Impact of COVID-19 on People Living with Rare Disease and their Families

Protocol Number: 2020-0299

Investigator/Consortium: Dr. Maurizio Macaluso

Version Information: 01_08Apr2020

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Protocol Synopsis

Protocol Number	2020-0299
Title of Study	Impact of COVID-19 on People Living with Rare Disease and their Families
Indication	Individuals with Rare Diseases and COVID-19
Study Objectives	Primary: 1. To estimate the proportion of patients who live with RD who have been diagnosed with COVID 19 infection; 2. To describe the characteristics of the COVID-19 presentation and the course of the infection (including treatment) among patients with RD; 3. To determine whether subgroups of patients defined by sociodemographic variables and geographic location, with particular rare conditions or comorbidities have been affected more frequently or have experienced increased severity of the infection; 4. To learn about the potential interaction between specific treatment regimens for rare diseases and COVID-19 infection, and specifically whether certain antibiotic, immunosuppressive, or anti-inflammatory drugs are associated with the frequency of COVID-19 infection and its severity; 5. To learn about the main concerns that individuals who live with RD and their families have with respect to COVID-19, and determine how the RDCRN can respond by providing information and advice through its network of experts, its consortia, and in collaboration with patient advocacy groups. Secondary: 1. To allow follow-up for patients and families who agree to provide contact information, and linkage of information collected in the survey with data maintained by the RDCRN for patients enrolled in RDCRN research studies.
Study Design	Online Survey
Study Center(s)	Cincinnati Children's Hospital Medical Center
Study Endpoint(s)	Primary: 1. Self-reported laboratory or clinical diagnosis of COVID-19 2. Self-reported symptoms, duration of the infection, hospital admission, and complications of the infection 3. Association between background variables (sociodemographic variables, geographic location, rare disease diagnosis and comorbidities) and endpoints for Aim 2 4. Association between self-reported ongoing treatment for rare diseases and self-reported COVID-19 infection (aim 1) and its severity as indicated by duration of the infection, hospitalization, need for assisted ventilation (aim 2); 5. Self-reported impact of the COVID-19 epidemic on access to care, access to special food/nutrition, demand for professional assistance to address stress, and coping. Secondary:

	1. Feasibility of linking information about the respondent with her/his records of previous or ongoing studies conducted by the RDCRN, willingness to participate in a follow-up survey whether or not the respondent has participated in RDCRN studies.
Study Treatment	None

Inclusion/Exclusion Criteria	Inclusion:
	  1. Individuals with a previous clinical diagnosis of a RD in the United States.
	  2. Individuals who currently are willing to provide information to the RDCRN.
	  3. Individuals who are 0 to 89 years old.
	      Or
	  4. Caregivers or parents of individuals who meet Inclusion Criteria 1 through 3 and are willing to respond on behalf of the patient.
	
	Exclusion:
	  1. Individuals reporting a disease diagnosis not meeting the definition of a RD in the United States or who currently lives outside the United States.

Sample Size	Approximately 5000 Respondents, but no maximum population
Statistical Analysis	We will employ descriptive statistics in initial analyses, which will guide more in-depth assessments of the associations of interest: key measures will be the prevalence rate of COVID-19 diagnosis, as a measure of the cumulative risk of infection through the time of the survey, and any changes in treatment regimen, symptoms. We will use common epidemiologic measures of occurrence (prevalence rates) and association (risk difference measures or ratio measures like the odds ratio) to assess COVID-19 prevalence across strata defined by sociodemographic variables, geographic location, groups of rare conditions. Stratified analyses or regression modeling will assess more complex questions such as whether the frequency or severity of COVID-19 infection vary within a category of rare diseases as a function of comorbidities or treatment of the underlying conditions. Whereas hypothesis testing procedures may be used in data analysis, we regard this survey as a measurement exercise and precision of the estimates Is the driving consideration. To provide a measure of the precision of the survey results, we will compute 95% confidence intervals of the key measures of occurrence and association.
Protocol Version	V01_04/08/2020

