TITLE:
Study protocol for the Innovative Support for Patients with SARS-COV-2 Infections Registry (INSPIRE): a longitudinal study of the medium and long-term sequelae of SARS-CoV-2 infection

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NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
ABSTRACT

BACKGROUND: Reports on medium and long-term sequelae of SARS-CoV-2 infections largely lack quantification of incidence and relative risk. We describe the rationale and methods of the Innovative Support for Patients with SARS-CoV-2 Registry (INSPIRE) that combines patient-reported outcomes with data from digital health records to understand predictors and impacts of SARS-CoV-2 infection.

METHODS: INSPIRE is a prospective, multicenter, longitudinal study of individuals with symptoms of SARS-CoV-2 infection in eight regions across the US. Included are adults fluent in English or Spanish, with self-reported symptoms suggestive of acute SARS-CoV-2 infection, enrolled within 42 days of having a US Food and Drug Administration approved SARS-CoV-2 viral test (i.e., nucleic acid amplification test or antigen test). Recruitment occurs in-person, by phone or email, and through online advertisement. A secure online platform is used to facilitate the collation of consent-related materials, digital health records, and responses to self-administered surveys. Participants will be followed for up to 18 months, with patient-reported outcomes collected every three months via survey and linked to concurrent digital health data; follow-up includes no in-person involvement. Our maximum expected enrollment is 4,800 participants, including 3,600 SARS-CoV-2 positive and 1,200 SARS-CoV-2 negative participants (as a concurrent comparison group). These data will allow assessment of longitudinal outcomes from SARS-CoV-2 infection and comparison of the relative risk of outcomes in individuals with and without infection. Patient-reported outcomes include self-reported health function and status, as well as clinical outcomes including health system encounters and new diagnoses.

RESULTS: Participating sites obtained institutional review board approval. Enrollment and follow-up are ongoing.
CONCLUSIONS: This study will characterize medium and long-term sequelae of SARS-CoV-2 infection among a diverse population, predictors of sequelae, and their relative risk compared to persons with similar symptomatology but without SARS-CoV-2 infection. These data may inform clinical interventions for individuals with sequelae of SARS-CoV-2 infection.
INTRODUCTION

The COVID-19 pandemic is associated with considerable morbidity and mortality. As of May 2021, > 32.6 million COVID-19 cases and > 580,000 attributed deaths have been detected in the USA [1]. Globally, > 160 million COVID-19 cases and > 3.3 million attributed deaths have been reported [2]. The clinical course of acute COVID-19 is well-described [3–7]. Post-acute COVID-19 is defined as persistence of symptoms or development of sequelae after 3 or 4 weeks from the onset of acute symptoms of COVID-19 [8–10]. This definition is further divided into subacute or ongoing symptomatic COVID-19, including symptoms from 4-12 weeks beyond acute COVID-19, and a chronic or post-COVID-19 syndrome, which includes symptoms persisting or present beyond 12 weeks of acute COVID-19 not attributable to alternative diagnoses [8,11]. Information on post-acute COVID-19 and long-term sequelae of SARS-CoV-2 infection is only recently emerging [12–15].

To characterize post-COVID-19 syndromes better, there is an urgent need for broader representation in study population selection to allow for representativeness and generalizability, to set objective outcomes that are not limited to symptoms but include illness events and clinical events, and to include SARS-CoV-2 negative individuals to ensure other effects of the pandemic are considered in the analysis (e.g. impact on livelihoods, mental health, food security, and mobility) [16]. Such work will help clinicians know what post-infectious sequelae to expect and who is at increased risk, will help ensure research findings can be compared across studies, and will move us towards addressing critical health care response needs.

To accelerate research during this critical time in the global COVID-19 pandemic, our research consortium designed a prospective longitudinal study to use patient-reported information linked to real-world data through the Innovative Support for Patients With SARS-COV2 Infections Registry (INSPIRE) hosted on a secure online platform (Hugo, Hugo Health LLC, Guilford, CT).
which imports health information from various sources with permission from participants. In this study, researchers follow a sample of individuals under investigation for SARS-CoV-2 over time, to collect patient-reported outcomes, interactions with the medical system (i.e., clinic visits, hospitalizations, laboratory test and medications prescribed) and outcomes of care as reported in the electronic medical record (EMR). The goals of this research are to understand the medium- and long-term sequelae of symptomatic SARS-CoV-2 infection, to describe predictors of sequelae as reported by individuals and as recorded in their EMR, and to assess the intersection of long-term sequelae of COVID-19 with other previously defined syndromes with overlapping features such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).
METHODS

Study design

This is a prospective, multicenter, longitudinal cohort study of individuals with acute symptoms consistent with SARS-CoV-2, including those with positive and negative diagnostic SARS-CoV-2 tests to compare those with and without SARS-CoV-2 infection (ClinicalTrials.gov Identifier: NCT04610515) [17].

