

## CLINICAL STUDY PROTOCOL



- **The Canadian COVID-19 Prospective Cohort Study**

**Protocol Version # 1.3**

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## UNIVERSITY HEALTH NETWORK

In collaboration with the Canadian Critical Care Trials Group (CCCTG), the Canadian Community ICU Research Network (CCIRNet) and the GEMINI Network



**COVID-19 IMMUNITY  
TASK FORCE**



**Canadian  
Frailty  
Network**

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**List of Abbreviations/ Terminology**

ACE2: Angiotensin I Converting Enzyme 2  
AJRCCM: American Journal of Respiratory and Critical Care Medicine  
APACHE II: Acute Physiology and Chronic Health Evaluation II  
ARBS: Angiotensin Receptor Blocker  
ARDS: Acute Respiratory Distress Syndrome  
ASH: Subarachnoid hemorrhage  
BRU: Biostatistics Research Unit  
CanCoGen: The Canadian COVID Genomics Network/Genome Canada  
CANCOV: Canadian COVID-19 Prospective Cohort Study  
COVIDCAS: Care-giving Assistance Scale  
CCCTG: Canadian Critical Care Trials Group  
CCIRNet: Canadian Community ICU Research Network  
CCRS: Complex Continuing Care Reporting  
CD-RISC: Connor-Davidson Resiliency Scale  
CFI: Canada Foundation of Innovation  
CFS: Clinical Frailty Scale Score  
CGeN: Canadian genome sequencing and analysis Network  
CIHI: Canadian Institute for Health Information  
CIHR Canadian Institute of Health Research  
CIS: Care-giving Impact Scale  
CITF: COVID-19 Immunity Task Force  
CRF: Case Report Forms  
CVA: Cerebrovascular accident  
DAP: Data Access and Publications committee  
DAD: Discharge Abstract Database  
DNA: Deoxyribonucleic Acid  
ECLS: Extracorporeal Lung Support  
EDTA: Ethylenediamine Tetraacetic Acid  
FIM: Functional Independence Measure  
GAD-7: General Anxiety Assessment Form  
GCP: Good Clinical Practice  
GEMINI: GEneral Medicine INpatient Initiative  
HCRS: Home Care Reporting System  
HRQoL: Heath-related Quality of Life  
ICES: Institute for Clinical Evaluative Sciences  
ICH: International Conference on Harmonisation  
ICU: Intensive Care Unit  
iPAD®: Internet-connected Personal Access Display Device Trademark

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KLK: Kallikrein-related peptidase

LIS: Acute Lung Injury Score

MD: Medicinae Doctor, Doctor of Medicine

MODS: Multiple Organ Dysfunction Score

MRC: Medical Research Council score

NACRS: National Ambulatory Care Reporting System

MV: Mechanical Ventilation

NCIP: novel coronavirus (2019-nCoV) infected pneumonia

NEJM: New England Journal of Medicine

NRS: National Rehabilitation Reporting System

ODB: Ontario Drug Benefit database

OHIP: Ontario Health Insurance Plan

OPB: Ontario Registered Persons Database

PCL-5: PCL-5 Trauma Score

PFT: Pulmonary Function Testing

PHI: Personal Health Information

PHIPA: Personal Health Information Protection Act

PRSS: Serine proteases

PQQ-9: Patient Health Questionnaire

RECOVER Program: REhabilitation and ReCOVER of survivors of critical illness and their family caregivers

REDCap: Research Electronic Data Capture

RNA: Ribonucleic Acid

RNLI: Reintegration to Normal Living Index

SARS: Severe Acute Respiratory Syndrome

SDM: Substitute Decision Maker

SF-36: Medical Outcomes Study Short Form -36 Questionnaire

SS: Medical Outcomes Study Social Support Scale

TaARI: The Thrombosis & Atherosclerosis Research Institute

TGHC: Toronto Grace Health Centre

THETA: Toronto Health Economics and Technology Assessment

TMPRSS: Transmembrane Protease Serine

TRI: Toronto Rehabilitation Institute

UHN: University Health Network

UofT – University of Toronto

6MWD: Six-Minute Walk Distance

6MWT: Six-Minute Walk Test

## CANCOV Protocol v1.3

### Protocol Summary

The Canadian COVID-19 Prospective Cohort Study (CANCOV)

#### Prospective Cohort Study

##### Sample Size

N= 2500

1000 hospitalized COVID-19+ patients (including 500 patients + caregivers dyads, and 1000 non-hospitalized COVID-19+ patients)

##### Study Population

1. NON-HOSPITALIZED COHORT: Non-hospitalized COVID-19 patients isolating at home (n=1000 patients) -- patients with mild severity of illness with a positive diagnosis of COVID-19 who have been sent home to self-isolate.
2. HOSPITALIZED NON-ICU COHORT: Hospitalized non-ICU COVID-19 patients and caregivers (approximately n=600 patients with 200 caregivers) -- patients with moderately severe illness admitted to general internal medicine (GIM) units with COVID-19 and their caregivers.
3. HOSPITALIZED ICU COHORT: Hospitalized ICU COVID-19 survivors and caregivers (approximately n=400 patients with 300 caregivers) -- critically ill patients who are admitted to the intensive care unit (ICUs) with COVID-19 and their family caregivers

##### Accrual Period

6-30 months

##### Study Design

Our investigator group is proposing a **Canadian COVID-19 Prospective Cohort Study (CANCOV)**. This will be a multi-centre, one-year follow-up of COVID-19 patients who are hospitalized in acute care hospitals (those admitted to general internal medicine wards and/or critical care units (ICU)) and non-hospitalized patients (those who were tested positive and asked to isolate at home). Our **overall objectives** are to determine short- (in hospital for hospitalized patients and 1-week outcome for non-hospitalized patients) and longer-term (1, 3, 6, and 12, up to 36) months post-acute hospital discharge/diagnosis) outcomes in patients and their caregivers, and the clinical, sociodemographic, genetic/ transcriptomic/epigenomic /immunological predictors of these outcomes. Our **overall hypothesis** is that clinical risk factors (including but not limited to age, baseline health, socio-demographic status, comorbid illness and candidate genetic/transcriptomic/epigenomic/ immunological /serological inflammatory /coagulation risk factors) are determinants of short- and long-term outcomes in patients with COVID-19.

##### Study Duration

2-5 years

##### Study Agent/ Intervention/ Procedure

The Canadian COVID-19 Prospective Cohort Study will be the first Canadian study to determine the short and long term outcomes of 3 cohorts of patients with COVID-19 infections (outpatients, hospitalized patients and critically ill COVID-19 survivors) and their family caregivers.