Investigator Agreement and Signature Page

Protocol Title: Impact of COVID-19 on People Living with Rare Disease and their Families

Protocol Number: 2020-0299

Amendment Number: N/A

Investigator Agreement:

I have read the protocol, appendices and procedure manual of the study indicated above. I agree that these documents contain all of the details necessary for me and my staff to conduct this study as described. I agree to conduct the study as described in this protocol and comply with all principles of Good Clinical Practice (GCP), as described in the United States Code of Federal Regulation (CFR) 21 Parts 11, 50, 54, 56, and 312 and the appropriate International Conference on Harmonisation guidance documents.

I will provide to all study personnel under my supervision copies of the study protocol, appendices and all other relevant information regarding the study provided to me by the Principal Investigator. I will discuss this material with them to ensure they are fully informed about the study.

_____   _____

Investigator (Printed)   Date

_____

Investigator Name (Signature)

_____

Institution (Clinical Site)

_____   _____

Sponsor Representative (Printed)   Date

_____

Sponsor Representative Name (Signature)

Abbreviation List

Abbreviation	Definition
CCHMC	Cincinnati Children's Hospital Medical Center
CFR	Code of Federal Regulation
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
DMCC	Data Management and Coordinating Center
GARD	Genetic and Rare Disease
MERS	Middle East Respiratory Syndrome
NCATS	National Center for Advancing Translational Sciences
ORDR	Office of Rare Diseases Research
PAG	Patient Advocacy Groups
RD	Rare Disease
RDCRN	Rare Disease Clinical Research Network
SARS	Severe Acute Respiratory Syndrome

Section 1: Key Roles

Primary Investigator:

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Section 2: Background
Section 2.1: Summary of COVID-19

The rapid, global spread of Coronavirus Disease 19 (COVID-19) has had pronounced implications on all aspects of life. The virus, which was first encountered in early December 2019 in Wuhan, China, has now spread to most of the globe.[1] Coronaviruses are single-stranded RNA viruses, which have a crown-like shape (giving rise to their name which comes from the Latin word *coronam*). This crown-like appearance is due to the presence of spike-like glycoproteins on the viral envelope.[2] There are seven subtypes of coronaviruses that can infect humans. The beta-coronaviruses, which include COVID-19, are capable of causing severe disease and death.[3]

The COVID-19 outbreak has shown similarity, in some regards, to the outbreaks caused by previous coronaviruses (Severe Acute Respiratory Syndrome [SARS] and Middle East Respiratory Syndrome [MERS]).[4] All three viral infections have been traced to zoonotic transmission, likely via bats and an additional animal source. All three infections are diagnosed based on symptoms, exposures, and imaging of the chest, with confirmation requiring nucleic acid testing. Symptoms include fever and cough, which can progress to lower respiratory tract disease.[2,4] The COVID-19 outbreak has noted cases including gastrointestinal symptoms and asymptomatic infections. In patients with symptomatic COVID-19 infection, disease progression begins after approximately a week, with symptoms including cough, fever, nasal congestion, and fatigue.[3] Infection can advance to dyspnea and pneumonia, with pneumonia generally occurring within the 2nd or 3rd week.

Examining the initial data from China (through January 29, 2020) regarding laboratory-confirmed cases (1099 cases), produced initial data about the clinical characteristics of the affected patients.[2] The median age of these cases was 47. Of the 1096 cases where gender was recorded, 637 patients were male (58.1%). Computed tomography (CT) scans performed on 975 patients with confirmed cases, showed ground-glass opacity (56.4%) and bilateral patchy shadowing (51.8%).[2]

In this initial study of the laboratory-confirmed cases, 9 cases were children age 0 to 14 years old. A separate study looking at 366 hospitalized children in China from January 7 to January 15, 2020, resulted in 6 cases of COVID-19 confirmed infection.[5] All six of the children were previously healthy as reported by family members. All six children had a high fever, cough, and four of the six had vomiting. Radiographic evaluation demonstrated pneumonia in four of the six children. All six children recovered after hospitalization, with hospitalization time ranging from 5 to 13 days.[5]

