Rationale, Background, objectives, design, methodology, statistical considerations, organization

Abbreviated Title: NIMH COVID Study

Protocol #: 20MN085

Version Date: 5/12/20

Title: Mental Health Impact of COVID-19 Pandemic on NIMH Research Participants and Volunteers

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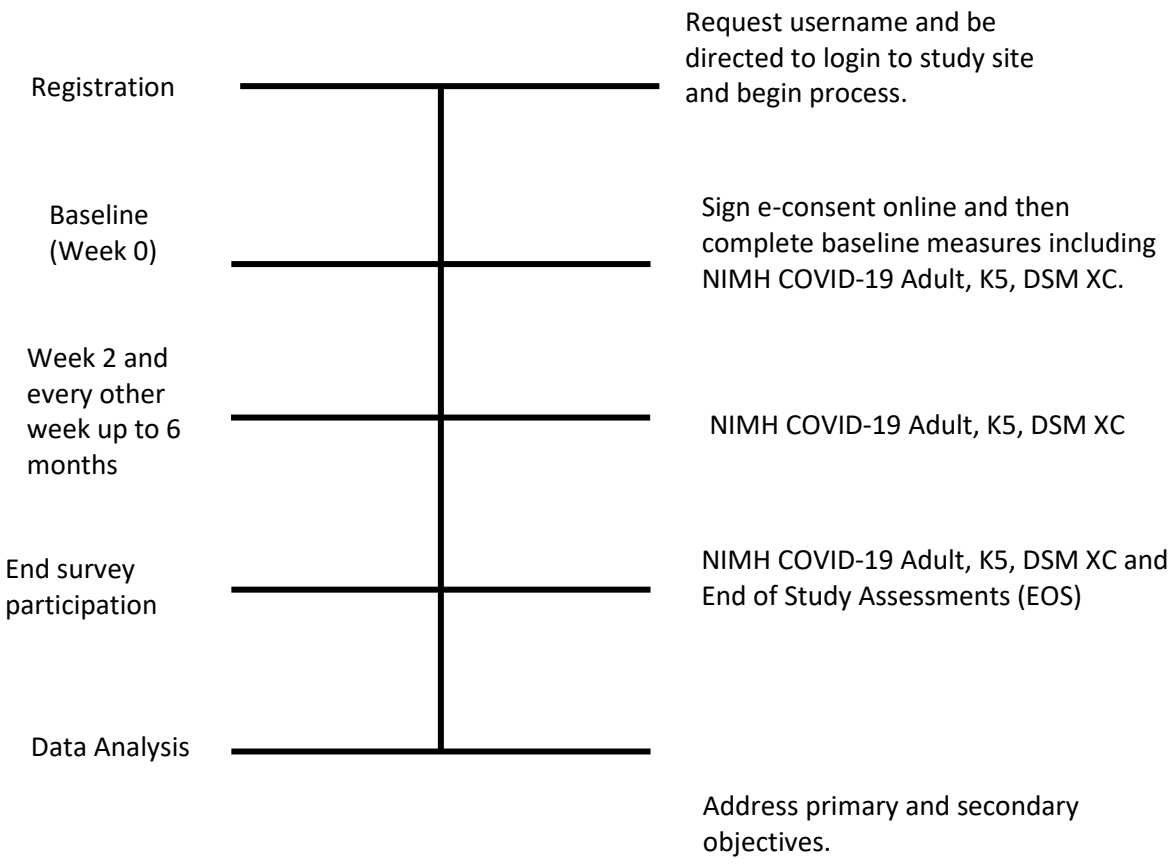
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Mental Health Impact of COVID-19 Pandemic on NIMH Research Participants and Volunteers
Study Description:	This protocol leverages existing NIMH studies and participants to accomplish time-sensitive research on the mental health impact of environmental stressors imposed by the COVID-19 pandemic. The study will describe the relationship between stressors related to COVID-19 and self-rated measures of mental health symptoms and distress among a range of participants including various patient populations and healthy volunteers. The utilization of a study website to consent and survey participants online is an efficient and timely way to collect research data during this unique public health crisis.
Objectives:	The primary objective is to describe the relationship between stressors related to COVID-19 and self-rated measures of mental health symptoms and distress among a range of participants including various patient populations and healthy volunteers. The secondary objectives are to determine whether existing mental health concerns moderates this relationship and to identify risk and resilience factors among study participants regarding the mental health impact of the COVID-19 pandemic.

