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| Study: | PETAL Repository of Electronic Data COVID-19 Observational Study |
| Acronym: | RED CORAL |


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## ABBREVIATIONS

**ABG** = Arterial blood gas
**ARDS** = Acute Respiratory Distress Syndrome
**CORAL**= COVID-19 Observational Study
**COVID-19** = Coronavirus disease due to SARS-CoV2
**ED** = Emergency Department
**$FiO_2$** = Fraction of Inspired Oxygen
**ICU** = Intensive Care Unit
**IMV** = Invasive Mechanical Ventilation
**ISARIC**= International Severe Acute Respiratory Illness Consortium
**MV=** Mechanical Ventilation
**NHLBI** = National Heart Lung and Blood Institute
**PETAL** = Prevention and Early Treatment of Acute Lung Injury
**P/F =** PaO2/FiO2 ratio
**$PaCO_2$** = Partial pressure of arterial carbon dioxide
**PACU** = Post anesthesia care unit
**$PaO_2$** = Partial pressure of arterial oxygen
**PBW** = Predicted Body Weight
**PEEP** = Positive End-Expiratory Pressure
**POCUS** = Point of care ultrasound
**Ppl** = Plateau pressure
**PS** = Pressure Support Ventilation
**PUI**= Person under investigation (Test pending for COVID-19)
**RED CORAL**= Repository of electronic data for COVID-19
**S/F** = SpO2/FiO2 ratio
**SARS-CoV2**= Severe acute respiratory syndrome coronavirus 2
**SOFA** = Sequential Organ Failure Assessment
**SBP** = Systolic Blood Pressure
**$SpO_2$** = Oxygen Saturation via pulse oximetry
**WHO** = World Health Organization

## DEFINITIONS

**CORAL:** PETAL Network's observation research program studying severe COVID-19. RED CORAL is a component of CORAL.

**Confirmed COVID-19:** Defined as a person with a laboratory confirmed SARS-CoV2 infection

**Extubation**: Removal of an orotracheal tube, nasotracheal tube, or unassisted breathing with a tracheostomy

**Home**: Level of residence or health care facility where the patient was residing prior to hospital admission

**Invasive Mechanical Ventilation (IMV)**: Assisted positive pressure ventilation delivered by a nasotracheal, orotracheal, or tracheostomy tube

**Mortality at hospital discharge:** This includes deaths from all causes at the time of discharge from the hospital

**Funder:** National Institutes of Health and the National Heart Lung and Blood Institute

**Study Day:** The day of presentation to hospital associated with COVID-19 admission is study day 1. The day of ICU admission is ICU day 1.

**Study hospital**: Defined as the hospital where the patient was enrolled in study procedures.

## 1. PROTOCOL SUMMARY

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| **Title** | PETAL COVID-19 Observational Study |
| **Short Title** | CORAL |
| **Clinical Phase** | Observational Study |
| **Number of Sites** | Participating PETAL hospitals |
| **IND Sponsor/Number** | Not Applicable |
| **Study Objectives** | **Primary Aim**<br>• Provide data for investigation of demographics, clinical characteristics, risk factors, care practices, outcomes and resource utilization of patients with severe acute COVID-19<br>**Secondary Aims**<br>• Characterize the severity and course of acute clinical manifestations of COVID-19<br>• Identify risk factors and create prediction models for COVID-19 outcomes, including acute respiratory failure, prolonged mechanical ventilation, cardiomyopathy, and death<br>• Describe care processes for hospitalized patients with COVID-19, including resource allocation, utilization of palliative care services, and causes of death<br>• Assess the state of emergency activation and capacity strain in the health systems providing care to hospitalized patients with COVID-19, in order to describe practice, and to inform interpretation of clinical care provision and outcomes. |
| **Study Design** | Retrospective observational study of hospitalized patients with COVID-19 |
| **Accrual Objective** | 1500 patients |
| **Study Duration** | 12 months |
| **Treatment Description** | Not Applicable |
| **Inclusion Criteria** | 1. Adult patient with confirmed COVID-19 within 14 days of hospital admission<br>2. Evidence of acute COVID-19, with fever or respiratory manifestations, as characterized by signs and symptoms |

