DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Heart, Lung, and
Blood Institute
Bethesda, Maryland 20892

June 14, 2022

[redacted]
Washington, D.C. 20510

Dear [redacted]

Thank you for your April 19, 2022 letter to Dr. Lawrence Tabak, Acting Director of the National Institutes of Health (NIH). Your letter posed a number of questions related to NIH's work to address post-acute sequelae of SARS-CoV-2 infection, or PASC. As the Director of the National Heart, Lung, and Blood Institute at NIH, I am pleased to respond to your inquiry.

1. What projects are currently funded as part of the NIH PASC Initiative?

The magnitude of the COVID-19 pandemic, the tremendous heterogeneity of post-acute symptoms and conditions, as well as mounting evidence of significant morbidity in the months following acute SARS-CoV-2 infection require a multi-pronged, multi-disciplinary research approach. As important, a diverse portfolio of sufficiently scaled and powered clinical studies is required to generate high-quality data that will provide the evidence base necessary to inform clinical practice and public health policy.

Toward this end, the NIH has launched the Researching COVID to Enhance Recovery (RECOVER) Initiative to improve understanding of and ability to predict, diagnose, treat, and prevent post-acute sequelae of SARS-CoV-2 infection (PASC), including Long COVID. The post-acute sequelae of SARS-CoV-2 infection are widely heterogeneous and vary across the lifespan and in different sub-populations, supporting the emerging view that PASC is not one but likely multiple conditions, which require multi-disciplinary approaches of sufficient scale to understand, treat, and prevent. RECOVER is a patient-centered initiative of national scale with inclusive diverse participation and community engagement. As briefly described below, RECOVER studies encompass longitudinal observational studies across the lifespan, clinical trials, ancillary clinical studies leveraging the cohort data and specimens, a patient registry, pathobiology studies, a mobile health platform, and EHR studies. The RECOVER Initiative was designed to understand fully the underlying biology of PASC and how best to treat those who are suffering.

RECOVER includes a **national longitudinal observational study** that is enrolling thousands of diverse participants including adult, pregnant, and pediatric populations from over 200 sites across the country, to fully understand the incidence, prevalence, and clinical signs and symptoms of the various forms of PASC and risk factors for their development. The clinical data and specimens from this study are necessary to provide the robust evidence base for the development of diagnostics, clinical monitoring strategies, as well therapeutics. Moreover, the data collected through this study will inform an understanding of and strategies to address ethnic

and racial disparities in PASC and its impact on pre-existing conditions and mental health effects.

The RECOVER initiative is also leveraging real-world data (RWD) that includes de-identified data derived from the electronic health records (EHRs) of over 60 million adult and pediatric patients accessible through the National COVID Cohort Collaborative (N3C), the PEDSnet consortium, and the National Patient-Centered Clinical Research Network (PCORnet). The RECOVER **EHR studies** are using advanced data science approaches, including artificial intelligence, machine learning, and natural language processing to better define PASC in all its forms, to discover and understand factors that influence the likelihood of developing PASC in adults and children, to understand PASC treatment strategies as quickly as possible, and to identify high-priority approaches to treat PASC in the populations most affected. While this work is ongoing, the RECOVER EHR studies have recently completed their initial set of analyses at national scale and are publishing results on several key clinical and public health issues, such as PASC and PASC sub-phenotypes; PASC cardiac complications; development of new onset diabetes mellitus as part of PASC; syndromic, systemic, and medication features of PASC; the impact of COVID-19 vaccination and viral variants on PASC; manifestations of PASC in children and adolescents; and racial, ethnic, and socioeconomic disparities in PASC. In addition, the RECOVER EHR studies are advancing and accelerating public health research regarding who has PASC by the development and broad dissemination of validated machine learning methods and usage of ICD-10 codes for identifying PASC; post-acute SARS-CoV-2 computable phenotype definitions; and best practices in the use of artificial intelligence, machine-learning, and natural language processing in the analysis of COVID EHR and other RWD.

RECOVER is also leveraging digital health technology with a **mobile health platform** being implemented now to enable broader and deeper engagement of participants, e-consent, and real time collection of personal sensor data on key variables such as heart rate, oxygenation, and sleep.

