ARIC Manuscript Proposal #4039

PC Reviewed: 5/17/22 **Status: _____** **Priority: 2**

SC Reviewed: _____ **Status: _____** **Priority:**

#30 - C4R Common Proposal Form

Project title: Epidemiologic features of recovery from SARS-CoV-2 infection in a US general population-based cohort: The C4R Study

Lead investigator(s):

Writing Group Chair: Elizabeth Oelsner (first author)
Senior C4R author: Wendy Post

Potential overlap

- Among approved C4R proposals (see website), which ones are the most similar to this proposal?
- Is there any potential overlap? Please explain and describe
    - If there is potential overlap, please summarize how this proposal is different

    This proposal is for the C4R core publication on COVID-19 recovery. Other papers focusing on specific features of recovery, PASC, and "long COVID" will leverage methods, including case definitions developed and concretized in this report, in order to answer subsidiary questions and hypotheses.

IRB Approval

- Does your institution have IRB approval for C4R? Yes
    - If yes, are you included on your institution's IRB? Yes

Funding

- Is there any funding anticipated for this proposal? Original OT funding
    - Source of funding and date of submission:
    - Timeline:

C4R cohort inclusion table:

Cohorts	Include: Yes / No	Co-author*	Comments**
ARIC	Yes		
CARDIA	Yes		
COPDGene	Yes		
Familial Interstitial	Yes		

Pneumonia/PrePF			
Framingham	Yes		
Jackson Heart Study	Yes		
HCHS/SOL	Yes		
MASALA	Yes		
MESA	Yes		
NOMAS	Yes	Mitch Elkind	
REGARDS	Yes		
SARP	Yes		
SPIROMICS	Yes		
Strong Heart Study	Yes		
Other***			

*If you do not have a co-author identified to represent a cohort, we will be happy to assist you in identifying one.
**Please justify exclusion of any C4R cohort from your proposal.
***If you anticipate including data from another cohort, please indicate which one(s).

Co-authors not already listed above:

Specific aims and hypotheses:

Specific Aim	Hypothesis
1. Describe the patterns of recovery from COVID-19 illness in C4R, including distribution of time-to-recovery and incidence and duration of specific symptoms.	The median time-to-recovery from SARS-CoV-2 and PASC symptoms will vary significantly among participants, with a substantial proportion of infected participants having cardiopulmonary and/or neurologic symptoms lasting longer than 3 months.
2. Examine predictors/correlates of delayed recovery, including host and viral/illness factors.	Delayed recovery from SARS-CoV-2 will be associated with pre-pandemic clinical and subclinical health conditions, greater severity of acute illness, secular factors (including changes in viral variants and treatments), and vaccination status.

3. Identify moderators and mediators for the effects of host/viral factors on delayed recovery.	The adverse effects of pre-pandemic clinical and subclinical health conditions will be substantially moderated by vaccination status and secular factors (different pandemic "waves") and mediated by severity of acute illness.

Do these aims relate to any of the C4R core research questions listed below? Please check all that apply.

☐ What are the major determinants of incidence and clinical severity of SARS-CoV-2 infection, and related disparities, across the US general population?

☐ What subclinical cardiopulmonary disorders increase the risk of severe COVID-19?

☒ What are the pulmonary complications of SARS-CoV-2 infection and COVID-19 illness and the risk of their occurrence?

☒ What are the risks of cardiovascular and cerebrovascular complications following SARS-CoV-2 infection?

☒ What are the neurological, cognitive, and psychiatric complications, including stroke, cognitive decline, and dementia, of COVID-19, and what are the predictors of persistent or delayed symptoms from COVID-19?

☐ How does lung structure associate with COVID-19 severity?

☐ Does COVID-19 cause long-term changes in lung structure?

☐ How do features of the innate and adaptive immune systems affect SARS-CoV-2 susceptibility?

☐ How do thrombo-inflammatory and endothelial activation profiles associate with risk of severe COVID-19 illness?