Section 2.2: Summary of the RDCRN

The United States defines a rare disease (RD) as one that affects fewer than 200,000 Americans. The European Union has slightly stricter criteria requiring a life-threatening or chronically debilitating condition that affects no more than five people per ten thousand. The Genetic and Rare Disease (GARD) information system run by the Office of Rare Disease Research (ORDR) at the National Center for Advancing Translational Sciences (NCATS) lists over 7000 disorders meeting the aforementioned criteria. While each of the 7000 disorders may affect a smaller number of individuals, cumulatively the burden is great. These RDs are often detected during infancy due to genetic errors and often have no treatment placing a significant burden on the patient's family, which can be especially difficult in resource-poor areas of the world.

To aid in progressing the diagnosis, management, and eventual treatment of RD the Rare Diseases Clinical Research Consortia (RDCRC) that comprise the Rare Disease Clinical Research Network (RDCRN) work together to enhance clinical trial readiness and establish best practices for the entire RD community. The RDCRN is funded by nine institutes of the National Institutes of Health, with additional assistance from institutes funding the individual RDCRCs that fall under their purview. The RDCRN Data Management and Coordinating Center (DMCC) provide infrastructure to facilitate coordinated efforts to enhance clinical trial readiness and establishing best practices.

The RDCRN consists of 20 to 25 RDCRC providing a wide range of patient demographics across the United States and the rest of the globe. Allocating this data source to the current COVID-19 pandemic will allow the collection of vital data on the impact of COVID-19 on individuals with RD.

Section 2.3: Clinical Trial Readiness

The COVID-19 outbreak is a rapidly developing global situation and continuing to collect data will be crucial for providing members of the RD community current and future care. Patients with RD have a unique challenge as they are often overlooked for large-scale clinical trials raising the risk that information regarding COVID-19 will be missed. This data will become increasingly important if COVID-19 becomes established as an annual pathogen, as most other respiratory pathogens are seasonal. These pathogens show an annual increase in incidence each winter, though timing can vary.[6] The data collected from this survey will aid in preparation for future studies and standard of care for the RD community against the potential re-emergence of COVID-19.

Section 3: Study Objectives

Section 3.1: Primary Objectives

1. To estimate the proportion of patients who live with RD who have been diagnosed with COVID-19 infection;
2. To describe the characteristics of the COVID-19 presentation and the course of the infection (including treatment) among patients with RD;
3. To determine whether subgroups of patients defined by sociodemographic variables and geographic location, with particular rare conditions or comorbidities have been affected more frequently or have experienced increased severity of the infection;
4. To learn about the potential interaction between specific treatment regimens for rare diseases and COVID-19 infection, and specifically whether certain antibiotic, immunosuppressive, or anti-inflammatory drugs are associated with the frequency of COVID-19 infection and its severity;
5. To learn about the main concerns that individuals who live with RD and their families have with respect to COVID-19, and determine how the RDCRN can respond by providing information and advice through its network of experts, its consortia, and in collaboration with patient advocacy groups.

Section 3.2: Secondary Objectives

1. To allow follow-up for patients and families who agree to provide contact information, and linkage of information collected in the survey with data maintained by the RDCRN for patients enrolled in RDCRN research studies.

Section 4: Study Design
Section 4.1: Description of Study Design

RDCRN will establish a registry with data elements from or about individuals with RD that will capture how they and their families are reacting to the COVID-19 outbreak. This registry will include subjects in the United States who are and are not currently enrolled in an RDCRN human subject research study. Individuals with RD will be recruited through advertisements posted to the websites of RDCRN consortia and organizations of patients and families (Patient Advocacy Groups [PAGs]), and through direct email campaigns conducted by the same organizations. Individuals interested in participating will be routed to a web portal that will gather eligibility information. Eligible individuals will be asked to agree to provide direct identifiers and contact information that will allow for follow-up interviews and future contacts to facilitate participation in RDCRN research. Individuals who are not comfortable sharing direct identifiers will be allowed to respond anonymously. Individuals who do not consent will be thanked for their interest and disconnected.