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| | such as fever, cough, dyspnea, tachypnea, hypoxemia, and infiltrates on chest imaging. |
| **Exclusion Criteria** | 1. Prisoners |
| **Study Stopping Rules** | There are no safety-related stopping rules |

## 2. TRIAL DESCRIPTION

### 2.1 Background

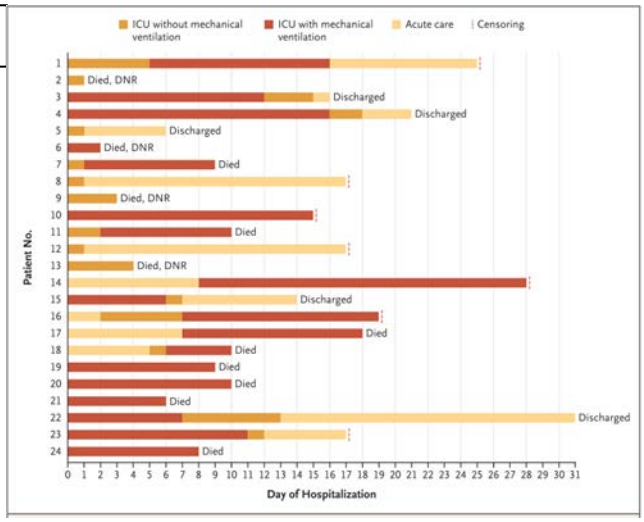
Not even three months have passed since the initial report of a cluster of 27 cases of pneumonia of unknown etiology in Wuhan, China on December 31st, 2019. One week later, the pathogen was identified as a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). By the end of January, there were nearly 8000 cases of coronavirus disease 2019 (COVID-19) in China and 80 travel-related cases confirmed outside China, leading to declaration of "a public health emergency of international concern" by the World Health Organization. In just three weeks more, there were over 70,000 cases and 200 deaths in China and 1000 cases around the world.[1] Since that time, COVID-19 has raged across the earth like wildfire. On March 28th, 2020, there were over 650,000 cases around the world, with over 115,000 in the US, and a global death toll of over 30,000; one week later, these numbers had doubled (over 1.2 million cases worldwide, over 63,000 deaths, and over 300,000 cases in the United States). By early May 2020, there have been over 4.5 million cases and over 300,000 deaths worldwide. The United States has been hard hit, with over 1.4 million cases and over 86,000 deaths on May 14, 2020.

The scientific literature regarding COVID-19 is, unsurprisingly, still in its infancy. The first large population-level report came from China late February, describing 44,415 patients with confirmed COVID-19. Most patients were between 30-79 years old, with only 3% of cases in people $\geq$ 80 years. Mild disease was common (81%), although it is not clear if care was received in a hospital setting. Hospitalized patients had signs of lower respiratory infection with cough, shortness of breath, and abnormal chest radiographs. Nearly 20% of patients were critically ill with hypoxemic respiratory failure. Overall case fatality rates was 2.3%, with the oldest and most severely ill at higher risk of death.[1]

Single center reports from China describe high rates of critical illness syndromes among hospitalized patients, with acute respiratory distress syndrome (ARDS) in 22-42%, arrhythmias in 16%, and shock in 11%. [2,3]Early reports describe prolonged respiratory failure and hospitalization, with extended periods of mechanical ventilation. Reports from 1-2 centers in China present clinical risk factors for ARDS and death, describing advancing age, co-morbid hypertension and diabetes, and fever. Patients with poor outcomes were more likely to have abnormal laboratory findings, including neutrophilia, evidence of organ dysfunction (thrombocytopenia and elevated liver enzymes, creatinine, and troponin) and markers of inflammation and dysregulated coagulation (including

interleukin-6, ferritin, d-dimer, prothrombin time).[2,4] Case fatality among the severely ill in these Chinese reports is very high, ranging from 49-95%.