Setting

Participants are enrolled from one of eight regions across the United States led by investigators at Rush University (Chicago, Illinois), Yale University (New Haven, Connecticut), the University of Washington (Seattle, Washington), Thomas Jefferson University (Philadelphia, Pennsylvania), the University of Texas Southwestern (Dallas, Texas), the University of Texas, Houston (Houston, Texas), the University of California, San Francisco (San Francisco, California) and the University of California, Los Angeles (Los Angeles County, California). The recruitment areas vary in terms of the population served to allow for ethnic and geographic diversity among study participants. As enrollment is through the internet and can be completed without assistance of research staff support, participants include those who have never been to the clinic or hospital for their symptoms and others who have been to the emergency department or hospitalized. Additionally, participants with any digital health portal can enroll in this study; participants’ health portals need not be those directly linked to the academic institutions listed above.

Participants

This study includes adult patients who are under clinical investigation for possible SARS-CoV-2 infection and who meet inclusion criteria outlined in Table 1. We include individuals with symptomatic presentation to determine comparative frequency of outcomes amongst
symptomatic individuals with and without SARS-CoV-2 infection: symptomatic individuals presenting with covid-like illness who test negative will act as controls for symptomatic individuals who have positive tests for SARS-CoV-2. Asymptomatic individuals are not eligible, given the anticipated lower rates of outcomes among asymptomatic individuals who test positive for SARS-CoV-2, and the significant heterogeneity in reasons for testing in asymptomatic individuals, such as screening for social, educational, occupational reasons and prior to routine clinical procedures. Individuals who self-report symptoms suggestive of acute SARS-CoV-2 infection, and are tested for SARS-CoV-2 within the last 42 days, are eligible to participate.

From study initiation through the summer of 2021, symptoms of acute SARS-CoV-2 was defined using the COVID-19 clinical criteria case definition (Table 2) [18]; beginning August of 2021, in order to capture less symptomatic individuals, the inclusion criteria were revised to require only one symptom among those listed in Table 2. Individuals for whom a SARS-CoV-2 test result cannot be confirmed are not eligible to participate in the study. Efforts are made to recruit participants from across the spectrum of COVID-19 illness severity, including individuals from outpatient (e.g., drive through testing with self-reported symptoms) to inpatient settings, and those cared for in intensive care units. We seek to enroll using a 3:1 case/control ratio to oversample those who are positive for SARS-CoV-2 on testing, while still ensuring an adequate control cohort for comparison.

**Table 1: Inclusion and exclusion criteria**

**Inclusion criteria:**

| a) Fluent in English or Spanish |
| b) Age 18 years or older |
| c) Self-reported symptoms suggestive of acute SARS-CoV-2 infection [19] |
| d) Tested for SARS-CoV-2 with any FDA-approved or authorized viral test (i.e., nucleic acid amplification test or antigen test [20]) within 42 days of enrollment |

**Exclusion criteria:**

| a) Unable to provide informed consent |
| b) Study team unable to confirm the result of a diagnostic test for SARS-CoV-2 |
Table 2: COVID-19 clinical criteria case definition (August 2020) [18]

In the absence of a more likely diagnosis,

At least TWO of the following symptoms:

- Fever (measured or subjective)
- Chills
- Rigors
- Myalgia
- Headache
- Sore throat
- Nausea or vomiting
- Diarrhea
- Fatigue
- Congestion or runny nose

Or any ONE of the following symptoms:

- Cough
- Shortness of breath
- Difficulty breathing
- New olfactory disorder
- New taste disorder

Or severe respiratory illness with at least ONE of the following:

- Clinical or radiographic evidence of pneumonia
- Acute respiratory distress syndrome (ARDS)

Participant Identification and Enrollment

Methods used to recruit potentially eligible participants vary by site, although each site applies the same eligibility criteria described in Table 1. Most sites screen for eligible participants among those tested for SARS-CoV-2 infection. With this process in place, we seek to enroll participants as close to their initial date of SARS-CoV-2 testing as possible. Identification and enrollment methods include: i) a member of the study team accesses the EMR to screen for potentially eligible individuals based on SARS-CoV-2 testing and reason for testing and contact eligible individuals, ii) participants learn of the study from a poster, brochure, or social media
and can enroll directly through the online portal, iii) research staff reach out to potentially eligible individuals in-person, over the phone, or by text or e-mail to offer and facilitate enrollment (e.g., contact information obtained from organizations including city and state agencies conducting SARS-CoV-2 testing). The method or combinations of methods used at each site are based on local IRB approval and practical considerations. Though minor differences exist across sites, the study eligibility criteria, online enrollment, and data collection methods are identical, which allows for compilation and comparison of data across sites.

**Variables and Outcomes**

Patient reported outcomes include self-reported disease-specific and generic outcomes (Appendix A) [21–23]. Health care utilization and clinical events are extracted from the EMR data via Hugo, ensuring uniform variable definitions across participating sites.

**Self-report of symptoms suggestive of SARS-CoV-2** are assessed using questions derived from the Centers for Disease Control and Prevention (CDC) Person Under Investigation for SARS-CoV-2 survey (Appendix A) [24]. This is not scored and has no predefined cutoff for the likelihood of COVID-19 illness.