Once an eligible individual agrees to participate, direct identifiers, contact information, and consent details will be kept in a separate physical file, while the data entry system will generate an ID number that will serve as a link between the identifier file and the survey response file.

Individuals who agree to participate will have access to a REDCap data capture module that will allow them to respond to the survey questions (see below, Section 6).

Section 4.2: Study Endpoints
Section 4.2.1: Primary Endpoint

Primary Aim 1: self-reported laboratory or clinical diagnosis of COVID-19.

Primary Aim 2: self-reported symptoms, duration of the infection, hospital admission, and complications of the infection.

Primary Aim 3: association between background variables (sociodemographic variables, geographic location, rare disease diagnosis and comorbidities) and endpoints for Aim 2.

Primary Aim 4: association between self-reported ongoing treatment for rare diseases and self-reported COVID-19 infection (aim 1) and its severity as indicated by duration of the infection, hospitalization, need for assisted ventilation (aim 2).

Primary Aim 5: self-reported impact of the COVID-19 epidemic on access to care, access to special food/nutrition, demand for professional assistance to address stress, and coping.

Section 4.2.2: Secondary Endpoints

Secondary Aim 1: feasibility of linking information about the respondent with her/his records of previous or ongoing studies conducted by the RDCRN, willingness to participate in a follow-up survey whether or not the respondent has participated in RDCRN studies.

Section 5: Study Enrollment
Section 5.1: Inclusion Criteria

Individuals must meet the following criteria:

5.   Individuals with a previous clinical diagnosis of a RD in the United States.
6.   Individuals who currently are willing to provide information to the RDCRN.
7.   Individuals who are 0 to 89 years old.

Or

8.   Caregivers or parents of individuals who meet Inclusion Criteria 1 through 3 and are willing to respond on behalf of the patient.

Section 5.2: Exclusion Criteria

1.   Individuals reporting a disease diagnosis not meeting the definition of a RD in the United States or who currently lives outside the United States.

Section 5.3: Study Recruitment

Individuals will be contacted through electronic mail through addresses already provided to the RDCRN and through advertising on websites maintained by the RDCRN consortia and PAGs. The goal is to recruit 5000 participants but there is not a maximum population as this is intended as a registry.

Section 5.4: Screen Failures

Individuals who do meet the eligibility criteria will be thanked for their interest in the study but will not be allowed to access the data entry module. While we can verify whether the participant has one of the 200 rare diseases studied by the RDCRN, we cannot systematically test whether a disease reported as rare that is not in the RDCRN list meets the US definition of a rare disease. Thus, we will accept any self-reported rare disease. We plan to compare all diagnoses reported with the list of over 7,000 disease entities maintained by the National Institutes of Health, but only at the analysis stage.

Section 5.5: Subject Withdrawal

Subjects will be free to withdraw from the study at any point. A survey that is not submitted will be considered a subject withdrawal under this protocol.

Section 6: Study Procedures

Section 6.1: Registry Data Collection

RDCRN DMCC will establish a registry that will capture the data elements requested in the data collection instrument (Appendix). This initial registry will be populated via a Web Portal by the RD patient, parent or provider as appropriate. Collected variables will include patient demographics (race, ethnicity, date of birth, gender), details about their COVID-19 infection, and the impact of the COVID-19 epidemic in the USA on access to routine care, special food items, and family life, including the impact of stay-at-home orders on mood and behavior, with associated demand for professional support to cope with stress and anxiety. The data collection tool will also be used to identify deaths among the respondents. A more detailed description, of the data elements, are in section 6.2 below.

We will use patient identifiers and contact information, as well as self-reported participation in RDCRN studies, to link survey results with more detailed data collected in the clinical research setting. Contact information will be shared with the RDCRN consortia the respondent is linked with to allow additional consortium-specific data collection.