Figure 1[5]




The first case series of critically ill patients in the United States is from King County, Washington, where 21 patients with COVID-19 due to community spread were hospitalized at a single hospital between February 20th and March 5th, 2020. All but one developed ARDS, 67% developed shock, and 33% had evidence of cardiomyopathy. As of March 17th, 14 had died, 5 remained critically ill, and just 2 had left the ICU alive.[5] The second case series, also from Seattle, described 24 critically ill patients, 18 of whom received mechanical ventilation (MV).[6] Median duration of MV was 10 days (interquartile range 7-12), but only four patients had successfully liberated from MV at the time of the report, while three remained ventilator dependent and 8 had died. Although informed by a small number of patients, this report demonstrates major challenges in the care and investigation of severely ill COVID-19 patients; duration of MV and hospitalization is often long, and critical illness may develop later than a week into hospitalization, as shown in **Figure 1.**

Currently, little is known about the epidemiology of COVID-19 in the United States. Best estimates as of mid-March suggested that 20-30% of confirmed COVID-19 cases required hospitalization, and that 5-12% of the overall population with confirmed COVID-19 required intensive care.[7] It is difficult to generalize these findings, given rapid changes in COVID-19 testing and profound evolution of the population at risk from day to day. There are key knowledge gaps regarding clinical characteristics, biology, risk factors, outcomes, and resource utilization for acutely ill COVID-19 patients, especially in the United States. There are no proven treatments, despite high health care utilization and high case fatality, particularly among the elderly and the critically ill. It is unclear how generalizable current knowledge of ARDS biology and treatment may be in COVID-19, since most biomarker profiling and approaches informing prognostication and treatment of ARDS have considered underlying bacterial infections, rather than viral infections.

Thus, there exists little understanding of biologic pathways that might be optimal for targeting therapeutics in this deadly syndrome, nor for understanding which patients are at highest risk for ARDS development or prolonged critical illness. Rapid expansion of cases across this country and others necessitates urgent study of severe acute COVID-19 in order to care for patients, inform and develop treatments, target therapeutics, prognosticate, and understand health system impacts.

## 2.2 Study Objectives

The epidemiology of patients hospitalized with severe COVID-19 has not been well defined, especially in the American context. There are significant knowledge gaps regarding demographics, clinical characteristics, trajectory of disease, timing of recovery, predictors of organ failure and death, resource utilization, and post-hospital outcomes. Furthermore, there exists limited understanding of biologic pathways activated by this viral syndrome and which patients are at risk for progression to more severe illness. There are reports of unusual features of COVID-19 critical illness, such as high prevalence of cardiomyopathy as well as catastrophic arrhythmias during recovery, which need further study. In response, the purpose of the RED CORAL study is to inform epidemiology and resource utilization through data collection and creation of a data repository.

### 2.2.1 Specific Aims

We will identify acute and critically ill patients with COVID-19 and collect detailed data from their hospital stay. We will contribute data to the WHO/ ISARIC COVID registry and to the scientific community in order to advance United States participation in studies of global epidemiology. We will use the data to increase understanding of the clinical course of COVID-19.

Our specific aims are to:

a. Provide data for investigation of demographics, clinical characteristics, risk factors, care practices, outcomes and resource utilization of patients with severe acute COVID-19
b. Characterize the severity and course of acute clinical manifestations of COVID-19
c. Identify risk factors and create prediction models for COVID-19 outcomes, including acute respiratory failure, prolonged mechanical ventilation, cardiomyopathy, and death
d. Describe care processes for hospitalized patients with COVID-19, including resource allocation, utilization of palliative care services, and causes of death
e. assess the state of emergency activation and capacity strain in the health systems providing care to hospitalized patients with COVID-19, in order to describe practice, and to inform interpretation of clinical care provision and outcomes

The Prevention and Early Treatment of Acute Lung Injury (PETAL) Network is a consortium of academic and affiliated hospitals across the United States, funded by the NHLBI to conduct clinical trials in patients with or at risk for critical illness, including ARDS. Our Network's goal is to improve outcomes of patients with acute and critical illness through research. We have deep expertise in severe acute respiratory infections and critical illness, and the existing infrastructure to rapidly investigate acute and critical illness caused by SARS CoV-2. We are integrated with complimentary efforts in children (PALISI), outpatients (CDC), and the global community (SCCM, WHO/ISARIC). We are perfectly positioned to investigate the burden of disease, severity of illness, clinical course, and impact on the health system of severe COVID-19.