### Primary Objective / Hypothesis

Our overall objective is to determine short- and longer-term (1, 3, 6 and 12, months post-acute hospital discharge or diagnosis for outpatients) outcomes in patients and their caregivers (inpatient population only), and the clinical, sociodemographic, genetic/transcriptomic/epigenomic/ immunological /serological / inflammatory / coagulation predictors of these outcomes.

Our overall hypothesis is that clinical risk factors (including but not limited to age, baseline health, sociodemographic status, comorbid illness and candidate genetic/transcriptomic/epigenomic/ immunological / serological / inflammatory / coagulation risk factors) are determinants of short- and long-term outcomes in patients with COVID-19 infections.

### Project #1 (P1): Genetic Profiling

Specific Objective: To identify host genetic variation associated with severe disease among outpatient and hospitalized patients with COVID-19, with particular emphasis on genes used for viral entry of the host. We will also conduct viral genome sequencing and T/B cell receptor sequencing to understand adaptive immune response.

**Project #2 (P2):** The transcriptomic, epigenomic, immunological, serological, inflammatory and coagulation host response to COVID-19

Specific Objective: To profile the transcriptomic and epigenomic response of the host to COVID-19 in infected individuals. In addition we are developing a biomarker assay for clinicians to predict risk for poor outcome and enable rapid selection of targeted therapies.

**Project #3 (P3A - outpatient + P3B - inpatient):** Sociodemographic and Clinical Profile on Short and long-term outcomes of COVID-19 outpatients and patients admitted to the general internal medical wards of participating institutions. Specific Objective: To identify the sociodemographic and clinical risk factors that are associated with poor short-term outcomes.

**Project #4 (P4):** 1, 2 and 3-Year Clinical, Functional, Mental Health and Quality of Life, Healthcare Utilization Outcomes for COVID-19 Survivors and Caregivers (in patient only). Specific Objectives: (1) To characterize physical, functional, neuropsychological, HRQoL, pattern and cost of health care utilization outcomes in COVID-19 survivors and family caregivers to 1, 2 and 3-years after hospital/ICU discharge or diagnosis (for outpatients). (2) To identify clinical risk factors and their association with 1, 2 and 3-year outcomes. These same outcomes apply to outpatients (no caregiver cohort) with follow up to 12, 24 and 36 months.

**Project #5 (P5):** Using AI to better understand prognosis and predictors of poor outcomes in hospitalized and non-hospitalized patients with COVID-19 infections. Specific Objectives: To develop prediction models for short-term and long-term outcomes in patients with COVID-19.

### Endpoints of the study

The Canadian COVID-19 Prospective Cohort Study will be the first Canadian study to identify 1, 2 and 3-year outcomes of patients with COVID-19 infections across the spectrum of illness severity (outpatients, hospitalized and critically ill inpatients infected with COVID-19) and their family caregivers.

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### 1.0 General Information

#### 1.1 The Canadian COVID-19 Prospective Cohort Study

#### 1.2 INVESTIGATORS (CO-LEADS PIS)

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Additional co-investigators are listed in Appendix.

### 2.0 Background Information

In December 2019, a novel coronavirus (COVID-19) was identified in Wuhan, China and is the current global pandemic<sup>1</sup>. The clinical course of COVID-19 varies: some are asymptomatic while others are acutely ill and need hospitalization. Some are able to clear the virus while others progress to ARDS and require mechanical ventilation (MV). Current data suggests that 80-85% of those infected have mild symptoms and are not hospitalized. Of those hospitalized, 60-80% will be discharged from hospital and 20-40% may need ICU care and ventilator support (approximately 4-6% of all COVID-19 positive patients). Short- and long-term outcomes are unknown for patients and caregivers and are crucial to inform large-scale public health planning and clinical care.

Our group has contributed foundational ICU outcomes work from our 5-year ARDS<sup>2,3</sup>, 1-year SARS<sup>4</sup> and RECOVER<sup>5,6</sup> programs. Each shows similar outcomes for patients including: neuromuscular/ neurocognitive dysfunction, mood disorders and diverse medical problems contributing to complex disability and significant healthcare use. Family caregivers are traumatized and suffer severe mood disorders. This program of research will be built on existing **GEMINI (General Medicine INpatient Initiative)** and **RECOVER Program (REhabilitation and ReCOVEry for survivors of critical illness and their family caregivers)** platforms which will provide the scaffolding for the clinical, basic and translational research projects as outlined.

#### 2.1 OUTCOMES OF INDIVIDUALS INFECTED WITH COVID-19

##### **2.1.1 Non-hospitalized COVID-19 Patients**

Although there have been some early reports of various symptoms and outcomes that are associated with COVID-19 infections, there is no systematic capture of non-hospitalized patients to determine the spectrum and duration of symptoms associated with COVID-19 infections and the factors that predict hospitalization compared to symptom free recovery.

### 2.1.2 Hospitalized non-ICU COVID-19 Patients

COVID-19 may lead to acute illness that warrants hospital and ICU admission. The most common acute illness is COVID-19 associated pneumonia. However, there have been many other presentations, including those of congestive heart failure, myocarditis, diarrhea, venous thromboembolism, stroke, acute kidney insufficiency, macrophage activation syndrome, which contributed to the need for acute hospitalization. Most of these patients are hospitalized under General Internal Medicine (GIM) wards in acute care hospitals. Determinants of factors that are associated with poor outcomes (defined as death or requiring mechanical ventilation / ICU care) are unknown.

### 2.1.3 Hospitalized ICU COVID-19 Survivors

A minority of patients with COVID-19-related pneumonia progress to develop hypoxemic respiratory failure requiring admission to an ICU and mechanical ventilation (MV). Early data suggest that these patients will require one or more weeks of MV because of complicating severe lung injury (the Acute Respiratory Distress Syndrome (ARDS))<sup>1,2</sup> which may be associated with multiple organ dysfunction and important long-term morbidity. Even though this group of patients is more modest in absolute numbers, they are the most resource intensive and will sustain the greatest disability following their COVID-related illness. Currently, long-term outcome data on critically ill COVID patients and their caregivers are unknown. No detailed in-person follow-up or comprehensive characterization of the functional outcomes, rehabilitative or healthcare needs of this COVID-affected group has been performed. Outcomes data from other long-term critically ill patient groups may be very helpful to inform possible COVID-19-related long-term morbidity.

