Hackensack Meridian *Health*

Real World Observational Database for COVID-19 Treatment and Outcomes

Principal Investigator:	Andrew Ip MD
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1 Responsible Parties

Table 1-1 Main responsible parties

Principal Investigator	Andrew Ip MD John Theurer Cancer Center at Hackensack University Medical Center 92 Second Street New Jersey, NJ 07601
Principal Analytic Group	COTA 101 Arch Street, 15th Floor Boston, MA 02110 Phone: (866) 648-3833
Participating Centers	Hackensack Meridian *Health* Network

2 Brief Synopsis

The principle objective of this observational database is to build research-grade real world data that will serve as platform to advance the scientific understanding and clinical care of patients with COVID-19.

1. Demographic, diagnostic, treatment and outcome data from centers throughout the Hackensack Meridian Health Network will be abstracted from the electronic health records of patients with confirmed or suspected COVID-19. This will be purely observational and no direction as to the care of the patient will be performed as part of this effort. There will be no research intervention(s) with the exception of collection of data from subjects currently receiving treatment or will/ or have had treatment at Hackensack Meridian Health Network. Data will be collected both retrospectively and prospectively.

1a. Data points to be collected will include, but are not limited to: age, gender, zip code, prior evaluation for COVID-19, tobacco history, race, site of care, healthcare worker, nursing home care, visits to ER, presenting features of fever/ cough/ dyspnea/ gastrointestinal/ mental status changes, days of symptoms, comorbidities, uses of antihypertensives, duration of hospitalization/ ICU care, presenting laboratory functions, presenting vital signs, need for oxygen support, dialysis/ ecmo use, treatment with hydroxychloroquine/ azithromycin/ remdesevir/ tociluzimab/ anti-inflammatory agents, arrhythmias/ QTc prolongation, enrollment on clinical trial, positive cultures, survival and cause of death. Additional data points may be added as needed however these points will only be collected related to their treatment and treatment related outcomes.

2. The data will be entered into a central HMH database hosted within the REDCap system (HIPAA compliant, secure)l)

3. A de-identified dataset will be sent to COTA for primary statistical analysis as requested by the research teams. COTA will also make available a data/analytic visualization tool (hosted on Tableau) for analysis by primary investigators.

4. De-identified data may also be sent directly to HMH investigators for their own analysis after appropriate Human Subject Protection Review.

5. Data may be made available to governmental agencies as requested.

Amendments and Updates

Amendment number: 04

Date: October 2, 2020

Table 2-1 Study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
01	April 5, 2020	Title Changed to capture RWD Outcomes for CoVID Population in HMHN.		Protocol will now allow for RWD Outcomes. This information will be utilized to determine best treatment options for CoVid Population.
02	April 23, 2020	Section 7.3		The HMH Biorepository (BioR) will be granted access to the database.
03	June 17, 2020	Section 7.4		The University of Miami will be granted access to only de-identified portions of the database.
04	August 20, 2020	Section 7.3		HMH Biorepository (BioR) collection clarification.
05	October 2, 2020	Section 5.1 and 7.3		Adding BI as a source of data in addition to EPIC.

3 Rationale

3.1 Rationale for an Observational Database in COVID-19

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by SARS-CoV-2 virus, a novel betacoronavirus discovered in Wuhan, China in December 2019. Subsequently, the disease has spread globally and outbreaks have been identified in over 100 countries. In China, data extracted from medical records of 1099 hospitalized patients and outpatients with laboratory confirmed COVID-19, revealed a summary of clinical characteristics. The most common symptoms were fever (43% on admission and 88.7% during hospitalization), cough (67.8%) and diarrhea (3.8%). On admission, ground-glass opacity was the most common radiologist finding on CT scans (56.4%). According to another recent Chinese study evaluation of 72,314 cases, 80% of patients presented with mild disease and the overall case-fatality rate was about 2.3%. (1)

A more complete understanding of the epidemiology, presenting features, role of co-morbidities in severity of illness, needs for and utilization of healthcare resources, effectiveness of therapeutic approaches including off-label use, and clinical outcomes is desperately needed. Well-designed clinical trials, although helpful in gaining regulatory approval of new agents, enroll only a fraction of available patients and may not always mirror “real world” scenarios. An outcome atabase may be able to provide rapid indicators of effective strategies. Collecting data from the electronic health records permits significantly detailed information to be analyzed while not interfering with the routine best medical care delivered by the treating physicians.

4 Registry Objectives

The principle objective of this Observation Outcomes Database is to build research-grade real world data that will serve as a platform to advance the scientific understanding and clinical care of patients with COVID-19 in order to provide best clinical treatment options.