## 3. RESEARCH APPROACH

### 3.1 Previous Work

There have been no similar studies of epidemiology of hospitalized patients with COVID-19 in the United States at this time, and only limited reports worldwide. There are growing efforts to create registries of patients with COVID-19 in the United States and around the world, including work by the WHO (ISARIC registry), the Centers for Disease Control (CDC-IVY), the Society for Critical Care Medicine (SCCM-VIRUS), and the pediatric community (PALISI). There are also proposals for bio-specimen collection, including the newly funded COVID Immunophenotyping study by NIAID, IMPACC. This PETAL proposal (CORAL) is deliberately designed to harmonize and synergize with these existing and proposed efforts.

At the same time, CORAL is unique, leveraging the expertise of PETAL in order to conduct detailed phenotyping of the clinical course, and outcomes of acutely and critically ill patients with COVID-19, and use this information to understand and improve clinical care, with a particular focus on critical illness. PETAL has successfully completed a large scale observational study of ventilator practices across Network hospitals, [8] and many of the PETAL hospitals, investigators, and staff contributed to a successful observational registry of pandemic H1N1 in 2009-2010 as part of the NHLBI ARDS Network and in conjunction with PALISI.[9] The proposed studies are feasible in our hands.

### 3.2 Overall Approach

RED CORAL is a multicenter, observational medical record review study of 1500patients with COVID-19 admitted to PETAL Network hospitals. Data Collection may occur remotely in order to accommodate stay-at-home orders and other social distancing procedures.

### 3.3 Study Population

RED CORAL will include adult patients with confirmed COVID-19 hospitalized at participating sites who have available clinical data. The study period will include patients who present for admission to study hospitals between March 1st and April 1st, 2020.

Inclusion criteria:

1. Adult patient with confirmed COVID-19 within 14 days of hospital admission
2. Evidence of acute COVID-19, with fever or respiratory manifestations, as characterized by signs and symptoms such as fever, cough, dyspnea, tachypnea, hypoxemia, and infiltrates on chest imaging.

Exclusion criteria:

1. Prisoners

### 3.4 Selection of Clinical Sites

RED CORAL will recruit at all volunteering PETAL Network hospitals. The only requirements are capacity to identify hospitalized patients with COVID-19 and resources to complete the case report forms with high fidelity. In addition, resources and procedures will be developed to facilitate the participation of hospitals outside of the PETAL Network as well.

## 4. STUDY PROCEDURES

### 4.1 Screening

Research staff sites will identify potentially eligible COVID+ patients hospitalized during the study period using medical records and lists maintained for clinical operations. A log of hospitalized COVID+ patients during the study period will be compiled by participating sites. This log will include simple information: patient name, medical record number, age, sex at birth, date of admission, admission location (ward or ICU), race and ethnicity. This log will be used to select patients and to describe the relationship between selected patients and the larger population. Patient names and medical record numbers from this log will only be used at the local sites and not transmitted to the Clinical Coordinating Center (CCC). Research staff will use the medical records for patients on the log to determine study eligibility. Patient names and medical record numbers will be removed from screening logs, which will then be uploaded by each site into REDCap. This information will be used to describe basic characteristics of the entire population of patients with COVID-19 hospitalized at PETAL hospitals between March 1$^{st}$ and April 1$^{st}$, 2020.

### 4.2 Enrollment

Patients admitted for hospitalization with test-confirmed COVID-19 may be eligible for inclusion in CORAL. The study period will be March 1$^{st}$ through April 1$^{st}$, 2020. Individual patients will only be eligible for inclusion once; if readmitted during the study period, the first hospitalization to a study hospital will be selected.

Each clinical center will be paid for entry of 125 patients. Patients should be selected beginning with the earliest cases, ideally at institutions within each center that can complete data entry most quickly. Patients should be selected chronologically at each site. If a clinical center cannot complete data entry rapidly or does not have 125 patients to contribute, the quota may be shared by other clinical centers. This will sum to 1500 patients across PETAL Sites. Beyond this quota, clinical centers may contribute additional patients, but will not be guaranteed compensation.

From this group of 125 patients, clinical centers will chronologically identify 25 patients who received care in the ICU for detailed data collection. Centers will receive additional compensation for this detailed data collection. Centers may choose to perform detailed data collection on all patients (floor, and ICU patients after the first 25) but will not receive extra compensation for doing so. All patients will be included via waiver of informed consent.