To date, the most comprehensively studied population of ICU patients requiring prolonged MV are those with ARDS. These data may be particularly informative for COVID-19 outcomes since this novel pneumonia is often complicated by ARDS leading to ICU admission and treatment. The Toronto ARDS Outcomes group has contributed significantly to the understanding of detailed outcomes in these patients to 5 years after their ICU stay<sup>8-10</sup>. Patients with severe ARDS associated with a wide variety of risk factors and co-existing co-morbidities share common long-term disabilities. These include muscle wasting and weakness and a spectrum of mental health and neuropsychological issues and other medical morbidities. Muscle wasting and weakness result in a decrease in exercise capacity, a decrement in physical functioning reported on Health-related Quality of Life (HRQoL) measures and persisting to 5 years after ICU discharge<sup>8</sup>. Pulmonary function in surviving patients is normal to near normal. Results indicate that age greater than fifty years is associated with a poor ability to recover physical HRQoL compared to younger patients. As well, this physical dysfunction influences cost accrued after hospitalization. Accordingly, the average cost for an ARDS patient to 2 years including their ICU stay was \$157,210 and the post-hospital costs were driven by hospital readmission and the need for inpatient rehabilitation to address weakness and functional disability<sup>10</sup>. Both patients and family caregivers suffer from important mood disorders and these are often the reason for hospital re-admission, often years after the index ICU stay<sup>11-15</sup>. The Toronto ARDS outcomes data are typical of other international ARDS outcomes studies which recruited younger patients with a median age between 40 and 50 years, and few associated comorbidities<sup>12</sup>.

Our RECOVER Program is a multi-phase, ongoing CIHR-funded Canadian multi-centre program to establish a continuum of care after critical illness for patients and families. RECOVER (Phase I) (2009-14) contributed a comprehensive description of physical and neuropsychological morbidity sustained by all

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medical and surgical patients after 7 or more days of MV and parallel impacts on their families and was published in the New England Journal of Medicine (NEJM)<sup>13</sup> and American Journal of Respiratory and Critical Care Medicine (AJRCCM)<sup>14</sup>. Disability at 7 days after ICU discharge determined one-year functional recovery trajectories, need for renal replacement therapy, hospital and ICU readmission, disposition and mortality. One year after ICU discharge, 20% of patients had moderate to severe depressive symptoms, and 25% reported symptoms of post-traumatic stress disorder. The current provincial RECOVER network partners will participate in the **CANCOV** study.

It is likely that ICU survivors of COVID-19 share many of these same sequelae as outlined above, but specific outcomes from COVID-19 remain to be determined.

#### 2.1.4 COVID-19 Family Caregivers

Outcomes of family caregivers of COVID-19 survivors are unknown, but may be informed by studies on ARDS caregivers which noted that depressed mood in ARDS survivors was an important contributor to caregiver depression.<sup>11</sup> In the stroke and elderly care-giving literature, caregivers who struggled in their care-giving role may contribute to poor rehabilitation outcomes for survivors<sup>15</sup> or threaten the sustainability of care at home.<sup>16,17</sup>

Recent research suggests that 57% of ICU survivors who received long-term MV still required the assistance of a family caregiver one year after their critical illness<sup>18</sup>. Existing evidence suggests that providing such care may have a negative impact on caregivers, including poor health-related quality of life compared with age- and sex-matched persons<sup>11</sup>, post-traumatic stress disorder<sup>19</sup>, emotional distress<sup>11,20-22</sup>, burden<sup>23</sup>, depression<sup>24</sup>, and anxiety<sup>25</sup>.

In a review of this small ICU caregiving literature, Johnson<sup>26</sup> concluded that caregivers experience more burden due to the patient's physical and psychological impairment, and managing complex technology in the home. Other aspects of the care-giving situation that contribute to poor caregiver health outcomes include lifestyle disruption due to their care-giving role<sup>11,22</sup> and provision of high levels of care<sup>11</sup> and long-term consequences for ICU survivor health<sup>10</sup>.

Findings from our completed RECOVER I multi-centre caregiver cohort<sup>27</sup> (n=180) showed that caregivers had prevalent mood disorders and almost 20% had persistent moderate to severe depressive symptoms at one year after ICU discharge of their loved ones and that mental health outcomes were related to caregiver mastery and intrinsic caregiving characteristics.<sup>27</sup> It is likely that caregivers of COVID-19 ICU survivors share many of these same sequelae as outlined above, but their specific outcomes remain to be determined.

**The CANCOV Study will provide the first, comprehensive characterization of one, two and three-year outcomes in caregivers of critically ill survivors of COVID-19. This large sample of caregivers will provide a detailed characterization of mental health outcomes and inform caregiver needs for future pandemics. This program of research will be built on existing GEMINI and RECOVER Program platforms which will provide the scaffolding for the clinical project as outlined.**

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### 2.2. RATIONALE FOR THE STUDY

There are many descriptive, mostly case-series, reports of outcomes after COVID-19 infection and their short-term sequelae but longer-term data in a spectrum of patients (from mild outpatient, to moderate GIM ward patients, to severe ICU patients) and family caregivers are lacking.

In this study, we are exploring the clinical, sociodemographic, multi-omic predictors of severity of illness in COVID-19 patient outcomes. By leveraging expertise from investigators across disciplines and divisions, we have constructed a suite of complementary projects that explore the genetic, transcriptomic, epigenomic and immunologic evaluation of COVID-19 infection across the illness and recovery trajectory during the acute illness and in the context of multidimensional long-term outcomes. We will utilize electronic data through the GEMINI network, and explore AI analyses and possible linkages to ICES data. Our proposed project will contribute new knowledge to outcomes in patients with COVID-19 infections and will inform large-scale public health planning, clinical care, and ongoing resource needs.

Our proposed CANCOV project will contribute new knowledge to outcomes in patients throughout the spectrum of severity with COVID-19 and their family caregivers, and will inform large-scale public health planning, clinical care, and ongoing resource needs for pandemic survivors.

### 2.3 SUMMARY OF THE KNOWN AND POTENTIAL RISKS

This observational study has minimal risks associated with it. As much information as possible will be collected from patient charts, electronic patient systems, etc. to limit the disturbance to the patient and family. As the patient population under investigation have been given a positive diagnosis for COVID-19 at some point, we will make every effort to minimize staff exposure to these patients while they are infectious, and limit use of PPE for research purposes.

All institutions will be following provincial COVID-19 guidelines for all patient visits. In-person visits will be deferred while patients are infectious. Follow-up in-person visits will be done after patients are deemed free from infection and allowed out of quarantine.

In addition, the CANCOV research team is part of a Canada wide government funded national initiative looking to understand the consequences of COVID-19 and the predictors of those outcomes. The CANCOV database may be shared with national and international research partners and may be entered into other national and international databases. This information may be used by academic researchers and commercial partners in Canada and around the world. It is possible that shared study data may be stored on centralized servers including outside the province of collection, and on cloud servers. Access to CANCOV data will be controlled by the CANCOV research investigators and the CANCOV Data Access and Publication (DAP) committee and will only be given to applicants who have obtained approval from a research ethics board and who have signed data/material transfer agreements and/or contracts with the lead institute (UHN). **The information provided to them will not include any personal identifying or health information, and there is minimal risk of identification.**

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**NON-HOSPITALIZED COHORT:** While patients are infectious and are in self-quarantine all study interaction will be done virtually or by phone. Once patients are no longer infectious, and cleared by their healthcare team, we are planning to have some/all follow up visits in person, or if not possible, then done virtually or by phone. This will depend on how the COVID-19 pandemic will evolve, how hospital policies evolve in the face of this pandemic, the availability of PPE for research staff/patients etc.