**Generic physical and mental health** is assessed using the PROMIS®-29 [25]. This measure assesses pain intensity using a single 0-10 numeric rating item, and seven health domains (physical function, fatigue, pain interference, depressive symptoms, anxiety, ability to participate in social roles and activities, and sleep disturbance) using five response options per domain ranging from “not at all” to “very much”. In prior studies, this measure exhibits high reliability and validity, correlating well with other physical and mental health surveys as well as with chronic disease. The PROMIS® instrument assesses health-related quality of life over the past seven days, except for two domains (physical function and ability to participate in social roles and
activities) which do not specify a timeframe. Raw PROMIS®-29 scores are re-scaled from raw scores of 8 (worst) to 40 (best) into standardized T-score with a mean of 50 and standard deviation (SD) of 10. A higher PROMIS® T-score represents more of the concept being measured. For negatively worded concepts like Anxiety, a higher score is worse. For positively worded concepts like Physical Function-Mobility, a higher score is better. Version 2.1 of the PROMIS®-29, which will be used in the present study, is rescaled into a generic, societal, preference-based summary score [26]. This is based on PROMIS® scores for Cognitive Function, Abilities, Depression, Fatigue, Pain Interference, Physical Function, Sleep Disturbance, and Ability to Participate in Social Roles and Activities. It is scaled from 0 (equal to death) to 1 (equal to perfect health). Version 2.0 PROMIS® scores can also be used to estimate a Health Utility Index Mark 3 preference score [27]. In other settings, differences of 0.03 to 0.1 in this preference score have been interpreted as being clinically important [28–30]. A cutoff of 0.7 is used to determine severe impairment [31].

Cognition is assessed using the survey questions from the Patient-Reported Outcomes Measurement Information System (PROMIS®) Cognitive SF 8 [32]. Raw PROMIS® Cognitive scores are re-scaled from raw scores of 8 (worst) to 40 (best) into standardized T-scores with a mean of 50 and standard deviation (SD) of 10. A higher score is interpreted as indicating greater cognition.

Health care process measures are assessed as ambulatory care and/or emergency department (ED) visits for symptoms related to COVID-19 illness as well as hospitalization (admitted to hospital overnight during study follow-up) as determined by data from the EMR.
Hospital-free and intensive care unit (ICU)-free survival are assessed as determined by data from the EMR [33]. Hospital-free survival is survival without any hospitalizations and ICU-free survival is survival without time spent in the ICU.

Additional outcomes assessed include post-infectious sequelae (e.g., dyspnea, cough) [34–36], post-traumatic stress disorder (PC-PTSD-5) [37], and exercise (exercise vital sign; 2 question survey to assess habitual physical activity) [38–40], using previously validated questionnaires.

Social determinants of health (e.g., housing, available social services, geographical location, and education) are assessed using a previously validated questionnaire [41].

Work and activity status are assessed using questions about returning to work, missed work and activity level (Appendix A).

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is assessed using the CDC Short Symptom Screener (Appendix A), following 2015 Institute of Medicine diagnostic criteria (Table 2) [42]. While the study design will allow for assessment of a range of clinical outcomes as well as correlation with various clinical syndromes, recognizing that early reports of post-COVID sequelae may overlap with ME/CFS, this syndrome is included as one of the specific outcomes assessed.

Table 3. Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

| Patients must have all four criteria: |
|--------------------------------------|
| 1. A substantial reduction or impairment in the ability to engage in pre-illness levels of activity (occupational, educational, social, or personal life) that: a) lasts for more than 6 months, and b) is accompanied by fatigue that is often profound, of new-onset (not lifelong), not the result of ongoing or unusual excessive exertion, and not substantially alleviated by rest. |
| 2. Post-exertional malaise (defined as worsening of symptoms after physical, mental or emotional |
exertion that would not have caused a problem before the illness).
3. Unrefreshing sleep (defined as not feeling better or less tired even after a full night of sleep despite the absence of specific, objective sleep alterations).
4. At least one of the following two symptoms:
   a. Cognitive impairment (defined as problems with thinking, memory, executive function, and information processing, as well as attention deficit and impaired psychomotor functions. These can be exacerbated by exertion, effort, prolonged upright posture, stress, or time pressure, and may have serious consequences on a patient’s ability to maintain a job or attend school full time).
   b. Orthostatic intolerance (defined as a worsening of symptoms upon assuming and maintaining upright posture as measured by objective heart rate and blood pressure abnormalities during standing, bedside orthostatic vital signs, or head-up tilt testing. Orthostatic symptoms can include lightheadedness, fainting, increased fatigue, cognitive worsening, headaches, or nausea that are worsened with upright posture (either standing or sitting) during day-to-day life and are improved (though not necessarily fully resolved) with lying down).