Rationale (300 words maximum)

Significance	Adverse effects of the coronavirus disease 2019 (COVID-19) pandemic on United States (US) health, economy, and society are widespread.[1] COVID-19 was the third-leading cause of death in the United States in 2020 and the second-leading cause of death in those over 85 years of age.[2,3] Prolonged symptoms and clinical abnormalities are observed in some COVID-19 survivors, raising concerns that post-acute sequelae of SARS-CoV-2 infection (PASC) or "long COVID" could pose an additional long-term health burden in a large proportion of the general population.[4]
Relevant prior literature	Numerous factors have been linked to the risk of PASC, although definitions of PASC have differed considerably from study to study. In a meta-analysis and systematic review of 29 studies that defined PASC as symptoms persisting more than 28 days post-acute infection, PASC was more common in women and varied by geographic region. Several of the studies included in the systematic review showed that increasing age and pre-existing conditions were variably associated with increased PASC risk, but the studies were too heterogeneous to perform meta-analyses for these factors and all findings were interpreted with caution.[5] A rigorous longitudinal multi-Omic study of several hundred COVID-

	19 patients, which defined PASC symptomatically, identified several "PASC anticipating factors," including comorbidities such as type 2 diabetes, congestive heart failure, and coronary artery disease, as well as reactivation of latent viruses during acute infection (e.g., CMV), and auto-antibodies [6,7] Nonetheless, this study was relatively small, relied on EMR-based definitions of pre-COVID health status, and studied patients at only 2-3 months of follow up despite emerging evidence for longer-term PASC.[8] Several large EMR-based studies have associated greater severity of acute illness with markedly increased risk of incident diagnoses of non-infectious acute and chronic health conditions, providing an alternative construct for PASC.[7-9] Longitudinal cohort studies with unbiased pre-pandemic health assessments are needed to determine the extent to which subclinical cardiopulmonary and neurologic health conditions may contribute to the observed increases in incident diagnoses following infection, potentially mediated by increasing the risks of more severe acute illness.
Summary of proposed study	This study will describe patterns of recovery from SARS-CoV-2 infection and to identify risk determinants and moderators and mediators of delayed recovery or "long COVID" in a multi-ethnic US general population-based sample of adults with robust pre-pandemic characterization of clinical characteristics.
Justification for use of C4R	Many studies of PASC have leveraged clinical registries and electronic medical record (EMR) data, which are more likely to capture severe COVID-19 outcomes and to include participants treated at major healthcare centers. C4R's population-based study design will support the study of PASC not only in people seeking healthcare but also in those with a range of symptom severity (including asymptomatic and mild infection) and underserved populations with limited healthcare access. Moreover, C4R's extensive pre-COVID phenotyping will allow reliable definition of consequences of COVID-19 infection and a unique opportunity to understand mechanisms and modifiers of risk and resilience for delayed recovery and "long COVID."

Data: Please indicate what C4R, cohort, or de novo data will be needed to accomplish the Aims.

- **C4R data** is defined as data collected under the C4R OT agreement: the wave 1 and wave 2 questionnaires, COVID events ascertainment, and the dried blood spot serosurvey.
- **Cohort data** is defined as data collected by the C4R cohorts as part of funded exams and ancillary studies. Ancillary study data use must be discussed with the relevant PI.
- ***De novo* data** is defined as data that you would like to collect as part of a new study. This requires ancillary study approval by C4R and also each included cohort and should be discussed with the C4R PI prior to proposal submission.

In filling out the following table, please review the **C4R data dictionary**, which includes C4R collected-data and selected cohort data. Inclusion of specific variable names from the data dictionary will expedite review. **Papers that do not include a COVID-related exposure or outcome are not suitable for review by the C4R P&P.**

	Variables needed	Details, questions and comments*
Outcomes	**COVID-Related outcomes** ☐COVID Infection ☐Acute COVID symptoms ☐COVID Severity ☐COVID Hospitalization ☐Death due to COVID ☐SARS-CoV-2 serology ☒Recovery from COVID ☐Reinfection with SARS-CoV-2 ☐Testing for SARS-CoV-2 ☐COVID Vaccine ☐Medications for COVID ☐COVID attitudes and beliefs ☐Behavior related to COVID ☐COVID exposures and risk mitigation ☐COVID pandemic effects on healthcare and finances ☐COVID Information sources ☐Psychosocial effects of COVID ☐Other COVID-related outcome: please comment in detail in the box on the right **Other outcomes** ☐Cardiovascular ☐Pulmonary ☐ Neurocognitive ☐Renal ☐Biomarkers ☐Psychosocial ☐Behavioral ☐Other non-COVID outcome: please comment in detail in the box on the right	Primary outcomes will be defined by data collected in W1 and/or W2 questionnaires. • Distribution of time-to-recovery, overall (time to self-reported "usual state of health") • Distribution of time-to-recovery for specific symptoms. • "Long COVID" as defined by time-to-recovery >30 or >90 days. • Symptoms commonly attributed to PASC in participants with history of infection.
Exposures	**COVID-Related exposures** ☒COVID Infection ☒Acute COVID symptoms ☒COVID Severity	Exposures will be defined by C4R data (questionnaire, DBS, events) and pre-COVID cohort data:

	☒COVID Hospitalization ☐Death due to COVID ☒SARS-CoV-2 serology ☐Recovery from COVID ☒Reinfection with SARS-CoV-2 ☒Testing for SARS-CoV-2 ☒COVID Vaccine ☒Medications for COVID ☐COVID attitudes and beliefs ☒Behavior related to COVID ☒COVID exposures and risk mitigation ☐COVID pandemic effects on healthcare and finances ☐COVID Information sources ☒Psychosocial effects of COVID ☐Other COVID-related outcome: please comment in detail in the box on the right **Other exposures** ☒Cardiovascular ☒Pulmonary ☒Neurocognitive ☒Renal ☒Biomarkers ☒Psychosocial ☐Other non-COVID exposure: please comment in detail in the box on the right	<u>Host factors</u> • Socio-demographic characteristics: age, sex, site, race, ethnicity, education • Anthropometry: height, weight, BP, spirometry • Past medical history: CV, pulm, neuro, renal • Behavioral: tobacco, alcohol, COVID risk mitigation <u>Viral/illness factors</u> • Date of infection (estimated variants, secular effects) • Treatment of infection (steroids, antivirals, other) • Symptoms of acute illness • Severity of acute illness • Antibody levels (by DBS) • Vaccination history
Covariates		

*For meritorious proposals, we will work with you to assess the status of data harmonization of variables of interest.

<u>Analysis plan</u>

- Primary analyst(s): Yifei Sun, PhD
- Brief statistical plan, organized by specific aim

Population: C4R participants infected with SARS-CoV-2 over the course of the study. Missing data patterns will be evaluated in order to determine the best approach, which could include multiple imputation or exclusion of cohorts with systematically missing data from some analyses.

Aim 1: Describe the patterns of recovery from COVID-19 illness in C4R.

- Distribution of time-to-recovery, overall and by symptom.

- Incidence of “long COVID” as defined by time-to-recovery >30 or >90 days.
- Prevalence of symptoms commonly attributed to PASC.

Aim 2: Examine predictors/correlates of delayed recovery, using time-to-recovery as the outcome and a survival analysis approach. In the primary analyses, time-to-recovery will be censored at 90 days following acute infection. Unadjusted Kaplan Meier curves will be used to evaluate relationships between recovery and each host and viral factor. Subsequently, Cox Proportional Hazards models will be sequentially adjusted by the same factors.

Aim 3: Test moderation and mediation of effects of host factors by severity of acute illness and other factors. To assess for potential effect modification by host or viral factors, three-way multiplicative interaction terms will be tested and fully stratified models will be explored. Race/ethnicity, vaccination status, and pandemic “wave” (defined temporally) will be pre-specified a priori as potential effect modifiers. Formal mediation models adapted to Cox Proportional Hazards will be used to test mediation; severity of acute illness will be pre-specified a priori as a potential mediator.

Table Shells

Additional considerations of primary importance to C4R approval -- please comment

- Inclusion of women and minorities
    - Treatment of sex as a biological variable
    - Appropriate analysis and interpretation of differences by race and ethnicity
- Consideration of social determinants of health
- Use (or non-use) of genetic data
- Respect for data sharing restrictions on Strong Heart Study & Jackson Heart Study data

References:

1. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. Science 2020.
2. Woolf SH, Chapman DA, Lee JH. COVID-19 as the Leading Cause of Death in the United States. JAMA 2021;325:123-4.
3. Andrasfay T, Goldman N. Reductions in 2020 US life expectancy due to COVID-19 and the disproportionate impact on the Black and Latino populations. Proc Natl Acad Sci U S A 2021;118.
4. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. The Lancet 2021;397:220-32.
5. Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global Prevalence of Post-Acute Sequelae of COVID-19 (PASC) or Long COVID: A Meta-Analysis and Systematic Review. medRxiv 2021:2021.11.15.21266377.
6. Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. Cell 2022;185:881-95 e20.
7. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nat Med 2022.
8. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. PLoS Med 2021;18:e1003773.
9. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature 2021;594:259-64.