4.1 Primary Objectives

4.11 Understand epidemiology including presenting features of the COVID-19 pandemic within the Hackensack Meridian Network

4.12 Explore the impact of co-morbidities and other patient factors on the severity of COVID-19

4.13 Understand need for hospitalization, ICU support and other healthcare resources among patients with COVID-19

4.14 Explore efficacy and toxicity of various treatment strategies including "off-label use" of medications in real world settings

4.15 Measure clinical outcomes including hospital discharges and survival

5 Research Methods

5.1 Registry Design and Collection

The Hackensack Meridian Health RWD Observational COVID-19, a descriptive observational database, is a multi-center initiative collecting data throughout the Hackensack Meridian Health Network (HMH).

The database will be drawn from the electronic health records of patients with confirmed or suspected COVID-19. HMH utilizes the EPIC system at most of the facilities, which will serve as the primary data source. Additional data obtained via other HMH staff and

bioinformatics can be added to the database as available and permitted. This includes but is not limited to data obtained either directly from EPIC or provided by other sources such as the HMH Business Intelligence Office (BI) to facilitate data extraction. Reports provided by BI can be entered directly into the REDCap database or kept separately (as pre-data supplements that might be added at a later time).

The database will be designed within the REDCap system. REDCap is a secure web application for building and managing online surveys and databases. While REDCap can be used to collect virtually any type of data (including 21 CFR Part 11, FISMA, and HIPAA-compliant environments), it is specifically geared to support online or offline data capture for research studies and operations.

The REDCap hosted universal observational database can export HIPAA compliant files for external analysis as part of the secondary research usage clause defined by the OHRP.

Data collection fields enumerating the common prognostic variables, treatment regimens and clinical outcomes have been designed by the principal investigator and the study team with input from the Centers of Disease Control and Prevention (CDC).

The abstraction process into the database will be performed by members of HMH who are approved to have access to the EPIC system or provided by BI. Outside abstraction, which would involve viewing of PHI, will not be permitted unless specifically granted by the IRB.

5.2 Analytic Design

COTA, a data and analytic company headquartered in Boston MA, was founded by physicians at the John Theurer Cancer Center at Hackensack University Medical Center (an HMH site) in 2011. The company is experienced in the handling of large observational databases. Current shareholders of COTA include Hackensack Meridian Health and some of its physicians. COTA currently has a business associate agreement with Hackensack University Medical Center and several additional HMH sites which would permit abstraction of PHI if required. COTA will only receive de-identified data to perform secondary research analysis.

Governmental agency (including but not limited to the CDC and FDA) have been contacted about this observational database and will be given access to data as requested.

5.3 Registry Population

5.31 Registry Population Inclusion Criteria

5.311 Confirmed or suspected COVID-19

5.312 Data available via the EPIC system

5.313 NO age restriction

5.314 NO pregnancy restrictions

5.4 Site Responsibilities

5.41 HMH abstract of data from the EPIC system.

5.42 All eligible patients with COVID-19 will be included.

5.5 Registry Data Collection

5.51 Research personnel approved by HMH will extract and organize data from the electronic health record into the database.

5.52 Data will be entered into the REDCap approved database only. All protected health information (PHI) will be handled to maintain HIPAA compliance. The REDCap system will store PHI but this information will not be exported for any analysis unless specifically approved by the IRB. In the REDCap forms, all PHI will be parked as "identifiers" and only deidentified datasets will not be exported and shared with anyone but the study team.

5.53 Key prognostic diagnostic fields, demographics, treatments, and outcomes will be populated with data. Structured and unstructured data in the patients' electronic records will be reviewed to complete the population of the registry. The database however is not

intended to be an all-inclusive representation of the medical chart. Daily laboratories of routine nature will not be collected.

5.54 Adverse events may be scored and recorded using the common toxicity criteria (CTC). However, it will be the treating sites responsibility to report to the authorities/manufacturers any serious adverse events in accordance with standards of care for the institution and in compliance with local/national regulations.

5.55 This initiative is meant to be an observational database. No additional testing or treatment will be required for enrollment of a patient. All clinical care, including diagnostic and therapeutic decisions, will be at the sole discretion of the patient's treatment team.

5.6 Variables

Data points will be collected from the electronic medical record (or other HMH sources as available for patients with confirmed or suspected COVID-19. A partial listing is detailed below:

5.61 Key demographic variables include age, gender, race, zip code, past medical history documented co-morbidities, smoking history, etc.

5.62 Key diagnostic variables include date of diagnosis (COVID testing), blood count at time of hospitalization and/or entry to ICU care, chemistry panel, ferritin, ddimer, c-reactive protein, IL-6 levels, etc.

5.63 Key therapeutic variables include use of hydroxycholaquine, azithromycin, ventilator support, dialysis support, pressor support, etc.

5.64 Key outcome variables include will include need for hospitalization, duration of hospitalization, need for icu/ventilator support, duration of icu support, and death. .