### 4.3 Data Collection

RED CORAL elements include all data needed for participation in the ISARIC/WHO registry, in addition to selected variables important for understanding COVID-19 in the context of acute and critical illness in the United States. Data will be collected in three modules: admission, daily and discharge or study termination. Timing and included data elements are presented in the table.

| CORAL Data Collection Timing & Description | | |
|---|---|---|
| Module | Timing | Data Elements |
| Admission | Calendar day of presentation to study hospital (Day 1) and 24-hour period | COVID testing, symptoms, demographics, exposures, comorbidities, home medications, vital signs, labs, supportive care & treatments, research trial enrollment, medications, ventilator settings |
| Daily Data | Focused: Days 1,4,8,15,21,28, & ICU Day 1<br>Detailed: Days 1-15, 21,28, & ICU days 1-15 | Vital signs, labs, supportive care & treatments, research trial enrollment, medications, ventilator settings |
| Discharge or study termination | Hospital discharge or study day 60 | Disposition, cause of death, care limitations, functional status, infections, organ support at discharge, summative treatments, summative complications, summative diagnostics |

The detailed mainly differs from the focused data collection in terms of daily data. For the study period, ICU patients with COVID-19 contributing to their need for hospital admission may be eligible for detailed data collection, which will include ICU days 1-15.

The case report form (CRF) is built in RED Cap which can be imported as a local instance or centrally through the PETAL CCC. Manual data entry of all elements into REDCap may not be required depending on the site's ability to extract data from the EMR. It is important for data collection to begin promptly so that these studies can rapidly inform care of the thousands of COVID-19 patients in hospitals.

### 4.4 Images for Repository

Data collection include abstracting presence of infiltrates as noted on radiologists' reports from chest radiographs and computed tomography (CT) scans. RED CORAL also will collect all clinical radiographs and CT scans available from the course of illness as well as clinically performed cardiac evaluations. All image types will be uploaded by study staff into the imaging coordinating center at the American College of Radiology's Center for Research and Innovation. We will use the TRIAD image collection system which removes all identifiers and codes images with study labels in DICOM format. The CORAL

Figure 3.
Chest CT of COVID-19 ARDS (ref. 5)

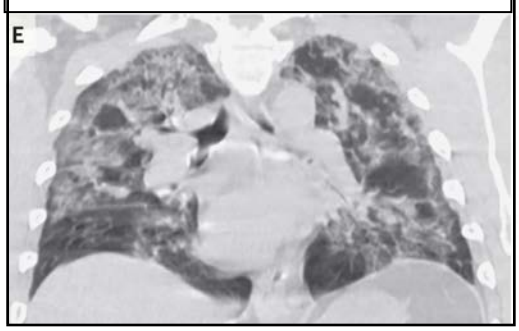


Image Repository will be maintained on ACR CRI servers through the course of the study. ACR CRI will collect all diagnostic images, create a link between the images and clinical data collected by PETAL, and archive images throughout study duration and after study close to make accessible to researchers.

### 4.5 Human Subjects Considerations

COVID-19 is a global pandemic. Obtaining information about patients with COVID-19 is an important response to a public health emergency. Given that this is a data repository of data and images that are available in the medical record and already being collected as part of routine care, the only risk of the research is loss of confidentiality. Patients hospitalized with COVID-19 at participating hospitals are eligible for enrollment regardless of age, gender, ethnicity, race, sexuality, or religion. Previous reports suggest that males may have higher rates of infection than females meaning that males might be slightly over presented – however, distribution of different demographics will be similar to the demographics of admitted patients. Children aged less than 18 years old appear to have milder disease when infected with SARS-CoV2 and in general, are not routinely hospitalized. As such, enrollment will be restricted to adults. However, data will be harmonized with aligned research efforts of pediatric patients.

### 4.6 Risks and Benefits of Participation

The only risk is potential invasion of privacy and stress. Data will be secured and password protected. RED CORAL is an observational study; there are no clinical benefits to participation. However, many patients report benefits of altruism through study participation. This study has the potential to help future patients with COVID-19 and those stricken in future pandemics.

### 4.7 Study Withdrawal or Discontinuation

Study withdrawal or discontinuation is not relevant to RED CORAL.