Endpoints:	The primary endpoints are descriptive data on stressors experienced as a result of the COVID-19 pandemic, and emotional, behavioral, and clinical symptoms. These endpoints will be measured repeatedly using an online platform for up to 6 months. These repeated measures will be combined with previously collected phenotype data on NIMH participants as allowed.
Study Population:	The sample size will be up to 10,000 and will include participants 18 years and older of both sexes, any gender, and health status. They must be English-speaking. The study population will include patient and volunteer participants who have consented for a NIMH study in the past as well as new participants from the general population who respond to advertisements for the NIMH COVID study but who have not previously been a NIMH study participant. The NIMH COVID study participants may or may not be local to the Metropolitan Washington DC area but since the study will be conducted entirely online, this is not relevant.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	The study will be situated at the NIH Clinical Center in the NIMH Office of the Clinical Director as a trans-NIMH Intramural Research Program protocol; adjunct NIMH researchers and protocols are included. The study itself will be conducted entirely online through a secure study website where consent and study measures will be completed and repeated as specified.
Description of Study Intervention:	There are no study interventions as this is a descriptive behavioral health survey study.
Study Duration:	The estimated time from study initiation to study completion is one to two years as this is a time-sensitive study whose results should be analyzed and disseminated rapidly.
Participant Duration:	It is expected that participants will participate in the study for up to 6 months with an option for recontact in the future.

1.2 SCHEMA


Registration
Request username and be directed to login to study site and begin process.
Baseline (Week 0)
Sign e-consent online and then complete baseline measures including NIMH COVID-19 Adult, K5, DSM XC.
Week 2 and every other week up to 6 months
NIMH COVID-19 Adult, K5, DSM XC
End survey participation
NIMH COVID-19 Adult, K5, DSM XC and End of Study Assessments (EOS)
Data Analysis
Address primary and secondary objectives.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Consent signed –	Baseline surveys -	Repeated surveys – Week 2	Repeated surveys – Week 4	Repeated surveys – Week 6	Repeated surveys – Week 8	Repeated surveys – Week 10	Repeated surveys – Week 12	Repeated surveys – Week 14	Repeated surveys – up to Week 24	End of study surveys
Informed consent	X										
Demographics		X									
Clinical history form		X									
WHODAS 2.0		X									X
FIGS		X									
AUDIT		X									X
Level 2 Substance Abuse		X									X
NIMH COVID-19 Adult survey		X	X	X	X	X	X	X	X	X	X
DSM XC		X	X	X	X	X	X	X	X	X	X
Kessler 5 (K5)		X	X	X	X	X	X	X	X	X	X
End of Study satisfaction survey											X
Possible future follow -up											

2 INTRODUCTION

2.1 STUDY RATIONALE

This protocol leverages existing NIMH studies and participants to accomplish time-sensitive research on the mental health impact of environmental stressors imposed by the COVID-19 pandemic. The study will describe the relationship between stressors related to COVID-19 and self-rated measures of mental health symptoms and distress among a range of participants, including various patient populations and healthy volunteers. The utilization of a study website to consent and survey participants is an efficient and timely way to collect research data during this unique public health crisis.

There have been widespread changes to normal social patterns of behavior and expectations in response to the public health crisis posed by the novel coronavirus (SARS-CoV-2) that can lead to the human illness, COVID-19. While the respiratory illness syndrome directly caused by this coronavirus has been a major focus of public health efforts, most experts also agree that there is a significant mental health toll as a result of government and public health mandates to slow the progression and flatten the

curve of infection, e.g. "social distancing". The environmental stressors such as constraints on activities, social contact, and access to resources are significant and are experienced by most Americans.