Participants will be contacted via email or through information posted to the individual PAG websites.

Section 6.2: Surveys

The data collection instrument comprises seven sections:

Section 1 includes eligibility and preliminary information criteria on whether the patient or a surrogate is interested in participating, whether the target respondent lives in the USA and has a rare disease, and whether the potential participant has participated in RDCRN research.

Section 2 includes an explanation of the study and asks three consent items: 1) agreement to respond to the survey, provide contact information and allow future contact for follow up interviews and opportunities for participating in rare disease research; 2) agreement to allow linkage of the survey results with data about the same individual provided as part of RDCRN studies; 3) agreement to respond to the survey without any identifiers (one-time, anonymous response).

Section 3 is restricted to individuals who agree to provide identifiers and includes name, date of birth, address, telephone number and email address to allow future contacts. Individuals who choose to respond anonymously will skip Section 3.

Section 4 includes sociodemographic variables (state of residence, age, gender and race/ethnicity), rare disease diagnosis including symptoms and comorbidities during the months preceding the COVID-19 epidemic in the USA, treatments received during the same period, smoking habits and use of THC-containing products and psychoactive drugs. It also includes questions about symptoms potentially overlapping with COVID-19 infection and access to COVID-19 testing.

Section 5 ascertains whether the respondent had a positive COVID-19 test or a clinical diagnosis of COVID-19 like respiratory syndrome after be beginning of the epidemic in the USA (March 2020).

Section 6 refers to the time period after the beginning of the epidemic in the USA (March 2020) and is restricted to respondents who did not have a positive COVID-19 test or a clinical diagnosis of COVID-19

like respiratory syndrome (i.e., did not respond Yes to the questions in Section 5). It includes a list of symptoms compatible with COVID-19, on disruption of treatment, access to special food related to rare disease management and access to medical care, whether stay-at-home orders affected their mood or behavior, and whether the respondent or family members had to seek professional help to cope with stress and anxiety. It asks a final question to ask if the target respondent died during the interval leading to the survey.

Section 7 refers to the time period after the beginning of the epidemic in the USA (March 2020) and is restricted to respondents who had a positive COVID-19 test or a clinical diagnosis of COVID-19 like respiratory syndrome (i.e., responded Yes to the questions in Section 5). It includes a list of symptoms compatible with COVID-19, on disruption of treatment, access to special food related to rare disease management and access to medical care, whether stay-at-home orders affected their mood or behavior, and whether the respondent or family members had to seek professional help to cope with stress and anxiety. It also asks about the course of the COVID-19 infection, the need for hospitalization and special treatment (assisted ventilation), the duration of the illness and whether the respondent received investigational drugs to treat COVID-19. It asks a final question to ask if the target respondent died during the interval leading to the survey.

Section 6.3: Biological Samples

Currently, there is no plan to collect biological samples.

Section 7: Safety

Section 7.1: Safety Parameters (AE, SAE, UE)

An adverse event is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not it was considered intervention-related (21 CFR 312.32(a)).

A serious adverse event is defined any untoward medical event that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or causes a congenital anomaly/birth defect.

An unanticipated event is an incident that meets all the following criteria:

- Unexpected in nature, severity, or frequency: Not described in the study-related documents such as the protocol, consent, or Investigator's Brochure or not expected based on the study population.

- Related to possibly related to participation in the research: Reasonably possible that the incident may have been caused by the procedures involved.

- Suggest that the research places subjects or others at greater risk of harm that alters previous risk/benefit ratio established.

Section 7.2: Adverse Event Reporting (Timeline and Procedures)

Since the study procedures are not greater than minimal risk and limited to the survey and previously collected data, SAEs are not expected. If any unanticipated events related to the research involving risk to the subjects or other happens during the course of this study these will be reported to the IRB. Unanticipated events that does not involve risks to the subjects or others will be summarized in a narrative and submitted to the IRB at the time of continuing review.