**HOSPITALIZED NON-ICU COHORT:** In order to protect research staff, only limited interactions with inpatient study participants will be done in person. At most hospitals in Ontario and other provinces, there will be one study coordinator appointed by each institution to organize all COVID-19 related studies at their site. This person will identify patients, introduce the study and obtain informed consent. Inpatients who are well enough to provide information while in hospital will be surveyed by study staff (over the phone/computer, via iPads etc), using MS Teams, OTN, or other video conferencing technology. The CANCOV study is utilizing REDCap (Research Electronic Data Capture) for data collection. De-identified REDCap forms can be emailed to participants for them to complete on any electronic device. If patients have their own electronic device, then this may be used for study communication. If they do not have their own electronic device, they will be offered the use of a study specific tablet for data entry. Each device will be disinfected following manufacturers best practice guidelines ([https://support.apple.com/en-us/HT204172?mod=article\\_inline](https://support.apple.com/en-us/HT204172?mod=article_inline)).

**HOSPITALIZED ICU COHORT:** Patients discharged from ICU and who have capacity will be interviewed by the RECOVER program or other CANCOV study personnel (by phone/computer, etc) and, if capable, will use an iPad for direct data entry, similar to the non-ICU cohort.

#### **ALL PATIENT COHORTS:**

Current best available evidence suggests that COVID-19 is not transmissible after approximately 8 days after symptom onset. Thus far, there have not been documented transmission events of COVID-19 from individuals 14 days or more after symptom onset. However, this period has not been specifically studied among patients who are immunocompromised who may theoretically be at risk for prolonged transmission, so we will require that type of patient has clinical resolution of COVID-19 disease for 14 days prior to in-person visit.

Current guidance therefore recommends only that a period of 10-21 days elapses from symptom onset, depending on local recommendations, before a patient can be cleared from COVID-19 precautions. The guidance also allows hospital to use discretion on which patients should require repeat testing for the purposes of clearance.

Patients who meet criteria for clearance will not require any additional precautions whatsoever. In general, study participants will be at least 1 month post-discharge or initial positive test before we are seeing them in person. In addition, healthcare providers will use PPE when seeing these patients.

Drawing blood from the arm may cause pain, bruising, lightheadedness, and, rarely, infection. All attempts will be made to draw research bloods at the same time as clinical samples, to limit exposure of staff to the patient and limit patient participant discomfort. Blood collected from inpatients with active virus will only be collected by trained staff with proper use of PPE, following strict COVID-19 specific protocols.

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Blood samples will only be handled by trained staff in laboratories that are certified to handle viral exposure safely. Each site will have a site specific protocol in place to match clinical best practice. Study specific blood collection will adhere to each site's established COVID-19 protocols. For example, at UHN, the PRESERVE study (COVID-19 biobank) is collecting bloods on inpatients at UHN and we have arranged to use those samples rather than draw new samples.

Blood samples will be requested from outpatients and discharged patients only when safe to do so, once clinical staff deem them free from infection and permitted to leave their home. Non-hospitalized participants required to attend a participating centre for clinical care during their infectious period, will have blood drawn for the study, if the centre has adequate precaution in place. Alternatively, a LifeLabs or other community lab (based on province) home visit may be arranged.

As part of the **CANCOV** follow up program, patients who are capable will also be asked to perform breathing, walking and muscle strength testing. Each of these may cause fatigue. Follow up clinics will be located within participating centres. Patients will be seen in follow up clinics once they are no longer infectious. We have conducted similar in-person follow-up visits with our SARS cohort.

**CAREGIVER COHORT:** There are no important risks to participating in this study. However, the interview and questionnaires/surveys may remind family caregivers of some upsetting times during their family member's illness with COVID-19.

#### **2.4 SUMMARY OF THE KNOWN AND POTENTIAL BENEFITS**

**ALL PATIENT COHORTS:** Patient participants will be provided extended follow up and any additional medical support required. Participation in this study will allow COVID-19 patients to have very close medical follow-up (especially those critically ill patients after ICU discharge who have a greater likelihood of complex illness and disability) and will keep them informed on their pulmonary, physical and neuropsychological recovery. Patients will have access to all information, a consult note will be dictated to their family physician and any additional needed specialty referrals will be facilitated. Additionally, participation in this study can also identify patients' ability to generate and maintain viral neutralizing antibodies.

**CAREGIVER COHORT:** The study will foster a better understanding of the impact of the caregiving situation for COVID-19 on caregiver health and well-being. Any caregiver medical concerns will also be facilitated through the one-year follow-up period.

#### **2.5 DESCRIPTION OF THE POPULATION TO BE STUDIED**

**1. NON-HOSPITALIZED COHORT:** Individuals who are community dwelling, over the age of 16, are COVID-19+ and never hospitalized for their COVID-19 infection are included. These individuals may be diagnosed by participating hospital emergency rooms / in-person assessment centres / virtual clinics. In addition, we will include individuals who were diagnosed from January 25, 2020. Recruitment will be multipronged, including sending patients invitation letters from circle of care clinicians, advertising in social media, websites, and posters, etc.

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**2. HOSPITALIZED NON-ICU COHORT:** COVID-19+ patients over age 16 admitted to acute care hospitals, GIM wards of participating hospitals will be invited to participate. Patients who were hospitalized prior to study start up (from January 25, 2020 to study start up) will be invited to participate in this study. Site investigators or physicians in the circle of care will send a letter to their discharged patients letting them know about the CANCOV study.

**3. HOSPITALIZED ICU COHORT:** COVID-19+ patients over age 16 who are critically ill and admitted to an ICU and/or required MV in participating hospitals will be invited to participate. Patients who were hospitalized prior to study start up will be invited to participate in CANCOV. Site investigators or physicians in the circle of care will send a letter to their discharged patients letting them know about the CANCOV study.

**4. CAREGIVER COHORT:** Up to 500 family caregivers of patients admitted to the GIM wards and ICUs of participating hospitals will be invited to participate.

### 2.6 STATEMENT OF COMPLIANCE WITH ICH GCP REGULATORY REQUIREMENTS

This study will be conducted in compliance with the protocol, ICH GCP and the applicable institutional regulatory requirements.