Data sources

Results for a SARS-CoV-2 viral test (i.e., nucleic acid amplification test or antigen test) are confirmed by the research staff either through visualizing the result in the EMR or by reviewing an image of the test result sent to the research staff by the participant. After an eligible patient enrolls in the study, a combination of self-reported information and information generated from the patient’s own health information is connected to the Hugo platform, collected, and sent to the study site over the 18-month follow-up period (Appendix A).

Self-reported data: Using Hugo, surveys including the variables outlined above are sent by electronic mail or text to participants at the research site every 3 months throughout the follow-up period (Figure 1). These responses are sent through the Hugo platform and then shared with the study team. Subjects use their personal smartphone, tablet, computer, or other electronic device to connect to the internet and answer surveys that ascertain their symptoms, health care use, health care experience, and physical, mental, and social health over an 18-month period.
Responses sent by participants are encrypted. To minimize participant burden, each data collection episode is designed to take approximately 15 minutes or less to complete.

**Figure 1. Participant Timeline**

**Patient-Centric Data Sharing:** Participants connect their own health system portal account with the Hugo platform at enrollment (Figure 2). Hugo is a web-based platform used to longitudinally collect data for this study. The Hugo platform gives patients the ability to collect and maintain their personal health records in a centralized, cloud-based account. Participants will create a Hugo account and connect the health system portal accounts they choose to connect with the Hugo platform. This may include patient portals from healthcare systems, pharmacies, laboratories, and insurers. Individuals direct Hugo to share their health records with the research team according to the terms in the informed consent. This information is sent from Hugo to the research analytic core and stored in accordance with their institutional policies. The specific portal-related information available through Hugo in use for INSPIRE includes hospital and clinical patient portals yielding current data on medications, appointments and visits, test orders and results, clinical notes, problems, diagnoses, vital signs, demographics, and immunizations. After the study, participants can maintain their Hugo account or opt to delete their account and data.

**Figure 2. Use of Hugo Health to capture participant data**

Participants can connect their health system(s) portal accounts with Hugo at set up but may need assistance if they have technical issues or if they do not complete this initial step at enrollment. Once participants create an account in Hugo and link their portals, no additional
actions are required to stream data into Hugo. Technical support from the enrolling site or clinical core is provided to resolve any difficulties setting up an account.

During the study, periodically Hugo downloads identifiable data outlined in the IRB protocol and consent form. Research sites have access to site-specific dashboards to track enrollment, identify which data sources are connected, and to monitor survey responses. Deidentified, individual-level data are sent from Hugo to the analytic team periodically for quality assurance and analysis.

**Human Subjects Considerations**

This study involves self-enrollment with an online consent process using an electronic consent form designed with easy-to-read language. The consent form is a click-through digital document where, after reading the document, the participant clicks to agree or disagree to study participation.

Electronic consent occurs through the Hugo platform. Participants are eligible to receive a small incentive for completion of each periodic questionnaire; the total value will be $100 over the course of the study. Researchers will not provide any information gathered through the study to clinicians engaged in treating the patient. Patients will be informed and reminded that their responses will not be provided to their healthcare team, both at the beginning of the study during the consent process and throughout the study on the regular questionnaires.

Ethics approval of this protocol has been obtained at each individual site including Rush University (protocol number: 20030902, approved 3/14/2020), Yale University (2000027976, approved 4/30/2020), the University of Washington (UW Human Subjects Division, STUDY00009920, approved 4/2/2020), Thomas Jefferson University (20p.1150, approved
1/21/2021), the University of Texas Southwestern Medical Center (STU 2020-1352, approved 2/3/2021), the University of Texas, Houston (HSC-MS-20-0981, approved 9/10/2020), the University of California, San Francisco (20-32222, approved 1/25/2021) and the University of California, Los Angeles (20-001683, approved 12/18/2020). The Yale University ethics approval includes the role as the analytic lead. Additionally, the Rush University ethics approval includes INSPIRE data storage on the Hugo platform and transfer of data to Rush for secure storage.

**Study size**

Our target enrollment is 3,600 people with SARS-CoV-2 infection confirmed by a positive SARS-CoV-2 viral test (i.e., nucleic acid amplification test or antigen test) and 1,200 people with a negative SARS-CoV-2 viral test. We expect that the age distribution of enrolled subjects will represent that of patients tested in each site. Four of the sites (Yale, Jefferson, Rush and UW) draw on smaller catchment populations so have planned enrollment of 400 subjects per site (300 individuals with SARS-CoV-2 and 100 individuals without SARS-CoV-2). Four sites (UT Southwestern, UT Houston, University of California, San Francisco, and University of California, Los Angeles) have larger catchment populations so have planned enrollment of 800 subjects per site (600 individuals with SARS-CoV-2 and 200 individuals without SARS-CoV-2).