Section 7.3: Study Suspension Criteria

The study may be suspended if it is recommended by the Primary Investigator or local IRB.

Section 7.4: Study Risks and Benefits

Section 7.4.1: Study Risks

The risk to participating in this study is a loss of confidentiality. Participants will be asked to provide information that could identify them. We will minimize the risk to patient confidentiality by maintaining direct identifiers and contact information in a database physically separate from the survey responses, using a registry ID number in our survey database and analysis systems. Individuals who are not willing to share direct identifiers and contact information may participate in the survey anonymously but will not be able to participate in follow-up data collection.

There may be previously unknown risks.

Section 7.4.2: Study Benefits

Participation in this study is not anticipated to have any direct benefits to the individuals involved. However, the information collected from this study may benefit individuals in the future. Select survey results that are deemed of importance by the RDCRN consortia and by the PAGs will be returned periodically to the community through reports posted to the RDCRN web site and disseminated to through the network as appropriate. The results, in aggregate form, will not allow re-identification of survey respondents.

Section 8: Statistical Considerations

We will employ descriptive statistics in initial analyses, which will guide more in-depth assessments of the associations of interest: key measures will be the prevalence rate of COVID-19 diagnosis, as a measure of the cumulative risk of infection through the time of the survey, and any changes in treatment regimen, symptoms. We will use common epidemiologic measures of occurrence (prevalence rates) and association (risk difference measures or ratio measures like the odds ratio) to assess COVID-19 prevalence across strata defined by sociodemographic variables, geographic location, groups of rare conditions. Stratified analyses or regression modeling will assess more complex questions such as whether the frequency or severity of COVID-19 infection vary within a category of rare diseases as a function of comorbidities or treatment of the underlying conditions. Whereas hypothesis testing procedures may be used in data analysis, we regard this survey as a measurement exercise and precision of the estimates Is the driving consideration. To provide a measure of the precision of the survey results, we will compute 95% confidence intervals of the key measures of occurrence and association.

World Health Organization estimates suggest that the prevalence of COVID-19 infection may be between 1% and 2%. Thus, if we achieve the target sample size of 5,000 respondents, and the rare disease population of patients is not at substantially different risk than the general population, we may obtain information about 50-100 COVID-19 cases. As the 95%CI of 50 observed events is 37-66 under the Poisson distribution, our estimate of the overall prevalence of COVID-19 infection among respondents (aim 1) will be very precise. For a sample size of 50, The 95%CI of a simple mean would be between +/-0.25 standard deviation units from the mean, suggesting adequate precision of measures such as the average duration of hospitalization (aim 2). The 95%CI for 10 observed events is 4.8-18; thus, estimates of the rate for any categorization of the respondents into 5-10 groups will vary from about one-half to twice the observed rate. This level of precision should be adequate to describe the variation in risk across population subgroups defined by sociodemographic characteristics, geographic location, or rare disease characteristics (aim 3). The precision of survey measures related to changes in access to treatment experienced by rare disease patients with or without COVID-19 infection is likely to be much higher, given the large number of respondents expected.

Section 8.1: Measures to Minimize Bias

Broad-based advertisement of the survey through the RDCRN consortia and Patient Advisory Groups will hopefully induce a large number of patients with rare diseases to participate. It is possible that individuals who have experienced COVID-19 infection will respond at a higher rate that individuals who have not, and the estimates of the prevalence of COVID-19 infection may be biased. On the other hand, information about the characteristics of patients with COVID-19 infections is likely to be representative of the characteristics of COVID-19 infection among rare disease patients. Also, estimates of the impact of the COVID-19 epidemic on access to care, treatment and special food rare disease patients who have not experienced COVID-19 infection are likely to be unbiased. Thus, this study is likely to provide important new information on the impact of COVID-19 on a highly vulnerable population.

Section 9: Source Documents and Access to Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a human subject research study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the human subject research study.