## 3.0 Study Objectives and Hypothesis

### 3.1 DETAILED DESCRIPTION OF THE OBJECTIVES AND THE PURPOSE OF THE STUDY

The **CANCOV** study will be the first Canadian study to provide a comprehensive evaluation of early and 1, 2 and 3-year outcomes of outpatient and hospitalized COVID-19 survivors and their family caregivers, their varied trajectories and associated clinical risk factors. Our **overall objectives** are to determine short- (in hospital) and longer-term (1, 3, 6 and 12, 18, 24, 30 and 36 months post-acute hospital discharge) outcomes COVID-19+ patients across the spectrum of symptom severity, including outpatients and inpatients from GIM and ICU wards and their caregivers, and the clinical, sociodemographic, multi-omic predictors of these outcomes. By leveraging expertise from investigators across disciplines and divisions, we have constructed a suite of complementary projects that explore the genetic, transcriptomic, epigenomic and immunologic evaluation of COVID-19 infection across the illness and recovery trajectory during the acute illness and in the context of multidimensional long-term outcomes.

#### **3.1.1 Primary objectives**

Our overall objectives are to determine short- (in hospital for hospitalized patients and 2-week outcome for non-hospitalized patients) and longer-term (1, 3, 6 and 12, 18, 24, 30 and 36 months post-acute hospital discharge/diagnosis) outcomes in patients and their caregivers, and the clinical, sociodemographic, genetic/ transcriptomic/epigenomic /immunological predictors of these outcomes. We have created a complimentary suite of studies:

#### ***Project #1 (P1): Genetic Profiling***

Specific Objectives: a) To identify host genetic variation associated with severity of disease among outpatients and hospitalized patients with COVID-19, with particular emphasis on genes used for viral

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entry of the host (ACE2 pathway), b) to determine impact of different viral strains on antibody response and patient outcomes, and c) To sequence T/B cell receptors at baseline, 6, 12, 24, and 36 months and correlate findings with serological data, clinical data, genomic data and viral strain.

#### ***Project #2 (P2): The epigenomic, transcriptomic, immunological, serological, inflammatory and coagulation host response to COVID-19***

Specific Objective: To profile the transcriptomic and epigenomic response of the host to COVID-19 in infected individuals. In addition, we will explore immunological, serological, inflammatory and coagulation responses of the host to COVID-19 virus. We will assess the antibody response (isotype, titer, antigen target and viral neutralization) across time and correlate these with genetic variation, viral strain and patient outcomes.

#### ***Project #3A (P3): Long term (12-36-month Outcomes of COVID19 Positive Patients Isolated at Home in the Community***

Specific Objectives: To identify the sociodemographic and clinical risk factors that are associated with recovery, hospitalization or death, and to investigate whether patients diagnosed with COVID-19 have associated stigma. Specific Methods: Patients who were discharged from Emergency Room, COVID-19 assessment centres and/or COVID virtual clinics will be recruited for this cohort. Consent and data collection will occur over the phone or via a virtual visit. Data collection for Projects 3, 4, and 5 are harmonized to provide a comprehensive understanding of the spectrum of disease severity.

#### ***Project #3B (P3): Sociodemographic and Clinical Profile on Short-term Outcomes of Patients Hospitalized in Acute Care Hospitals***

Specific Objective: To identify the sociodemographic and clinical risk factors that are associated with poor short-term outcomes.

#### ***Project #4 (P4): 1, 2, and 3-Year Clinical, Functional, Mental Health and Quality of Life, Healthcare Utilization Outcomes for COVID-19 Survivors and Caregivers***

Specific Objectives: (1) To characterize physical, functional, neuropsychological, HRQoL, pattern and cost of health care utilization outcomes in COVID-19 survivors and family caregivers up to 3-years after hospital/ICU discharge (2) To identify clinical risk factors and their association with 1-year, 2-year and 3-year outcomes.

#### ***Project #5 (P5): Using AI to better understand prognosis and predictors of poor outcomes in hospitalized and non-hospitalized patients with COVID-19 infections***

Specific Objectives: To develop prediction models for short-term and long-term outcomes in patients with COVID-19.

### **3.2 STUDY HYPOTHESIS**

Our overall hypothesis is that clinical risk factors (including but not limited to age, baseline health, socio-demographic status, comorbid illness and candidate genetic/transcriptomic/epigenomic/immunological risk factors) are determinants of short- and long-term outcomes in patients with COVID-19.

## 4.0 Study Design

This is a prospective national multi-centre one to three-year follow-up study of COVID-19 patients involving academic and community acute care hospitals, as well as assessment centres and virtual clinics in Ontario, Quebec, Alberta, British Columbia, Nova Scotia and New Brunswick:

- University of Toronto affiliated hospitals: University Health Network-UHN (Toronto General and Toronto Western Hospitals), Mount Sinai Hospital, St. Michael's Hospital, and the Sunnybrook Health Sciences Centre
- Toronto Rehab Hospitals: Toronto Rehabilitation Institute (TRI) and Toronto Grace Health Centre (TGHC)
- Community Hospitals: Trillium Health Partners (Mississauga Hospital and Credit Valley Hospital), Markham Stouffville Hospital, and William Osler Health System; Niagara Health Regional Campus (CCIRNet), Baycrest Health Sciences, and Mackenzie Health
- Other Ontario Hospitals: St Joseph's Healthcare - Hamilton McMaster; University; London Health Sciences Centre - Western University; Kingston General Hospital - Queen's University; The Ottawa Hospital - University of Ottawa.
- Quebec: McGill University Hospitals
- Nova Scotia: Halifax and Dartmouth Health Centres
- Alberta: Alberta Health Hospitals
- British Columbia: University of British Columbia Hospitals

COVID-19 patients across the spectrum of disease severity will be followed in three distinct cohorts:

**1. NON-HOSPITALIZED COHORT** – patients who are well enough to self-isolate at home will be enrolled as soon as possible after diagnosis and followed for 12-36 months after the start of symptoms or first positive test (whichever is earlier). Dr. Cheung will coordinate with other site PIs and co-Is to follow these patients and will see patients at the 1 month, 3 month, 6 and 12 months either in person or virtually.

**2. HOSPITALIZED NON-ICU COHORT** – patients who are hospitalized in participating acute care hospitals will be enrolled as soon as possible after admission and followed for 1 to 3 years post hospital discharge. A parallel cohort of their family caregivers will also be recruited. Dr. Cheung will work with Drs. Rawal, Abdelhalim, MacMillan, Chan, Tang and an expanding team of investigators to follow these patients via virtual care and at participating centres.