We estimated the power to detect relative differences in outcome rates between those who are symptomatic and test positive for SARS-CoV-2 as compared to those who are symptomatic but test negative for SARS-CoV-2. These power calculations are agnostic to the outcome of interest but based on the aim to examine relative differences in long-term outcomes between individuals with and without SARS-CoV-2 based on and between age strata. For comparison of ME/CFS incidence in SARS-CoV-2 infected vs uninfected, power calculations are based on the null hypothesis that there is no difference between individuals with and without SARS-CoV-2 in the outcome rate.
The assumptions used to generate these power calculations include both elements outside the study’s team’s control (e.g., baseline outcome rate in individuals without SARS-CoV-2) as well as elements amenable to changes in study design (e.g., individuals with SARS-CoV-2 strata group size). Assumptions include:

- 3,600 individuals with SARS-CoV-2 and 1,200 individuals without SARS-CoV-2
- Baseline outcome rate in individuals without SARS-CoV-2: 2.5% with the contingency that the baseline outcome rate may vary between age strata (18-40 years, 41-64 years, ≥ 65 years)
- Outcome rate in individuals with SARS-CoV-2: presented as scenarios based on absolute or relative differences from baseline outcome rate in individuals without SARS-CoV-2. Also presented under the likely scenario that outcome rates vary between age strata
- \( \alpha = 0.05 \) (fixed)

Under conservative assumptions, the planned sample has 97.8% power to detect an absolute outcome rate difference of 2.5% between individuals with versus without SARS-CoV-2 infection. The power to detect a relative difference in outcome rates is highly sensitive to both the actual baseline outcome rate as well as variation in baseline outcome rates between age strata. The study would have adequate power (conventionally defined as 0.8) to detect a difference as small as 5% in outcomes with 1,224 total participants (25.5% of total planned enrollment) enrolled in a 3:1 ratio, or 918 COVID+ and 306 COVID negative (Table 4).

### Table 4. Event Rate Difference Between Groups

| Power | 0.07 vs 0.05 | 0.10 vs 0.05 | 0.15 vs 0.05 | 0.20 vs 0.05 |
|-------|--------------|--------------|--------------|--------------|
|       | Total N      | COVID (+)    | COVID (-)    | Total N      | COVID (+)    | COVID (-)    | Total N      | COVID (+)    | COVID (-)    | Total N      | COVID (+)    | COVID (-)    | Total N      | COVID (+)    | COVID (-)    |
|       |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |

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Statistical methods

Statistical analyses will describe disease course and outcomes, including the characterization of specific symptoms and duration of symptoms, health care utilization (emergency department, hospitalization, post-acute care) with clinical (morbidity/mortality) and patient-reported health status outcomes as well as recovery (early and late disease sequelae). Baseline and demographic characteristics will be summarized by descriptive summaries (e.g., means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender, medians, and quartiles for skewed data). Analyses will:

- Compare health status at baseline and follow-up between persons in the same age group who test SARS-CoV-2 positive and negative at initial test.
- Characterize health care utilization (ambulatory and ED visits, hospitalizations, post-acute care, telehealth visits) among SARS-CoV-2 positive participants by age and compare these to SARS-CoV-2 negative participants.
- Characterize and compare health outcomes by age and SARS-CoV-2 status: emergency or ambulatory care, admission to hospital); ICU-free survival;\(^{16}\) hospital-free survival; and subsequent patient-reported health status (cognition; physical health; mental health; and return to work).

We will use statistical modeling to estimate the association between key covariates and outcomes, including evaluating interactions by age. We plan to use survival analysis techniques to analyze time to outcome events, logistic regression for binary outcomes (e.g., hospitalization versus no hospitalization), Poisson or Cox regression for count data (e.g., number of...
hospitalizations over time), and linear regression models for continuous outcomes (e.g., PROMIS-29). Multiple imputation will be considered to handle missing covariate and outcome data in these analyses [43]. Chained equations will be used to impute each variable with missing data. Sensitivity analyses will be conducted using missing categories for covariates and including only people with non-missing outcome information.

We will use statistical analyses to address the risk of ME/CFS and other health conditions in those with versus without SARS-CoV-2 infection as risk difference or risk ratios or odds ratios, as appropriate. We will also adjust for additional patient-level factors of interest, including age, sex, race/ethnicity, income, and presence of specific underlying conditions such as hypertension and diabetes. We anticipate that as more is learned about the clinical courses of persons with symptomatic SARS-CoV-2 infection, additional covariates of interest available from electronic record data will be assessed for their association with adverse outcomes.

**Data monitoring**

Periodic reports of de-identified data from participants at each site are exported from the Hugo data management system for monitoring and analysis by the study cores. These data will be used to monitor the adequacy of recruitment, with due consideration to the balance of subjects with positive versus negative tests as well as their age distribution, and completeness of follow-up questionnaires.