Section 10: Quality Assurance

Quality control procedures will be implemented beginning with the data entry system and data quality control checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written standard operating procedures, the monitors will verify that the human subject research is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, Good Clinical Practice, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all study related sites, source data/documents, and reports for the purpose of monitoring and auditing by the NCATS Program Officer if so required, and inspection by local and regulatory authorities.

Section 11: Ethics

Section 11.1: Ethical Standards

This study will be conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

Section 11.2: Institutional Review Board

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or IRB, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the Investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The Investigator should provide a list of EC/IRB members and their affiliate to the sponsor upon request.

Section 11.3: Informed Consent

A waiver of documented consent and parental permission will be requested from the IRB, due to the minimal risk posed by this study and the infeasibility of collecting signed informed consent documents from participants who remotely complete the survey online. The completion of a survey by a minor is a minimal risk activity that does not impede upon risks and does not usually require parental permission outside of the context of research. All participants will receive a study information document that includes all necessary elements (e.g., who is conducting the research, reason for the research, that participation is voluntary, the cost of participation, risks of participation, benefits of participation, how confidentiality will be maintained, and so forth). Completion of the survey will be acknowledgement of consent to participate.

Individuals will be informed that they may answer anonymously and that they may choose not to respond to individual questions.

Section 11.4: Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the

research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

Section 11.5: Future Use of Collected Samples

Data collected for this study will be analyzed and stored at the RDCRN funded Data Management and Coordinating Center. After the study is completed, the de-identified, archived data will be transmitted to a cloud-based repository maintained by the DMCC and use of the data for secondary analyses will be governed by the RDCRN data sharing policies.

Section 12: Data Handling and Record-Keeping
Section 12.1: Data Collection and Management Responsibilities

Data collection is the responsibility of the study staff at the site under the supervision of the site Primary Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

The DMCC will develop, test, and maintain the data capture system using a web-based data collection system, REDCap, as the primary source of data entry and storage. REDCap is a software toolset and workflow methodology for electronic collection and management of research and clinical trial data developed by Vanderbilt University, with collaboration from a consortium of institutional partners including the University of Cincinnati Academic Health Center. The REDCap system provides a secure, web-based application that is flexible and provides: 1) an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry; 2) HIPAA-compliant and 21 CFR Part 11-ready audit trails for tracking page views, data manipulation and export procedures; 3) record locking and electronic signature functions; 4) fine grained control of user rights to view and manipulate data, and tool to sequester data access for multiple sites; 5) a report builder for reporting, monitoring and querying patient records; and 6) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

Study data will be entered into REDCap, supported by the DMCC. The REDCap system complies with all applicable guidelines to ensure patient confidentiality, data integrity, and reliability. All data management best practices including quality controls and data validation procedures will be applied to ensure the validity and accuracy of the clinical database. A data management plan will be developed which will describe the data collection process, database development, quality control processes and reporting.

Section 12.2: Study Records Retention

In compliance with Protection of Human Subjects regulations, (45CFR Part 46), records related to the conduct of this trial, including but not limited to source documentation, case report forms, informed consent forms, essential study documentation, and documentation of IRB activities, will be retained by the Investigator for a period of 3 years following the official close of the study. Such records may be preserved in hardcopy, electronic or other media form and must be accessible for inspection and copying by authorized representatives of HHS, NIH, the study sponsor and/or their representatives at reasonable times and in a reasonable manner. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the Investigator when these documents no longer need to be retained.

Section 12.3: Protocol Deviations

A protocol deviation is any noncompliance with the human subject research protocol, GCP, or manual of procedures requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. Given the nature of this study protocol deviations are not expected. As participants are allowed to skip questions, a skipped response will not be considered a protocol deviation.

Section 12.4: Publication Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

Section 13: Study Administration and Conflict of Interest

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Section 14: References

[1] Guan, W.-j., et al. (2020). "Clinical Characteristics of Coronavirus Disease 2019 in China." N Engl J Med.

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Section 15: Appendices