2.2 BACKGROUND

The importance of the NIMH COVID study is supported by a wide-ranging literature demonstrating the downstream effects of stressful life events, including affective responses and alterations in neuroendocrine systems. However, despite the clear relationship between stress and disease, there is less agreement about what kinds of stressors lead to specific physiologic, emotional or behavioural responses, and how those responses are affected by sociodemographic variables and an individual's illness history and biological and genetic vulnerabilities (Cohen et al, 2016; McLeod et al 2016). With regard to mental illness specifically, Kendler and colleagues studied the effect of life events such as loss, humiliation, entrapment, and danger in predicting the onset of major depression and generalized anxiety (Kendler et al, Arch Gen Psych 2003). The current situation of the COVID-19 pandemic presents a natural experiment in how human beings experience and are affected by a pandemic that is rapidly evolving and disrupting normal life (Wise et al, 2020; Brooks et al, 2020).

The NIMH Intramural Research Program (IRP) has a long history of studying major mental illnesses, both through deep phenotyping studies and treatment development projects. There is also a large body of research conducted on healthy volunteers who contribute to methods development and serve as an important comparison population. There are both NIMH principal investigators (PIs) and adjunct investigators at NIMH. By adjunct investigator, we are specifically referring to NIH Intramural Research Program Principal Investigators who have a formal affiliation with NIMH. One of the AIs for this study, Lauren Atlas, Ph.D, is a PI at the National Center for Complementary and Integrative Health IRP but is also an adjunct investigator at NIMH IRP (https://www.nimh.nih.gov/research/research-conducted-at-nimh/principal-investigators/adjunct-investigators.shtml). These investigators enroll patients with treatment resistant depression, schizophrenia and psychosis spectrum disorders, anxiety disorders and other clinical conditions. These clinical populations, who are well characterized and studied, have yielded a rich and large clinical dataset from which the proposed COVID study can benefit. For example, combining COVID-19 study data with existing data on participants could identify risk and resilience factors that might otherwise not be apparent from the online surveys alone but are more meaningful when paired with already gathered clinical data.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To describe the relationship between stressors related to COVID-19 and self-rated measures of mental health symptoms and distress among a range of participants including various	Online self-report questionnaires gathered at 2-week intervals: NIMH COVID-19 Adult survey: assesses the stressors experienced as a result of the COVID-19 pandemic.	The availability of repeated measurement will allow us to establish whether changes in

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
patient populations and healthy volunteers.	DSM XC: assesses symptoms of mental illness, including substance use. Kessler 5: assesses psychological distress.	stressors related to COVID-19 are associated with changes in mental health symptoms and distress within subject.
Secondary		
The secondary objectives are to: 1) Determine whether existing mental health concerns moderates the relationship between stressors related to COVID-19 and self-rated measures of mental health symptoms and distress. 2) To identify risk and resilience factors among study participants regarding the mental health and behavioral impacts of the COVID-19 pandemic.	In addition to the outcomes described for the primary aim, online self-report questionnaires gathered at baseline: Demographic form: assesses basic sociodemographic factors such as age, sex, gender. Clinical history form: assesses history of psychiatric and medical illness. WHODAS: assesses functioning across six domains, including cognition, mobility, self-care, getting along, life activities, and participation. FIGS: Family history of mental illness AUDIT: assesses behaviors related to alcohol use disorder. Level 2 Substance use form: assesses behaviors related to substance use disorder. Other participant-level information gathered as a result of their previous participation in NIMH associated protocols, such as clinical phenotype data as allowed by previous protocols.	In order to determine whether the participant has existing mental health concerns, we must collect information a variety of symptoms related to mental health. We hypothesize that certain participant-level characteristics may be related to the mental health and behavioral impacts of the COVID-19 pandemic. For this exploratory aim, we will evaluate a variety of sociodemographic, clinical, and behavioral variables.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Tertiary/Exploratory		
N/A	N/A	N/A

4 STUDY DESIGN

4.1 OVERALL DESIGN

This proposal will leverage the depth and breadth of NIMH clinical studies to rapidly respond to a time-sensitive and unique opportunity to study the mental health impact of the COVID-19 epidemic on patients and volunteers who are current or past participants in NIMH research studies, many of whom are drawn from specific clinical populations, e.g. anxiety or mood disorders. The intent of this proposal is to create a mechanism to facilitate the recruitment of NIMH research participants to join an online trans-NIMH initiative to track emotional and behavioral responses to the COVID-19 pandemic over time. The study would involve a request that NIMH investigators and adjunct investigators be allowed to recontact previous research participants, who signed consents that allow data sharing, to offer enrollment in the COVID study. Participation would be completely voluntary with the option to withdraw at any time. These repeated measures will be combined with previously collected phenotype data on NIMH participants to better characterize risk and resilience factors regarding emotional and behavioral health in response to stressful environmental factors. We may discover not only predictors of significant negative responses, but also which clinical populations may be more vulnerable and what type of interventions might be tested in future pandemics. In addition to existing NIMH participants, the study could also involve recruiting additional volunteers who respond to advertisements about the COVID study.