**Reporting**

The results of this study will be reported using the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for reporting observational studies [44]. We intend to disseminate the results as rapidly as possible to help contribute to the COVID-19 response.
Research partnership

This research will benefit from the contributions of a Patient Advisory Board. This group provides valuable perspective and guides our research team on issues pertaining to participant engagement, survey data collection, and will assist with interpretation of study findings and communicating results to the general population. Additionally, this study is conducted in collaboration with colleagues from the CDC. Scientists from the CDC assisted with study design and will remain engaged as we evaluate and disseminate the research findings.
DISCUSSION

Expected key results

Our prospective cohort study is designed to gain critical information needed by clinicians in the USA and globally regarding medium and long-term sequelae of SARS-CoV-2 infection. Prior limited experience with people infected with SARS-CoV-2 suggests that age as well as race and ethnicity are important risk factors for SARS-CoV 2 infection and for poor outcomes in the acute setting [20,45–48]), but predictors of medium- and long-term outcomes have not been well-described. Moreover, there is a need to leverage digital assets and tools to harness data from both patients and providers to quickly define the clinical epidemiology of COVID-19. Creating such a platform and assessing its value to address priority questions would have immense significance for the nation.

To date, there has been a relative lack of epidemiological studies designed to provide robust evidence of incidence, risk factors, and natural history of sequelae of SARS-CoV-2 infection. Existing studies are limited by multiple potential biases in study design. Many prior studies of SARS-CoV-2 infection recruited from single rather than multiple centers, which may overestimate the relationship between baseline factors as well as treatment exposures and outcome and thereby lack generalizability [49–51]. In addition, many have preferentially recruited patients who are hospitalized or receive intensive care, who have greater acuity or severity of illness and could be at greater risk of long-term sequelae than those who are treated in an ambulatory setting. In contrast, our recruitment of participants testing for SARS-CoV-2 with acute symptoms of illness from community (e.g. drive up testing sites), clinic, emergency, and in-patient settings reduces the likelihood of selection bias [52].

Prior studies which lack concurrent controls who have similar symptoms or require similar health care utilization characterize the burden of SARS-CoV-2 infection, but, by the nature of their
design, cannot describe the relative risk of sequelae compared to those who do not have SARS-CoV-2 infection but who have another viral infection. Social distancing and receipt of intensive care are both associated with initial and long-term social, emotional, well-being and health sequelae [53,54]. The effects of increased social isolation affecting individuals’ social, emotional, and functional well-being regardless of infection with SARS-CoV-2, further emphasizes the need for including individuals not infected with SARS-CoV-2 to generate evidence on the incidence of sequelae of COVID-19 illness.

Emerging evidence suggests that a significant proportion of individuals infected with SARS-CoV-2 experience ongoing clinical symptoms several months after acute infection. Among a cohort of 4,182 participants testing positive for SARS-CoV-2 evaluated in the COVID Symptom Study with the majority from the UK (88%), the US (7%), and Sweden (4.5%), 13% reported symptoms greater than 28 days after onset, with fatigue (98%) and headaches (91%) the most commonly reported symptoms [55]. Additionally, 4.5% of all participants had \( \geq 56 \) days of symptoms and 2.6% had \( \geq 84 \) days of symptoms [55]. In a large prospective cohort study from Wuhan, China, with in-person evaluations of 1,733 patients at 6 months from symptom onset, 76% of patients reported at least one symptom with the most commonly reported symptoms being fatigue/muscular weakness (63%), sleep disturbance (26%), and anxiety/depression (23%) [56]. Among a cohort of 180 participants in the Faroe Islands who had reverse transcription-polymerase chain reaction positive COVID-19 tests, 53% reported persistence of at least one symptom after a mean of 125 days from symptom onset [57]; the most persistent severe symptoms reported were fatigue, loss of smell and taste, and arthralgias [57]. In Italy, among 143 patients discharged from the hospital after acute COVID-19 with a mean follow-up of 60 days from first symptom onset, 87% of patients had persistent symptoms with the predominant symptoms being fatigue (53%), dyspnea (43%), arthralgia (27%), and chest pain,
(22%) and with 44% experiencing a worsening quality of life [58]. A US-based study using historical comparator groups with viral lower respiratory tract illness and propensity matching demonstrated that 14% of adults ≤ 65 infected with SARS-CoV-2 had at least one new clinical sequelae requiring medical care after the acute phase of the illness; this was nearly 5 percentage points higher than the historical comparator group [59]. Similar findings of persistent symptoms have been reported in other studies across the world [12,60].

Recent studies have also reported changes in renal function, metabolic response, cardiovascular systems, and neurological changes persisting in the post-acute phase of SARS-CoV-2 infection [61]. Of note, a considerable proportion of those previously infected with SARS-CoV-2 develop new clinical sequelae that were not present during the acute illness and that require medical attention; new clinical sequelae include chronic respiratory failure, cardiac arrhythmia, hypercoagulability, encephalopathy, peripheral neuropathy, amnesia, diabetes, liver test abnormalities, myocarditis, anxiety and fatigue [62]. There remains uncertainty regarding the incidence of sequelae, the range of impacts on individuals, the factors associated with risk for development of sequelae, and the natural history/time course of the sequelae. Given the high global rate of SARS-CoV-2 infection, this information is critical to guide care following SARS-CoV-2 infection amongst vast numbers of individuals. This evidence could potentially highlight individuals at higher risk for complications who may require more intensive follow-up and facilitate earlier intervention and guide targeting of primary or secondary interventions [63]. Further, dissemination of findings from this research may increase COVID-19 vaccination acceptance, helping to prevent sequelae from SARS-CoV-2 infection.