5.65 Key treatment center variables include hospital type (academic/ community), number of cases per hospital.

Data Analysis

5.71 COTA will provide basic descriptive analysis of the COVID-19 patients in a de-identified aggregated fashion. Survival and healthcare utilization analysis with time variables will utilized censoring and the Kaplan-Meier methodology. Multi-variable analysis for associations between demographic and/or treatment variables and key outcomes will be performed. Additional analysis will be performed per review of the data.

5.7 Quality Control

Unlike traditional data sources (ie, claims databases) the full medical record is analyzed by the abstractors allowing deep medical variables to be characterized. The principal investigators and COTA will perform statistical reviews to uncover "obvious" inaccuracies. However, the data will not undergo formal secondary reviews for accuracy. Investigators should understand the limitations of an observational database in drawing any conclusions.

6 Protection of Human Subjects

This document is a study protocol for an observational database study. This study is to be conducted according to United States and international standards of Good Clinical Practice (CFR Title 21 parts 11, 50, 54, 56, 312, International Conference on Harmonization and the Declaration of Helsinki), applicable government regulations and Institutional research policies and procedures.

6.1 Informed Consent

The Principal Investigator believes that the elements for a full waiver of consent under 45 C.F.R. §46.116 are met. Specifically, in order to waive consent the following requirements must be met:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; as COVID-19 populations have received treatment and have been discharged or deceased.

The study protocol represents an observational review of patients with confirmed or suspected COVID-19. No interventions are required for enrollment of patients into this database. There will be no direct contact any patient. Protected health information (PHI) will not be made available (pursuant to the HIPAA Privacy Rule as described below) and only aggregate data will be disclosed. The data collection will be conducted across HMH network drawing information from a variety of healthcare settings, with data drawn principally from the electronic health records utilized by the network. It would not be practical (item 3) by the Investigators to obtain consent across the network (which includes multiple hospitals and clinics across the state) as no contact will occur between the study team and the potential subjects. This is an observational study. The subjects will be receiving standard of care therapy at multiple sites, with their consent for the care per usual practice, and will not be made aware of the collection of the data nor will their treating physicians as to keep the therapy unbiased by participation in this study.

Furthermore, this study will involve only collection of data that has or will be obtained for care of the patient/subject. Thus the study may be considered “secondary research” under the revised common rule that became effective January 2020. Unlike the pre-2018 rule exemption for secondary use of information and biospecimens, the Final Rule has no requirement that the information and biospecimens must be pre-existing at the time that the investigator begins the research; prospective collection is permitted.

Although the information will involve collection of the data from PHI and the REDCap database will need to have identifiers in place to permit data entry, the analysis will only be performed on de-identified datasets which will be exported to the research teams (COTA or other investigators). The REDCap system is HIPAA compliant and requires study team access. Identified datasets will not be shared. Thus the identifiers are not available to the research analytic teams and will not be shared.

Lastly, although not funded a governmental agency, the data may be shared with governmental agencies (including the CDC) as part of public health concerns.

6.2 HIPAA Privacy Rule compliance

The diagnostic evaluations and clinical outcomes of all patients with COVID-19 in HMH centers participating in this registry will be drawn from the EPIC system which contains PHI. The collected data will be entered into the REDCap system which will contain PHI. Both systems are secure, meeting HIPAA compliance, and may only be accessed by authorized personnel.

All data analysis will be conducted on exported de-identified data, under the secondary use clause. NO PHI will be publically disclosed unless requested by governmental agencies.

6.3 IRB

The Hackensack University Medical Center Institutional Review Board will serve as the IRB of record for this study for the Hackensack Meridian Network.

7 Disseminating and Communicating Registry Results

7.1

HMH, the principal investigator, and/or HMH sub-investigators may choose to publish information in the medical literature and/or at national meetings based on this registry. Any investigator will be required to recognize the data source in compliance with the journal standard practice. NO PHI may disclosed. If PHI is to be shared with other HMH investigators regarding separate IRB retrospective projects, this will be identified and written in the separate IRB approved protocol.

7.2

HMH, the principal investigator, and/or HMH sub-investigators may release data (de-identified) or analytic findings to governmental agencies as requested.

7.3

The HMH Biorepository (BioR) will be granted access to the database and any pre data, supplements or queries provided to the RWD study as the BioR is collecting the same clinical information from patients who have either provided consent for this collection or for any other specimens that have been acquired as per the BioR's protocol. The BioR will follow the internal SOP of the database and will not release personal health identifiers (PHI) to researchers.

7.4

The University of Miami will be granted access to only de-identified portions of the database as they are externally validating a risk score HMH has developed. They also will be developing a separate risk score on predicting intubation in COVID-19 patients and we anticipate an ongoing collaboration of sharing data

8 Data Ownership

Data contributed to the HMH registry will become the property of HMH. It may be utilized for commercial purposes by HMH in de-identified HIPAA compliant fashion.

9 References

1. Z Wu, JM. McGoogan: Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA (2020 Feb 24), 10.1001/jama.2020.2648