This proposal to initiate an urgent NIMH research study on COVID-19 is justified by the following reasons: 1) The PI and her study team are experienced with conducting online consent and surveys using a study website and these methods are necessary for conducting safe research during this pandemic which must be done online and remotely, 2) the PI and her team have a history of conducting trans-NIMH IRP initiatives and have collaborated with more than 10 NIMH PIs and 18 protocols that conduct research with adults, 3) the protocol is sponsored by the NIMH Office of the Clinical Director and therefore has a centralized mission to help all NIMH studies/PIs/adjunct investigators that will efficiently and equitably coordinate a time-sensitive project.

The study will use a NIH supported web-based platform, Clinical Trials Survey System (CTSS) to create a NIMH COVID-19 study website that will support electronic consent, online surveys and secure data repository. The website will be integrated with the Clinical Trials Data Base (CTDB) run by National Institute of Child Health and Human Development (NICHD), which securely stores data from the study in a HIPAA compliant manner. Using this website and data infrastructure will allow rapid deployment of the proposed COVID study.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study that is proposed is descriptive in nature and due to the current public health imperative to conduct work remotely and safely, will be conducted fully online. The rapid pace of change in the government's response at local, state and national levels means that a repeated measure design is best suited for this situation. Participants will provide baseline demographic information to allow for stratified analyses at a later point. Because this study is new, it is difficult to predict the accrual rate and number or the type of participants it will attract.

5 STUDY POPULATION

The sample size will be up to 10,000 and will include participants 18 years and older of both sexes, any gender, and health status. This sample size is an estimate of the number of individuals who have been in NIMH studies in the past and might respond if recontacted. The number of enrolled participants per year in NIMH IRP studies is close to 1,400. In addition, there are others who might join the study from the general public. They must be English-speaking. The study population will include patient and volunteer participants who have consented for a NIMH or NIMH affiliated study, e.g. NCCIH, study in the past as well as new participants from the general population who respond to advertisements for the NIMH COVID study but who have not previously been a NIMH study participant. The NIMH COVID study participants may or may not be local to the Metropolitan Washington DC area but since the study will be conducted entirely online, this is not relevant.

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. 18 years of age and older.
2. Able to read and write English.
3. Able to provide informed consent online using study website.

5.2 EXCLUSION CRITERIA

1. There are no exclusion criteria for this study.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants will be recruited under this protocol using IRB-approved materials utilizing different methods. The primary group that will be recruited are participants in NIMH studies who will be contacted by the staff who work with a specific NIMH investigator or adjunct investigator and has access to contact information for these participants. Potential participants for the NIMH COVID study who have previously been in a different NIMH protocol will be contacted by someone who is listed on that protocol as a PI or AI. Flyers about the study could be sent to these individuals that direct them to the study website. Phone calls can also be made to inform past NIMH study participants about the COVID study. The table below lists the protocol numbers and titles from which we plan to recruit participants for the NIMH COVID study, the Principal Investigators and relevant Associate Investigators (on these protocols who are also an AI on the NIMH COVIS study), and whether the study consent is explicit or silent about data sharing.