**3. HOSPITALIZED ICU COHORT** – patients who are admitted to ICUs at participating hospitals will be followed for 1 to 3 years post-ICU discharge. A parallel cohort of their family caregivers will also be recruited. Patients enrolled at UHN hospitals (Toronto General and Toronto Western Hospitals) and St Michael's Hospital will transfer directly to collaborating rehab hospitals (TGHC/TRI) for inpatient rehabilitation and follow with the RECOVER Program. Outcome variables will be collected at each time point. Dr. Herridge will follow all patients from teaching and community Toronto hospitals with assistance from other site PIs and critical care fellows. Dr. Meggison and Dr. Rudkowski will follow subjects from Ottawa and Hamilton, respectively. Dr. Slessarev, Honarmand, Bosma will follow London patients:caregivers and Dr. Boyd will follow those from Kingston. Dr. Tsang will perform follow-up in Niagara.

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We will be recruiting COVID-19 patients who were diagnosed on or after January 25, 2020 into this study on a competitive recruitment basis. As such, access to hospital data will be requested from patients who were discharged from the hospital.

We are exploring the outcomes for COVID-19 patients across the spectrum of illness severity, from mild (outpatient), to moderate (GIM ward patients) to severe (ICU patients). We anticipate that enrolled patients may move between groups as symptoms increase in severity (e.g. outpatients may have to be hospitalized or GIM patients may require ICU admission). Therefore, patient group allocation will be determined by **their most severe symptoms**. In light of this, a GIM patient who is moved to the ICU, will be followed via the ICU arm of the study, even though they may return to GIM through their recovery. Similarly, if an outpatient participant is hospitalized, they will be followed according to the hospitalized non-ICU inpatient pathway.

### 4.1. DATA COLLECTION SCHEDULE AND METHODS

There are three distinct pathways for data collection with less intense data collection for those patients with milder symptoms. However, there are similar components being collected at similar time points so that measures can be compared across the continuum of the spectrum of illness severity.

We will maximize data collection from patient charts, electronic patient systems, etc. to limit disruption to the patient and family. We will use virtual study visits (e.g. via Microsoft Teams, Ontario Telehealth, Other provincial secure healthcare platforms) using tablets, email, and computer/mobile app communication where possible.

Left-over blood samples from clinical collection at baseline will be requested from participating hospitals. Nasopharyngeal, oral, and nasal swabs collected clinically will be tracked so that viral genome sequencing results can be connected to data in CANCOV.

Hospitalized patients (those who are well enough and have capacity, mainly those on GIM wards) will be given a study specific tablet (iPAD®), if available. The tablet will be encased in a protective single use bag before patients will have access, and will be used by the patient throughout their stay. Healthcare providers will deliver the study tablet to the patient during their scheduled care so that no extra personal protective equipment will be used. Once the study patient has completed their use of the tablet, it will be decontaminated based on currently available information from the manufacturer (e.g. [https://support.apple.com/en-us/HT204172?mod=article\\_inline](https://support.apple.com/en-us/HT204172?mod=article_inline)) or other safety information.

If the tablet (iPAD) is not available, or the patient is too disabled to use the tablet, or if the patient prefers, an in-person or over the phone/computer/etc. virtual interview with study staff will be done to complete baseline information.

Follow up information will be collected at follow up clinic visits according to study schedule. We will ask participants to use study tablets (iPAD) to directly enter data into the study database. If not available, paper forms will be used.

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For patients unable to attend clinic (e.g. limited access to hospitals/clinics, patient is not well enough to travel, etc), we will conduct visits over the phone, or using Ontario Telehealth, other provincial telehealth systems, or secure Microsoft Teams video visits. If patients have access to a device, then they will have the option of complete surveys on line using a secure link. If none of these options is feasible for the patient, then the team will offer a home visit as we have done in prior studies.<sup>13,14</sup> Home visits will only be done once patients are no longer infectious and for patients who are not well enough to travel due to extended illness (most likely ICU survivors but may include others who have been significantly disabled due to COVID-19).

Caregivers will be provided a link to secure fillable study related forms/questionnaires. They will have the option to complete forms (paper or electronic) in person if they are attending the follow up visits with the patient or via phone/virtual meeting using UHN Microsoft Teams, etc., or by mail with a prepaid return envelope.

Discharged patients who are recruited after their hospital discharge will follow their respective timeline for data collection, depending on whether they were hospitalized on a GIM ward or ICU setting. We anticipate that discharged patients who have been instructed to continue self-isolating will NOT leave their homes. Blood samples will be requested from discharged patients only when safe to do so, once they are deemed free from infection and allowed to leave their home by clinical staff. For patients who enter the study at their 6 month post-diagnosis time point or later, an extra study visit may be conducted at the 8-9 month time-point.

We will offer an optional extension in study participation, with visits at 18, 24, 30 and 36 months, and other clinically warranted time points as required. Extension data/sample collection will mirror collection at visits up to 12 months.

#### **4.1.1 Non-Hospitalized Cohort:**

Patients who have been diagnosed with COVID-19+ with no or mild symptoms, and asked to self-isolate at home will be followed up to 36 months and will have study visits (either virtual or in person when possible) at 1, 3, 6 and 12 months plus optional extension time points at 18, 24, 30, and 36 months.

We anticipate that outpatients who are self-isolating will NOT leave their homes. Blood samples will be requested from outpatients only when safe to do so, once they are deemed free from infection and allowed to leave their home by clinical staff – usually at the 1-month time point. If study patients are being consented at an institution that is able to collect these samples safely, then samples at consent will also be collected. Similarly, if these patients must attend a centre for clinical care, and the centre is able to safely collect samples at 1-2 weeks post diagnosis, we will request an additional sample (no clinic visits solely for research purposes will be done while patients are infectious). In addition, LifeLabs or other community lab services in other provinces are able to safely provide home visits to infectious patients and collect de-identified research samples. This will be assessed on a site specific basis.

If an outpatient participant requires hospitalization for their COVID-19 symptoms, they will be moved to the GIM or ICU arm, depending on admission ward, and complete the study follow up as per the new study arm.