Other important aspects of the RECOVER Initiative include:

- **Pathobiology studies** (soon to be awarded) will identify mechanisms underpinning clinical phenotypes and symptomatic manifestations and help to understand the pathology in multiple organs/systems that have led or will lead to clinically significant health problems. Analyses of clinical data and biospecimens from the longitudinal studies will contribute to our understanding of the cause(s) of PASC, help identify biomarkers, enable risk stratification, contribute to the development of new therapeutic targets, and inform the design of PASC clinical trials.

- A systematic and standardized **autopsy study** at scale is underway to comprehensively identify the effects of SARS-CoV-2 infection on organs/tissues throughout the body for the purpose of understanding the pathobiology of PASC and informing the development of diagnostics, clinical monitoring, and potential treatment and prevention strategies.

- Preparations are underway for **clinical trials** with solicitation of clinical trial applications and the selection of the Clinical Trials Data Coordinating Center, which will provide overall project coordination, administration, data management, trial design, and

biostatistical support for a wide variety of RECOVER trials. The clinical trials are described in more detail below.

NIH has also established a suite of expert core components that provide critical operational, scientific, and coordination support to RECOVER studies:

- The **Clinical Science Core** (CSC), managed by the New York University Grossman School of Medicine, coordinates and oversees the RECOVER research consortium, which consists of more than 200 researchers at more than 30 institutions; develops clinical protocols through a consultative process that includes patients; and establishes methods for monitoring studies, including recruitment, data quality, and adverse events. To further inform RECOVER research, the CSC also conducts strategic communication and engagement efforts with key stakeholders, including patients and healthcare providers.

- RECOVER PASC **Reading Centers** provide state-of-the-art analytic techniques, expertise, and operational support for the imaging and physiological testing performed in the RECOVER adult and pediatric cohorts, including a quality control program to standardize test data acquisition protocols and monitor site performance. Awards are being made for eleven Reading Centers at six institutions across the country.

- The RECOVER **Data Resource Core**, managed by Massachusetts General Hospital, is responsible for data harmonization, integration, and management; enabling tracking and searchability of results across all sources of RECOVER data, from clinical studies to electronic health records; providing expertise in statistical analyses; and data standardization, access, and sharing.

- The RECOVER **Biorepository Core** (RBC), housed at the Mayo Clinic, provides a secure central repository for biospecimens collected as part of the RECOVER longitudinal studies. For PASC-related biospecimens maintained at Investigator sites or elsewhere, the RBC also functions as a "virtual" repository, tracking sample availability and location and incorporating information about the biospecimens, e.g., type of sample, volume, associated clinical data, and any limitations on use.

- The RECOVER **Administrative Coordinating Center**, managed by RTI International, provides research oversight and monitoring support in addition to support for communications activities, coordination of work groups, and protocol development.

When does the agency plan to launch clinical trials to test potential therapeutics and treatments, in addition to ongoing observational studies?

Clinical trials to identify safe and effective treatment and preventive strategies for PASC are a priority for NIH. Data from RECOVER and other studies underscore the need to test a wide range of interventions, given the diversity of clinical signs and symptoms and the variation in clinical conditions across the adult and pediatric populations. NIH has established a dedicated **Clinical Trials Data Coordinating Center** to implement and manage multiple interventions addressing symptoms/symptom clusters and underlying mechanisms of pathobiology of PASC. NIH has also issued a solicitation for well-designed clinical trials testing a range of interventions to address symptoms/symptom clusters and underlying mechanisms of

pathobiology. Clinical trial development is being informed through a consultative process with engagement of patient, practitioner, and research communities regarding symptoms/symptom clusters, outcome measures, and interventions.

Inclusion of diverse populations in the clinical trials, including those typically underrepresented in biomedical research, will be paramount for the generalizability and applicability of the results. As our understanding of underlying mechanisms leading to post-acute sequelae of SARS-CoV-2 infection improves through the other RECOVER research activities, additional candidate interventions will be evaluated and selected for testing. The first trials are anticipated to be launched by the Fall of 2022.