Protocol number	*Title*	*PI*	*AI on protocol*	*Consent data sharing status*
17-M-0181	Recruitment and Characterization of Healthy Research Volunteers for NIMH studies	Joyce Chung	Maryland Pao Jeanne Radcliffe Shruti Japee	explicit
01-M-0254	The Evaluation of Patients with Mood and Anxiety Disorders and Healthy Volunteers	Carlos Zarate	Elizabeth Ballard Lawrence Park Monique Ernst	explicit
14-M-0114	Cognitive vs. Emotional Psychopharmacological Manipulations of Fear vs. Anxiety	Monique Ernst		explicit
01-M-0185	Arousal and stress on classical conditioning	Christian Grillon	Monique Ernst	explicit
02-M-0321	fMRI investigation of explicit cue and contextual fear	Christian Grillon	Monique Ernst	explicit
03-M-0093	Predictability and aversive expectancies in anxiety and depressive disorders	Christian Grillon	Monique Ernst	explicit
93-M-0170	Regional Cerebral Blood Flow studies of object perception, identification, localization, and memory.	Leslie Ungerleider	Shruti Japee	explicit
10-M-0047	Top-Down Attentional Control of Visual Processing	Leslie Ungerleider	Shruti Japee	explicit
15-AT-0132	Neural and psychological mechanisms of pain perception	Lauren Atlas	n/a	explicit
17-AT-0155	Sociocultural and biobehavioral influences on pain expression and assessment	Lauren Atlas	n/a	explicit

80-M-0083	Bipolar Disorder Genetics: A Collaborative Study	Francis McMahon, M.D.	n/a	explicit

Adult individuals who respond to study advertisements or contact NIMH study staff and are interested in participating the NIMH COVID study will be referred to the online study website to initiate consideration for enrollment. The website will be hosted on the Clinical Trials Survey System (CTSS) platform of the Clinical Trials Database (CTDB) run by NICHD.

Study flyers may be used and may be distributed electronically on websites. Flyers will link back to the study website. The study information will be included on the NIMH Join A Study website or other landing page with IRB-approved content. Listserv announcements may be used and distributed to sites such as NIH Parenting listserv or NIMH Outreach Partners. Listserv Text will be sent electronically to listserv administrators. An email with text ad will be sent to the administrator of the listserv to post. All text ads will include the required disclaimer language. The administrator will choose whether to share the ad with their list. We will retain copies of all correspondence with the administrator of each listserv and submit as requested to the IRB.

Social media and other websites may be used: short text announcements may be used on NIMH, NIH, CC, or other social media accounts using IRB-approved language, directing users to the website. Keyword or contextual keyword searching on the internet may be used with IRB-approved keywords and language. Participants may also find the study website by using Google or other online search engines.

All advertisements and flyers will be used as submitted. Color and size of the ads may change but will be changed proportionally throughout the ad and will not be used to change the emphasis of the material.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 SCREENING PROCEDURES

While not technically a screening procedure, individuals who are interested in participating in this study must provide identifiers to be given a username and password. These identifiers are collected prior to study consent and include first and last name and email address. The participant name and email address are needed to confirm if the respondent has previously been a NIMH research participant and for the study staff to remind participants to complete repeated surveys every two weeks. The code that links identifiers to the study ID number will be kept in secure password protected files and will only be accessible to study staff.

Potential participants follow the following procedures that are on the study website:

- Visit the study website (nimhcovidstudy.ctss.nih.gov) to receive instructions on getting a username.
- Email their name to the study team and indicate if they have previously been in a NIH research study.
- Once logged in, they will be directed to review the consent form and indicate agreement by clicking on a box on the online electronic consent.

- After consent, they will be able to complete and submit the online study questionnaires.
- Every two weeks, they will be notified by the study team by email when it is time to repeat some study questionnaires.
- When the study ends, they will be asked to complete a set of end-of-study questionnaires.

STUDY MEASURES

Baseline Assessments:

- NIMH COVID Study Demographic Questionnaire: Collects sociodemographic factors such as: age, sex, gender, race, ethnicity, first 3 digits of zip code, local setting, transportation, education, marital status, household income, employment, languages spoken, how learned about study and motivation to join.

- NIMH COVID Study Clinical History Checklist: collects history of mental and medical illness and treatment, medications, and family medical history.