**Strengths and limitations**

Our cohort study integrates detailed self-reports of participants with automated capture of their EHR information to provide more comprehensive data than traditional approaches. This
innovative method enables capturing of baseline medical conditions, accounting for intermediate events between SARS-CoV-2 infection and sequelae, and objective assessments over time. Merging self-reported and digital data in this manner paves the way for similar research into long-term sequelae in other disease entities, including non-infectious illnesses such as trauma. Using the on-line digital platform to collect patient-oriented outcomes enables us to adapt the survey content in real time as new information emerges. Additionally, there is the potential for this cohort to be engaged in future research as new questions arise relating to long-term sequelae, therapies and other related issues. Recruitment design strengths include the inclusion of participants with a range of disease severity, including participants with and without a history of hospitalization. Additionally, we seek to recruit participants who are ethnically diverse and geographically dispersed. Further, our design includes concurrent controls with negative SARS-CoV-2 diagnostic results to overcome the variable exposure to healthcare access as well as to COVID-19 mitigation strategies implemented in the community (e.g., masking mandates, shutdowns) which could otherwise bias assessment of the risk of patient-reported outcomes. Finally, our planned sample size is intended to detect rare events among the study population.

Our design anticipates and addresses study limitations as feasible. Inclusion in the INSPIRE study requires participants to have a sufficient degree of technology literacy as well as periodic access to the internet which may introduce selection bias into who is able to participate. There are large differences in the use of desktop or laptop computers between Black (58%) or Hispanic or Latino persons (57%) vs. White (82%) individuals [64]. Importantly, about 80% of Black, Hispanic or Latino persons, and White adults own a smartphone; lack of availability of a smartphone should not be a barrier to enrollment of racial/ethnic subgroups in this study. We worked to overcome challenges related to technology literacy by offering support at the time of enrollment and throughout the study to troubleshoot problems such as linking digital health portals to the Hugo platform and completing quarterly surveys. We anticipate that individuals
with COVID-19 and symptomatic illness are more likely to have the outcomes of interest, therefore, enrollment is limited to individuals who are symptomatic prior to SARS-CoV-2 testing. We will not be able to determine risks of outcomes among asymptomatic individuals who test positive for SARS-CoV-2 with this design. Finally, there is the potential for bias by self-selection to enroll by participants whose COVID-19 illness has not resolved. To mitigate against this, we required that enrollment occurred within 42 days of SARS-CoV-2 infection diagnosis. At the analysis stage, sensitivity analysis can describe long-term symptoms as a function of time between onset and enrollment.

Given the prospective longitudinal design of this study, there is an inherent risk of attrition and loss-to-follow-up of participants. To limit this potential problem, each research site monitors research participants’ progress and invites them to re-engage if they do not complete their quarterly survey. While the preferred means of contact varies between sites, this may include through email, short message service (i.e., text), or telephone reminder. Additionally, participants are incentivized to participate with a monetary reward for survey completion as described above (consent and ethics section).

Another possible limitation is risk of poor data quality and misclassification. With this study design which incorporates digital health data, some data is passively acquired and thereby data quality is dependent on the accuracy of electronic medical records. We believe that coupling these digital health data with the self-reported data will enhance the accuracy and completeness of available information. There is also potential for bias from unmasking underlying health conditions identified during the study that were not known until after the SARS-CoV-2 infection resulting in misclassification of pre-existing diagnoses as sequelae of COVID-19. As feasible, we will evaluate indications of undiagnosed health conditions by evaluating data from the EHR.
There is a plausible risk of misclassification bias from inaccurate diagnostic test results of COVID-19 tests at enrollment. Despite the reported high sensitivity and specificity of SARS-CoV-2 diagnostic testing [65,66], some participants could be misclassified as having or not having acute SARS-CoV-2 infection. Participants with false negative test results are classified as controls but can still have increased risks of long-term sequelae, which may bias our results towards the null. As well, participants’ SARS-CoV-2 status can change over time due to repeat exposure and repeat diagnostic testing. We inquire about repeat SARS-CoV-2 testing and results during quarterly surveys and we will also look for related data during electronic medical record review.