2. **Of the $1.15 billion Congress appropriated to support long COVID research, how much funding remains? What other funding streams, if any, exist to support research on PASC?**

Funds for the RECOVER initiative are being used to implement the necessary in-depth and national scale approach to understanding, preventing, and treating PASC, including Long COVID. NIH has either obligated or committed $1.15 billion for planned/outyear RECOVER activities. Working on an accelerated schedule, as of June 2, 2022, NIH has already obligated approximately $701 million. The remaining funds, approximately $449 million, will be used in planned obligations to cover FY22 and additional outyears for RECOVER studies. NIH is unaware of any other dedicated funding streams available to support research on PASC, including Long COVID.

3. **What barriers is the NIH facing in recruiting participants for the NIH's PASC initiative, particularly individuals from the communities hardest hit by the pandemic? How does the agency plan to address these challenges?**

While recruitment into the RECOVER longitudinal observational study is progressing, several challenges in the implementation of the RECOVER initiative as originally planned have emerged that are requiring real-time innovation and adaptation, including:

- Strong competition for research-related skilled employees has hindered core and site hiring, resulting in delays in local site activation and study implementation. To streamline local site implementation of the study protocols and facilitate patient participation in studies, study protocols have been adapted to improve local site workflow and reduce the burden of both participation and implementation.

- Enrollment of certain categories of study participants: RECOVER studies are enrolling research participants with PASC, participants who are acutely infected with SARS-CoV-2, and participants who were previously infected and do not presently have PASC (to serve as control cases in the study). The latter two groups of participants are critical to our ability to understand recovery and the biological events that impair recovery. This understanding is necessary to identify risk factors and inform the development of targeted therapeutics and prevention strategies. However, recruitment into RECOVER studies of these two groups has been particularly challenging due to a number of factors, including: the decline in the number of cases of acute SARS-CoV-2 infection seen earlier this year;

the milder symptomatology associated with the Omicron variants making patients less likely to seek medical attention; and the rapid expansion of home testing, which makes it difficult to identify and recruit acute cases. In addition, the extremely high transmissibility rates of recent variants mean that a large proportion of individuals have been infected and consequently it is difficult to find individuals to participate in the study who have not been infected, and those who have not been infected may not be as motivated to participate as those who were infected.

A variety of strategies are being explored to raise awareness of the RECOVER Initiative and facilitate recruitment of both acute cases as well participants without acute SARS-CoV-2 infection. These strategies include hyper-local media outreach, leveraging the reach of social media, search engine optimization strategies, local community outreach, and education, and leveraging SARS-CoV-2 testing programs and point-of-care settings as recruitment platforms. In addition, an interactive map providing easy access to the location and contact information of RECOVER enrolling sites is now available. Further, RECOVER is collaborating with NIH-community-based programs (Community Engagement Alliance Against COVID-19 Disparities (CEAL)) and local RECOVER site community advisory boards.

- Enriching enrollment of communities disproportionately affected by SARS-COV-2 infection is a critical goal for RECOVER and helps support an overarching goal of promoting health equity. This is accomplished in part by the inclusion of diverse participants reflective of the demographics of the pandemic in the United States. Toward this end, clinical cohort institutions were selected for participation that have a proven track record in reaching communities hardest hit by the pandemic. For example, RECOVER includes the Institutional Development Award (IDeA) states clinical research network and its clinical coordinating center is one of the main hubs for the RECOVER adult cohort study. In addition, a Research Centers in Minority Institutions (RCMI) site is also serving as one of the main hubs for the study. We are monitoring the diversity of enrollment closely, and one of the challenges we've found is that there is limited awareness of PASC in some communities. We are working with the NIH Community Engagement Alliance Against COVID-19 Disparities (CEAL), patient and community groups, and our patient engagement core to raise awareness and facilitate participation in RECOVER studies. By providing participant-facing materials in a variety of languages, we hope to further facilitate enrollment of diverse participants.

4. **How can Congress support NIH research on the long-term health effects of COVID-19? Would additional funding or authorities support these efforts**?