- Family Interview for Genetic Studies (FIGS): Records family history of mental illness among first degree relatives. (NIMH Repository and Genomics Resource, 2005)

- WHODAS 2.0: assesses functioning across six domains, including cognition, mobility, self-care, getting along, life activities, and participation. (Gold, 2014)

- Alcohol Use Disorders Identification Test (AUDIT): assesses behaviors related to alcohol use disorder. (WHO, 2001)

- DSM-5 Level 2 Cross Cutting Symptom Measure Substance Use Adult (DSM Substance Use): assesses behaviors related to substance use disorder. (American Psychiatric Association, 2013)

- DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure – Adult (DSM XC) – 23 item survey of mental health symptoms with item #11 removed which asks about thoughts of hurting yourself (Suicidal ideation) (Narrow, 2013; Mahoney et al, 2020; American Psychiatric Association, 2013)

- Kessler 5 (K5): modified 5 item version of a survey that asks about psychological distress and has been used to screen for the risk of mental disorders in large population studies. (Kessler, 2002, 2003; Australian Government, 2018)

- NIMH COVID-19 Adult Survey: modified survey developed specifically by NIMH and other researchers who want to assess the mental health impact of the COVID-19 pandemic. This version was modified for adults based on a version for adolescents spearheaded by Argyris Stringaris in the NIMH IRP.

Repeated Biweekly Questionnaires:

- DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure – Adult (DSM XC)
- Kessler 5 (K5)
- NIMH COVID-19 Adult Survey

End of Study Assessments:

- WHODAS 2.0
- Alcohol Use Disorders Identification Test (AUDIT)
- DSM-5 Level 2 Cross Cutting Symptom Measure Substance Use Adult (DSM Substance Use)
- DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure – Adult (DSM XC)
- Kessler 5 (K5)
- NIMH COVID-19 Adult Survey
- NIMH COVID Study Satisfaction Survey

The study measures will ask about mental health symptoms and distress but will not ask about suicide because the online and remote nature of the study means that it is not feasible to contact participants in real time and intervene. However, because the study will involve collecting repeated measures on sensitive topics, such as distress and mood, it is possible a participant may report high levels of mental health symptoms or show trends in worsening of symptoms that could indicate a need to seek care. At a minimum, we will provide links to national and local mental health resources, such as hotlines, and guidance on steps to take to seek care or support. We state at the bottom of the NIMH COVID-19 Study Adult Survey: "We appreciate your responses. Please know that because the study is being done online and your responses will not be monitored in real time, we will not be making contact with you. If you have any emergent issues or are feeling unsafe, please use the crisis text line, text "home" to 741741 or the National Suicide Lifeline 1-800-273-TALK (8255) which is operated 24 hrs. a day, 7 days a week." Also, if appropriate, study staff will provide information about mental and medical health resources for the Metropolitan Washington, DC area and/or direct participants to appropriate federal government online resources or information.

While not collected as part of this study, the type of existing data that would be used for secondary analyses are clinical phenotype data, e.g. diagnostic assessments, behavioral and neuroimaging data, physiologic/biologic data, medical conditions, cognitive and clinical assessments. The data that will be used for these analyses are those that are permitted to be shared by the previous protocols and consents.

7 STATISTICAL CONSIDERATIONS

7.1 STATISTICAL HYPOTHESIS

- Primary Endpoint: We hypothesize that the degree of stressors related to COVID-19 will be positively related to contemporaneously measured severity of mental health symptoms

and distress. *Null hypothesis: There is no relationship between degree of stressors related to COVID-19 and the severity of mental health symptoms and distress.*

- Secondary Endpoint(s):
    - We hypothesize that the relationship between degree of stressors related to COVID-19 and contemporaneously measured severity of mental health symptoms and distress will be stronger (i.e., more positive) among participants with existing mental health concerns compared to those without existing mental health concerns. *Null hypothesis: The relationship between degree of stressors related to COVID-19 and mental health symptoms and distress does not differ between participants with and without existing mental health concerns.*
    - We hypothesize that certain participant-level characteristics such as clinical phenotype characteristics may be related to risk and resilience factors regarding the mental health and behavioral impacts of the COVID-19 pandemic. For this exploratory aim, we will evaluate a variety of sociodemographic, clinical, and behavioral variables. *Null hypothesis: The relationship between degree of stressors related to COVID-19 and mental health symptoms and distress does not differ between participants by sociodemographic factors such as age, sex, health status and income level.*

7.2 SAMPLE SIZE DETERMINATION

A formal sample size calculation is not feasible for several reasons. We do not have information about the distributions of the outcome and predictor in this sample, i.e. COVID-19 stressor survey as it is a newly developed measure. We also do not know about within-subject correlations (since we have repeated measures). Therefore, we propose to use a sample of convenience which is open to past NIMH research study participants, and those who respond to advertisements for the COVID-19 study.