Figure 4.1.1 CANCOV Data Collection Schedule for **NON-HOSPITALIZED COHORT**

Data Collected COVID19+ PATIENT	Collection Time Points#									
	* First Contact After Diagnosis	*7 days	1 month	*3 months	*6 months	*12 months	*18 months	*24 months	*30 months	*36 months
<b>CONSENT PROCESS</b>										
Patient Eligibility Checklist	X									
CAM/ Capacity Assessment	X									
Informed consent documentation	X									
<b>GENERAL INFO</b>										
Site & Contact Info	X									
Study Visit	X	X	X	X	X	X	X	X	X	X
Patient Profile	X									
Sociodemographics	X Form PR-1		X Form PR-1a	X Form PR-1a	X Form PR-1a	X Form PR-1a	X Form PR-1a	X Form PR-1a	X Form PR-1a	X Form PR-1a
Burden of comorbid illness & Complications Medications Primary Daily Activity & Work status	X (ask re: prior to current illness)		X	X	X	X	X	X	X	X
<b>SYMPTOMS/FUNCTIONAL/QUALITY OF LIFE/ MENTAL HEALTH</b>										
Symptom checklist Borg Dyspnea scale	X	X	X	X	X	X	X	X	X	X
<ul style="list-style-type: none"> <li>• The Simple “FRAIL” Questionnaire</li> <li>• SARC-F Screen for Sarcopenia</li> <li>• Simplified Nutritional Assessment Questionnaire (SNAQ)</li> <li>• RAND 36-Item Short Form Health Survey 1.0 (SF-36 v1)</li> <li>• CD Resilience Scale (CD-RISC-2item)</li> </ul>	X (ask re: prior to current illness)		X	X	X	X	X	X	X	X
<ul style="list-style-type: none"> <li>• Reintegration to Normal Living Index</li> <li>• Stigma Scale</li> </ul>			X	X	X	X	X	X	X	X
<b>PHYSICAL MEASURES</b>										
<ul style="list-style-type: none"> <li>• Physical Exam</li> <li>• Six Minute Walking Test (6MWT) with Oximetry</li> <li>• MRC Score for Muscle Strength</li> </ul>			X		(X)	(X)	(X)	(X)	(X)	(X)
Pulmonary Function Test (PFT) If clinically warranted only			(X)		(X)	(X)	(X)	(X)	(X)	(X)
<ul style="list-style-type: none"> <li>• Acute Functional Independent Measure (Acute-FIM)</li> <li>• Clinical Frailty Scale (CFS)</li> <li>• Rapid Cognitive Screen</li> </ul>		X	X		X	X	X	X	X	X
<b>HEALTHCARE USE</b>										
<ul style="list-style-type: none"> <li>• Complementary medicine usage (CMU)</li> <li>• Health Care Utilization (HCU)</li> </ul>	X (ask re past 1 year)	X	X		X	X	X	X	X	X
<b>BLOOD WORK</b>										
Serum / Plasma / DNA/ RNA / (PBMCs) (Total of ~35-45ml, ~2-3 tablespoons)	(X)†	(X)†	X	X	X	X	X	X	X	X
Study Discharge Form (incl. mortality)	X	X	X	X	X	X	X	X	X	X

# Data/sample collection time points are counted from day of first symptoms or day of initial positive test, whichever is earlier.

\*Visits may be conducted by phone or video interview/email/mail if participant unable to attend hospital.

†Samples will be collected only if patient is attending a participating centre for clinical care or by LifeLabs home visit.

Items in **BLUE** are administered by RA using CRFs.

Items in **RED** are direct patient/caregivers facing questionnaires/surveys.

Items in **PURPLE** can be for participants to fill out directly or administered/ filled out by RA.

NOTE: Bracketed items indicate visits that may take place, depending on patient’s symptoms.

NOTE: Other visit time points may be done for clinical purposes or for additional sample collection.

#### 4.1.2 Hospitalized Non-ICU Cohort:

All patients will undergo standardized data collection while in the hospital (baseline – discharge) (via chart abstraction and linkage to electronic patient records data dump through GEMINI in order to limit the burden to admitted patients) and post discharge (1, 3, 6 and 12 months post discharge). **Patients who have been discharged** prior to study start up from participating centres will be approached for study participation. Follow up will occur from baseline (date of consent) to 12 months post hospital discharge plus optional extension time points at 18, 24, 30, and 36 months.

Figure 4.1.2.1 CANCOV Data Collection Schedule for HOSPITALIZED NON-ICU COHORT

Data Collected COVID19+ PATIENT	Collection Time Points to 3 years post-hospital discharge									
	In Hospital		Follow up (post discharge)							
	Admission	7 days post admission/ discharge (whichever 1st)	1 month	3 months	6 months	12 months	18 months	24 months	30 months	36 months
<b>CONSENT PROCESS</b>										
Patient Eligibility Checklist	X									
CAM/ Capacity Assessment	X									
Informed consent documentation	X									
<b>GENERAL INFO</b>										
Site Info & Contact Info	X									
Study Visit	X	X	X	X	X	X	X	X	X	X
Patient Profile	X									
Sociodemographics	X Form PR-1		X Form PR-1a	X Form PR-1a	X Form PR-1a	X Form PR-1a	X Form PR-1a	X Form PR-1a	X Form PR-1a	X Form PR-1a
<ul style="list-style-type: none"> <li>Burden of comorbid illness &amp; Complications</li> <li>Medications</li> <li>Primary Daily Activity &amp; Work status</li> </ul>		X (prior to current illness)	X	X	X	X	X	X	X	X
<b>SYMPTOMS/FUNCTIONAL/QUALITY OF LIFE/ MENTAL HEALTH</b>										
<ul style="list-style-type: none"> <li>Symptom checklist</li> <li>Borg Dyspnea scale</li> </ul>	X	X	X	X	X	X	X	X	X	X
<ul style="list-style-type: none"> <li>The Simple "FRAIL" Questionnaire</li> <li>SARC-F Screen for Sarcopenia</li> <li>Simplified Nutritional Assessment Questionnaire (SNAQ)</li> <li>RAND 36-Item Short Form Health Survey 1.0 (SF-36v1)</li> <li>CD Resilience Scale (CD-RISC-2item)</li> </ul>		X (prior to current illness)	X	X	X	X	X	X	X	X
<ul style="list-style-type: none"> <li>Stigma Scale</li> <li>Reintegration to Normal Living Index (RNLI)</li> <li>Post-traumatic Stress Disorder Checklist-5 (PCL-5)</li> </ul>			X	X	X	X	X	X	X	X
Post discharge Questionnaire			X							
<b>PHYSICAL MEASURES (In person follow up only)</b>										
<ul style="list-style-type: none"> <li>Physical Exam</li> <li>Six Minute Walking Test (6MWT)</li> <li>MRC Score for Muscle Strength</li> </ul>			X	X	X	X	X	X	X	X
Pulmonary Function Test (PFT) If clinically indicated only			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
<ul style="list-style-type: none"> <li>Clinical Frailty Scale (CFS)</li> <li>Acute Functional Independent Measure (AcuteFIM)</li> <li>Rapid Cognitive Screen (RCS)</li> </ul>		X	X	X	X	X	X	X	X	X
<b>HEALTHCARE USE</b>										
<ul style="list-style-type: none"> <li>Complementary medicine usage (CMU)</li> <li>Health Care Utilization (HCU-1)</li> </ul>		X (year prior to admission)	X	X	X	X	X	X	X	X
Hospital Outcomes		X								
<b>BLOOD WORK</b>										
Serum / Plasma / DNA/ RNA / (PBMCs) (~ 35-45ml total, ~2-3 tablespoons )	X	X	X	X	X	X	X	X	X	X
Study Discharge Form (incl. mortality)	X	X	X	X	X	X	X	X	X	X

Visits may be conducted by phone or video interview/email/mail

Items in BLUE are administered by RA using CRFs.

