path for these patients. ***This proposal evaluates the utility of computer-based evaluation of COVID-related cognitive fog and the relative efficacy of two intervention strategies to treat moderate cognitive impairment using a randomized trial which will inform the design of a future adaptive trial***. We plan to study 120 post-COVID patients seen in the Long-COVID clinic over the next 12 months with moderate or severe cognitive fog to assess the type and severity of neurocognitive impairment using computerized neuropsychological testing (BrainCheck). We will randomize to **either 1) dCBT with coaching (RxWell**) **versus 2) stimulant medication (amphetamine/dextroamphetamine), as part of the study embedded in clinical care, to provide data to inform design of future larger phase adaptive trials.** BrainCheck is

an FDA-approved technology to provide rapid, mobile cognitive assessment with venture investment and partnership with UPMC Enterprises. RxWell is a mobile app, developed and housed at UPMC Health Plan, with health coaches employed by UPMC. Both technology solutions improve access in an era of shortage of neuropsychologists and mental health providers. Stimulants have documented safety and effectiveness in helping neurocognitive deficits in conditions with similar deficit such as ADHD, post-concussion, and other inflammatory medical conditions.

We will evaluate effects of treatments on **cognitive impairment (primary aim)** and emotional distress (depression), satisfaction with life, work disability and health care utilization (secondary outcomes) over 3 months. Findings will provide inform and guide the design for the next phase adaptive clinical trial. These results will be generalizable to treating other common neuroinflammatory cognitive deficits such as that which follows ICU admission for sepsis or respiratory failure or following chemotherapy.

Select the item(s) that best support(s) your research

- ✓ **Promotes research with new approaches and innovations in care.**
- ✓ Incorporates the concept of comparative effectiveness and/or embedded and **adaptive designs,** which allows researchers to rapidly test multiple treatment approaches more efficiently than traditional clinical trials and with quicker, more applicable results.
- ✓ Supports a current UPMC focused initiative, including (but not limited to) those with aggressive approaches to cancer, gastrointestinal, heart disease **and neuroscience.**

Problem statement: (COVID-19 threatened the health of millions of Americans and others across the globe. After acute illness, prolonged effects called Long-COVID extract much from sufferers; data driven methods to address and manage these symptoms are lacking. Cognitive fog and emotional distress are common longer-term consequences after COVID-19. In our clinic, 80% of Long-COVID patients report persistent cognitive fog and 46% of these have at least moderate depressive severity. Both inflammatory and non-inflammatory factors may cause the cognitive and depressive symptoms.

We propose two efficient solutions that advance the treatment of reversible cognitive impairment secondary to COVID, which may apply to other medical conditions. ***Our two interventions approach the problem from different perspectives- one targeting cognitive fog associated with depression, the other the cognitive fog directly***. For depression with cognitive fog, a digital cognitive behavioral solution with health coaches offers cognitive rehabilitation strategies. For cognitive fog without depression, a stimulant medication known to reduce cognitive impairment in other chronic medical conditions will be used. Preliminary findings from this project will provide the necessary data to write a competitive federally supported proposal to fund a larger-scale adaptive design study. This next phase proposal will also incorporate learnings from this preliminary study to personalize intervention strategies to target specific cognitive domains of impairment. We will seek both federal funding and internal funding (UPMC Enterprises) for this next larger phase.

Summary of Project

Design Summary: Randomized trial of dCBT versus stimulant to treat cognitive impairment +/- depression in adults with Long-COVID.

Aim 1: Test efficacy of two interventions for improving cognitive impairment (primary outcome) and emotional distress (depression), life satisfaction, work disability, and medical utilization (secondary

outcomes). Assess effect of demographic and COVID symptom characterization variables on treatment efficacy.

Hypothesis: Stimulant therapy will outperform dCBT for patients with cognitive impairment alone and dCBT will outperform stimulant for cognitive impairment and depression.

Aim 2: Define the important response characteristics in these patients to inform design of a larger adaptive clinical trial evaluating treatment options for COVID-related cognitive impairment.

Methodology: Participants with confirmed Long-COVID cognitive impairment assigned with a 1:1 allocation to either arm using a permuted block design stratified by depression severity. Participants will complete computerized neurocognitive assessments and other study measures at baseline, 1.5 (interim) and 3 months after randomization.

Inclusion: Patients with Long-COVID between ages of 21-65; moderate cognitive impairment (MOCA$\leq$18) present for at least 3 months; access to a smartphone.

Exclusion: No history of dementia, psychosis, mania, addiction or current conditions requiring immediate hospitalization. No history of stimulant failure. No current cardiac condition

Interventions:

1. RxWell is a mobile application that consists of CBT techniques[1] and a health coach who provides in-app guidance and risk mitigation. Coaches will receive training to provide cognitive rehabilitation tips. Usage will be tracked.

2. Standardized dosing of amphetamine/dextroamphetamine monitored monthly with response-based titration to maximum dose of 20 mg bid[2] with side effects tracked. To date, patients with post-COVID fog have tolerated stimulants well.

Clinical flow and recruitment rates for registry study make 12-month recruitment completion feasible.

Primary outcome: Cognitive impairment

Measures:

Montreal Cognitive Assessment (MOCA) (10 minutes[3]) A validated screening tool for detection of mild cognitive impairment.

BrainCheck Neurocognitive Assessment (15 minutes): FDA-approved validated automated remote neurocognitive assessments in multiple domains[4].

ImPACT (20 minutes) is an FDA-approved computerized neurocognitive concussion assessment tool[5].

Secondary outcomes: depression (PHQ8), satisfaction with life (SWLS), disability (Sheenan Disability Scale), and health care utilization (ED and outpatient visits).

Statistical Analysis:

Aim 1: Intent-to-treat analyses stratified by depression severity. We evaluate three-month outcomes using linear regression models with assigned intervention depression severity and the corresponding baseline score as independent variables. Longitudinal linear mixed effects regression models with time, intervention, depression severity and corresponding baseline scores will assess treatment effects at 1.5 and 3 months and with interactions between intervention and time-points tested. Multivariable models include prespecified demographic and COVID symptom characteristics as covariates.

Aim 2: We will build a seamless Phase 2 to Phase 3 design with defined decision rules to determine whether interventions, including dCBT and stimulant, will "graduate" to the Phase 3 adaptive clinical trial. Bayesian analyses of accumulated data (including data from Aim 1) are performed on a prespecified schedule until stopping criteria are met. For a comparison of interventions, we may conclude superiority, inferiority or futility which can depend on pre-defined stratification variables. We anticipate that a response adaptive randomization (RAR) will be applied in Phase 3 such that the proportion of participants who receive each intervention will be determined based on the predicted probability that the intervention is optimal considering all accrued outcome data. Findings from Aim 1 will be used in simulations to estimate sample size requirements and to evaluate the operating characteristics of the adaptive clinical trial.

References

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