### 4.8 Statistical Considerations

It is anticipated that there will be thousands of patients eligible at PETAL hospital for entry into the registry and cohort. This proposal is to begin by collecting data on 1500 patients. It is difficult to predict what proportion of included patients will be acutely ill, critically ill, receiving mechanical ventilation, developing ARDS, receiving prolonged mechanical ventilation, and dying during initial hospitalization—early reports have been small and incomplete. Describing these aspects of the clinical epidemiology, with special attention to ARDS and cardiac complications, and course of acute severe COVID-19 is an important early contribution from this work.

RED CORAL proposes to focus early efforts on describing the clinical characteristics of COVID-19. Similarly, early efforts will focus on identifying risk factors and developing prediction models for key outcomes (including respiratory failure, shock, cardiac complications, prolonged mechanical ventilation, and death). These analyses need to be completed and published expeditiously in order to make an impact on clinical care and

research in the early days of the COVID-19 pandemic. There will also be plans for data cleaning, model validation, analysis, and publication of findings from the final study population. There are many important research questions that these data will be able to address. Statistical analysis plans will be developed and approved before any analyses begin.

We have identified key research questions and will refine more as additional information accumulates. We will estimate the proportion of patients with ICU admission, respiratory failure, prolonged mechanical ventilation (more than 7 days of mechanical ventilation), and death We will estimate the duration of mechanical ventilation, ICU stay, and hospital stay. Using both floor and ICU patients, we will estimate what proportion are in each state of the COVID Outcome Scale on days 8, 15, 21 and 28. Increasing the size of the sample will increase the precision around these estimates. We will then use the number of patients in each outcome group to design adequately powered multivariate models.

We anticipate sufficient power to evaluate at least 20 variables for association with these outcomes of respiratory failure, prolonged mechanical ventilation, and death. We will focus on key demographic factors, such as age, sex at birth, comorbidity, race/ethnicity, and pre-morbid functional status. We will develop multivariable models to evaluate the association of additional laboratory and physiologic variables with these outcomes and compare with existing risk prediction models.

The sample size for the overall cohort was determined to allow early hypothesis testing on at least 300 patients with respiratory failure and 200 patients who die from COVID-19. This number of patients with expected outcomes are required to create appropriately adjusted multivariable models to predict outcomes, and to look for associations between treatments and outcomes

### 4.9 Data management, data sharing, quality assurance and security of data

Data collected by study staff will contain identifiers at local sites. For transmission of data to the PETAL CCC, a unique study identifier will be assigned to each subject. All RED CORAL data will be shared in order to facilitate rapid knowledge generation and dissemination. this study was specifically designed to allow data sharing with the ISARIC registry. RED CORAL data and images may be shared with other projects, both at the site and network level, provided that human subjects' protections are followed. CORAL's case report forms, data dictionaries, and REDCap builds will be available on the public-facing PETAL website. The CORAL committee will work with the PETAL CCC and Steering Committee to create a solid approach to early data sharing that accelerates knowledge while minimizing potential threats of invasion of privacy. Sharing of data will be reviewed by the PETAL Network Natural History Committee, according to current PETAL network policies.

ISARIC data elements from all completed cases will be shared with ISARIC's Oxford Data Coordinating center. The PETAL Network will receive reports from ISARIC describing numbers and features of the cases contributed. In addition, these data will be easily shared with other efforts to understand COVID-19 and will be expeditiously made publicly available.

Data quality and consistency of approach to data collection is very important. We will follow the previously successful approach to multi-faceted quality assurance which includes: (1) use of Manuals of Operation for training and reference, (2) regular meetings between local Investigators and study coordinators to answer questions and ensure consistency in evaluations across study sites, (3) regular conferences between all Investigators for the same purposes, (4) ongoing quality assurance review and training updates, (5) data entry into a database with extensive automated checks of data validity, and (6) ongoing review of descriptive statistics by Investigators with detailed review of selected data. We will use best practice physical and electronic security and back-up procedures as well.

### 4.10 Privacy and Confidentiality

Data will be collected into the HIPAA compliant REDCap database. Only study personnel will have access to the REDCap database. The CCC will download data from the database with limited identifiers (limited to dates and zip codes). Identifiers will only be shared in accordance with all relevant human subjects' protections.

### 4.11 Record Retention

One year after the primary manuscript is published or after data collection ends, whichever is last, any identifiable data in the database will be deleted and the data will be transferred to an NIH controlled, de-identified database.

## 5. REFERENCES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