7.3 STATISTICAL ANALYSES

7.3.1 General Approach

The analytic model will be a generalized linear mixed model; parameter estimates from these models will be presented alongside 95% confidence intervals and two-tailed t-tests of their difference from zero. However, following current American Statistical Association guidelines (Wasserstein et al, 2019), we will not set a threshold for statistical significance and instead will interpret the parameter given its magnitude and precision. For this same reason, we will make no corrections to p-values for multiplicity.

We make no a priori hypotheses about potential covariates, and plan to include none in the primary or secondary analyses. However, based on the results of exploratory data analyses, variables which are observed to be related to both predictor and outcome variables will be included in post-hoc sensitivity analyses.

Details about the models used to evaluate the primary and secondary endpoints follow.

7.3.2 Analysis of the Primary Endpoints

The analytic model will be a generalized linear mixed model which predicts the outcome (mental health symptoms or psychological distress) from fixed effects of the COVID-19 stressor score and group membership (current or history of psychiatric diagnosis versus no current or history of psychiatric diagnosis). To account for repeated measurement within participant, and to ensure that the interpretation of the slope of COVID-19 stressor score is a within-subject effect, we will specify both a random intercept and random slope of COVID-19 stressor score. We will determine the appropriate covariance structure for these random effects (e.g., variance components, unstructured) via model fit indices. The type of the outcome variable will dictate the distribution specified for the relationship between predictor and outcome; for continuous outcomes (e.g., Kessler 5 score) we will assume a normal distribution and for categorical outcomes (e.g., presence of particular symptoms on the DSM XC) we will assume a binary logistic distribution. We will evaluate the remaining assumptions about the residuals (e.g., homoscedasticity) via visual inspection of plots, and will adjust the model as necessary to accommodate those assumptions. Missing outcome data will not be imputed.

The parameter associated with our hypotheses is the fixed slope of the COVID-19 stressor score in predicting mental health symptoms or psychological distress. Although our primary objective is to evaluate the main effect of COVID-19 stressor on the outcome, because we also hypothesize a specific moderating effect of participant group (history of/existing mental health condition versus healthy volunteer), we must first quantify this interaction. If there is a meaningful interaction, the main effect cannot be interpreted independently and will instead be interpreted for each group. The slope (or slopes, in case of an interaction) along with its 95% confidence interval, will be presented alongside a two-tailed t-test of its difference from zero. However, following current American Statistical Association guidelines (Wasserstein et al, 2019), we will not set a threshold for statistical significance and instead will interpret the parameter given its magnitude and precision.

7.3.3 Analysis of the Secondary Endpoint(s)

To address our secondary objectives, we will evaluate a variety of participant-level variables from existing data that relate to clinical phenotype, e.g. diagnostic assessments, behavioral and neuroimaging data, physiologic/biologic data, medical conditions, cognitive and clinical assessments as moderators of the relationship between stressors and outcome (i.e., risk and resilience factors). As described in the primary endpoint section, the putative risk/resilience factor will be entered into the primary model and the interaction between the putative risk/resilience factor and COVID stressor score will be the parameter of interest.

7.3.4 Baseline Descriptive Statistics

The secondary objective of this study evaluates the presence of current or history of psychiatric illness as a moderator of the relationship between COVID stressor and mental health response. Because participants are not randomly assigned into these groups, these groups are likely to differ on other sociodemographic factors. During the exploratory data analysis phase, we will evaluate baseline characteristics to determine whether any are related to group membership and outcome and would therefore potentially confound results. In sensitivity analyses, any variables identified in this way will be entered as covariates into the primary and secondary analysis models.

7.3.5 Sub-Group Analyses

This is not an intervention study and therefore no subgroup analyses are required. As described above, demographic variables will be explored as putative covariates.

7.3.6 Tabulation of individual Participant Data

Data will be analyzed in aggregate and individual participant data will not be listed.

7.3.7 Exploratory Analyses

There may be future amendments related to this protocol regarding new exploratory analyses including machine learning approaches and combined analyses with previously collected NIMH participant data.