**Conclusions**

Upon the conclusion of the study, we will be able to quantify the burden of long-term SARS-CoV-2 sequelae as well as characterize predictors of sequelae. Additionally, data from INSPIRE will offer insight into diseases with overlapping signs and symptoms of COVID-19, such as ME/CFS, to help understand differences and similarities between these viral conditions, as well as how people with underlying disease and subsequent COVID-19 experience these illnesses. We will be better poised to develop prevention and treatment strategies and to tailor these strategies for the most at-risk subsets of the population. The results will inform clinicians and public health authorities and will help prepare for future SARS-CoV-2 surges.
APPENDIX A: INSPIRE Survey Specifications

[intend to publish as a supplement]
APPENDIX B: Acknowledgement of Participating Sites and Personnel

Rush University, Administrative Core & Enrolling Site

Core Investigators: Bala Hota, MD; Robert A. Weinstein, MD

Core research team: Katherine Koo, MS

Site Investigators: Michael Gottlieb, MD, Site Principal Investigator

Site research team: Michelle Santangelo, MPH

Yale University, Analytic Core & Enrolling Site

Core Investigators: Arjun Venkatesh, MD, MBA, MHS; Erica Spatz MD, MHS; Andrew Ulrich, MD

Core research team: Zhenqiu Lin, PhD; Shu-Xia Li, PhD; Huihui Yu, PhD; Mengni Liu, MS; Jeremiah Kinsman, MPH

Site Investigators: Arjun Venkatesh, MD, MBA, MHS; Erica Spatz MD, MPH; Andrew Ulrich, MD

Site research team: Jeremiah Kinsman, MPH; Michelle Opare, BS

University of Washington, Clinical Core & Enrolling Site
Core Investigators: Graham Nichol, MD, Principal Investigator; Matthew Thompson, MD, MPH, DPhil, Principal Investigator

Core research team: Jill Anderson, BSN, RN, Clinical Core Program Manager; Kari Black, BA, Grant & Finance Manager; Dana Morse BSN, Research Coordinator; Anoushka Fernandes BSc, Research Assistant.

Site Investigators: Kelli N. O’Laughlin, MD, MPH, Site Principal Investigator; Nikki Gentile, MD, PhD, Co-Investigator; Kari Stephens, PhD, Co-Investigator

Site research team: Rachel E. Geyer, MPH, Research Coordinator; Victoria Lyon, MPH, Program Manager; Sophie C. Morse, BA, BS, Research Assistant; Karen Adams, BA, Regulatory Specialist; Michael Willis, AS, BSHS, Research Assistant

Thomas Jefferson University, Enrolling Site

Site Investigators: Anna Marie Chang, MD, MSCE, Benjamin Slovis, MD, MA

Site research team: Morgan Kelly, BS, Alaina Hunt, BA, Kyle Norton, BA, Mubazar Ishfaq, BA, Paavali Hannikainen, BS, Melanie Chalfin, BA, Lindsey Shughart, Hailey Shughart, BA, Nicole Renzi, RN

University of Texas Health Science Center at Houston, Enrolling Site

Site Investigators: Mandy Hill, DrPH, MPH, Site Co-Principal Investigator; Ryan Huebinger Site, MD, Co-Principal Investigator; Summer Chavez, DO, MPH, MPM, Site Co-Investigator

Site research team: Elizabeth Vidales MD, MPH; Leslie Johnson BS
University of Texas Southwestern Medical Center, Enrolling Site

**Site Investigators:** Ahamed H. Idris, MD, PI; Samuel McDonald, MD, Co-I

**Site research team:** Paula Arellano-Cruz, Research Coordinator; David Gallegos, Research Associate

University of California, Los Angeles, Enrolling Site

**Site Investigators:** Joann Elmore, MD, MPH (site PI), Lauren Wisk, PhD

**Site research team:** Raul Moreno, BA, Dayna Clayton, BA, Annie Lee, PhD, Michelle L’Hommedieu, PhD, Chris Chandler, BA

University of California, San Francisco, Enrolling Site

**Site Investigators:** Robert Rodriguez, MD; Ralph C. Wang, MD, MAS; Juan Carlos Montoy, MD, PhD

**Site research team:** Robin Kemball, MPH; Virginia Chan, Cecilia Lara Chavez, Angela Wong
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### Figure 1. Participant Timeline

| TIMEPOINT                                      | Enrolment | Post-enrollment | 3 mos. | 6 mos. | 9 mos. | 12 mos. | 15 mos. | 18 mos. | tx |
|------------------------------------------------|-----------|-----------------|--------|--------|--------|---------|---------|--------|----|
| ENROLLMENT:                                    |           |                 |        |        |        |         |         |        |    |
| Eligibility screen                            | X         |                 |        |        |        |         |         |        |    |
| Informed consent                              | X         |                 |        |        |        |         |         |        |    |
| ASSESSMENTS:                                   |           |                 |        |        |        |         |         |        |    |
| Age, gender, symptoms of SARS-COV-2 infection, recent health care use, social determinants of health | X         |                 |        |        |        |         |         |        |    |
| Outpatient visit, emergency department visit, hospitalization, intensive care stay, death, physical and mental health (PROMIS-29), cognitive SF-8, hospital-free survival, intensive care-free survival, dyspnea, cough, exercise, social determinants of health, work and activity status, myalgic encephalomyelitis/chronic fatigue syndrome | X         | X               | X      | X      | X      | X       | X       | X     |
| Preexisting conditions                        | X         | X               | X      | X      | X      |         |         |        |    |
Figure 2: Use of Hugo Health to capture participant data