Our understanding of the complexity and broad range of conditions encompassed in PASC has evolved substantially since the time of the original appropriation, and it is clear that NIH must further accelerate and expand existing efforts and capacity to test a wider range of interventions, as well as develop assays for the diagnosis and monitoring of patients. This could be achieved through additional and/or expanded activities including:

- **Expand the scope of the RECOVER clinical trial portfolio to encompass the broad range of treatment and prevention strategies necessary for PASC**. Given the tremendous heterogeneity of post-acute symptoms and conditions, as well as the mounting evidence of serious morbidities, such as cardiovascular disease, stroke, diabetes mellitus, and mortality in the months following acute SARS-CoV-2 infection, an increasingly wide range of interventions will need to be tested in RECOVER clinical trials. Additional resources are necessary to expand the clinical trial portfolio to include testing of the full range of interventions needed to address the many patient symptoms and clinical conditions that can follow acute SARS-CoV-2 infection. Such interventions include drugs (e.g., anti-viral, immunomodulatory), devices, and rehabilitation (e.g., cardiopulmonary and cognitive behavioral). Furthermore, as results emerge from RECOVER (and other) pathobiology studies that shed light on the mechanisms causing PASC, we anticipate that additional and targeted as-yet-unidentified candidate treatment and preventive strategies will be elucidated and require testing in clinical trials in the future. In addition, leveraging consented EHR/RWD will facilitate the rapid and efficient recruitment of participants with key phenotypic characteristics that match the study inclusion criteria.

- **Accelerate and enhance enrollment into RECOVER studies**. RECOVER is aimed at understanding how patients recover from acute SARS-CoV-2 infection, ways to promote full recovery, and ways to treat and prevent PASC. To achieve these important goals as rapidly as possible, a variety of strategies are being explored to raise awareness of PASC and the RECOVER initiative and promote recruitment of inclusive, diverse populations. These strategies include media campaigns, expanding use of social media, optimizing search engines, enhancing local community outreach, developing tailored recruitment materials, and leveraging a variety of clinical recruitment platforms.

- **Extend and expand the collection and analysis of longitudinal clinical data, as well as EHR/RWD to understand the longer-term consequences of SARS-CoV-2 infection for patient health**. Integration of longitudinal cohort data, clinical trial data, and EHR/RWD data and resources in RECOVER is critical to the development and testing of clinical monitoring, treatment, and prevention strategies. The analysis of these large-scale data can also inform health care decision-making, as well as the development and implementation of treatment guidelines and public policies. Given emerging evidence about significant longer-term consequences of acute SARS-CoV-2 infection, it will be important to study the post-acute sequelae beyond the next 2-3 years (as currently funded) by extending the duration of RECOVER clinical cohort studies and data resources, as well as EHR/RWD studies leveraging invaluable clinical data from over 60 million adult and pediatric patient records.

- **Expand and enhance development of assays to identify various forms of and risk factors for PASC**. PASC, including Long COVID, is increasingly understood to be a multiple and wide-ranging set of conditions with extensive heterogeneity of symptoms. This emerging view points to the need to expand the capacity of RECOVER to fully characterize the various forms of PASC and identify specific patient sub-phenotypes to inform clinical studies and patient stratification, help identify patients at risk for Long

COVID, and design targeted therapeutic approaches. Application of state-of-the-science immunophenotyping testing and other clinical characterization assays from designated reference laboratories will ensure high quality, consistent results. These ancillary studies would leverage clinical data and specimens collected from RECOVER longitudinal cohorts and clinical trials.

- **Enhance and expand RECOVER strategic engagement and communication activities**. As the magnitude and duration of the impact of SARS-CoV-2 infection on individuals' lives and well-being continue to grow, there is a corresponding need to refine and significantly expand the current RECOVER communications infrastructure to engage strategically with patient, caregiver, and health care provider communities to incorporate their experience and expertise into RECOVER activities. These efforts require engagement of highly specialized expertise in high-impact communications around complex research and clinical topics.

Thank you for your interest in the NIH's efforts to study long COVID. We will also provide this response to [redacted]

Sincerely,

Gary H. Gibbons, M.D.
Director