Items in RED are direct patient/caregivers facing questionnaires/surveys.

Items in PURPLE can be for participants to fill out directly or administered/ filled out by RA.

NOTE: Bracketed items indicate visits that may take place, depending on patient's symptoms.

NOTE: Other visit time points may be done for clinical purposes or for additional sample collection.

A parallel cohort of family caregivers will be followed. Caregiver participants who's family member has agreed to the study extension will also be offered an optional extension period from 18-36 months.

**Figure 4.1.2.2 CANCOV Data Collection Schedule for CAREGIVER COHORT for HOSPITALIZED NON-ICU PATIENTS**

Data Collected COVID19+ CAREGIVER	Collection Time Points to 3 years after critical illness									
	In Hospital		Follow Up							
	Admission	Discharge	1 month	3 months	6 months	12 months	18 months	24 months	30 months	36 months
<b>CONSENT PROCESS</b>										
Caregiver Eligibility Checklist	X									
Informed consent documentation	X									
<b>Site Info &amp; Contact Info</b>	X									
Study Visit	X	X	X	X	X	X	X	X	X	X
Caregiver Profile	X									
Caregiving Questionnaire			X							
<b>Sociodemographics, Comorbidities, &amp; Medications</b>			X Pr-1	X PR-1a	X PR-1a	X PR-1a	X PR-1a	X PR-1a	X PR-1a	X PR-1a
<b>QUALITY OF LIFE / MENTAL HEALTH</b>										
<ul style="list-style-type: none"> <li>• RAND 36-Item Short Form Health Survey 1.0 (SF-36v1)</li> <li>• CD Resilience Risk Scale (CD-RISC-2item)</li> <li>• Post-traumatic Stress Disorder Checklist-5 (PCL-5)</li> <li>• Caregiver Assistance Scales (CAS)</li> <li>• Caregiving Impact Scale (CIS)</li> <li>• Personal Gain Scale</li> <li>• Pearlin's Alternative Mastery Scale</li> <li>• Medical Outcomes Study Social Support Scale (SS)</li> <li>• Complementary and Medicine/ Health Care Use (CMU)</li> </ul>		X	X	X	X	X	X	X	X	X
Study Discharge Form	X	X	X	X	X	X	X	X	X	X

Visits may be conducted by phone or video interview/email/mail

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NOTE: Other visit time points may be done for clinical purposes or for additional sample collection.

**4.1.3 Hospitalized ICU Cohort:**

Patients will undergo standardized follow-up at 7 days and 1, 3, 6, and 12 months after ICU discharge. **Patients who have been discharged** prior to study start up from participating centres will be approached for study participation. Follow up will occur from baseline (date of consent) to 12 months post hospital discharge, plus optional extension time points at 18, 24, 30, and 36 months.

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**Figure 4.1.3.1 The CANCOV Data Collection Schedule for HOSPITALIZED ICU COHORT (following the RECOVER program schedule)**

Data Collected COVID19+ PATIENT	Collection Time Points to 3 years after critical illness									
	In Hospital		Follow up (post ICU Discharge)							
	ICU Stay	7 days post ICU discharge	1 month	3 months	6 months	12 months	18 months	24 months	30 months	36 months
Patient Eligibility Checklist	X									
CAM/ Capacity Assessment	X	X	X	X						
Informed consent documentation	X	X	X	X						
<b>SITE INFO &amp; CONTACT INFORMATION</b>	X	X								
Study Visit	X	X	X	X	X	X	X	X	X	X
Patient Profile	X	X								
<b>SOCIODEMOGRAPHICS</b>	X Form PR-1	X Form PR-1	X Form PR-1a	X Form PR-1a	X Form PR-1a	X Form PR-1a	X Form PR-1a	X Form PR-1a	X Form PR-1a	X Form PR-1a
<b>ICU DATASET</b>										
<ul style="list-style-type: none"> <li>ICU Baseline Data Form</li> <li>Daily ICU Data Form</li> <li>Course During ICU Stay Form</li> <li>ICU Outcomes Form</li> <li>ICU Re-admission Form</li> </ul>	X									
<ul style="list-style-type: none"> <li>Burden of Comorbid Illness &amp; Complications</li> <li>Medications</li> <li>Primary Daily Activity &amp; Work Status</li> </ul>		X (ask prior to illness)	X	X	X	X	X	X	X	X
<b>SYMPTOMS /QUALITY OF LIFE / MENTAL HEALTH</b>										
<ul style="list-style-type: none"> <li>Symptom checklist</li> <li>Borg Dyspnea Scale</li> </ul>	X	X	X	X	X	X	X	X	X	X
<ul style="list-style-type: none"> <li>The Simple "FRAIL" Questionnaire</li> <li>SARC-F Screen for Sarcopenia</li> <li>Simplified Nutritional Assessment Questionnaire (SNAQ)</li> <li>RAND 36-Item Short Form Health Survey 1.0 (SF-36v1)</li> <li>CD Resilience Scale (CD-RISC)</li> <li>Stigma Scale (SS)</li> <li>Reintegration to Normal Living Index (RNLI)</li> <li>Post-traumatic Stress Disorder Checklist-5 (PCL-5)</li> <li>Patient Health Questionnaire-9 (PHQ-9)</li> <li>General Anxiety Disorder (GAD-7)</li> </ul>		X (except SS; RNLI)	X	X	X	X	X	X	X	X
Post Discharge Questionnaire			X							
<b>PHYSICAL/FUNCTIONAL MEASURES - ICU Survivors</b>										
<ul style="list-style-type: none"> <li>Physical Exam</li> <li>Six Minute Walking Test (6MWT) with Oximetry</li> <li>MRC Score for Muscle Strength</li> <li>Clinical Frailty Scale (CFS)</li> <li>Functional Independence Measure (FIM)</li> <li>Rapid Cognitive Screen (RCS)</li> </ul>		X	X	X	X	X	X	X	X	X
Pulmonary Function Test (PFT)			X	X	X	X	X	X	X	X
<b>HEALTHCARE USE (costs/resources)</b>										
Health Care Utilization		X (past 1 yr)	X	X	X	X	X	X	X	X
Hospital Outcomes			X	X	X	X	X	X	X	X
<b>BLOOD WORK</b>										
Genetic Markers/Serum Collection Epigenomics / Transcriptomics	X (Day 1,3,7)	X	X	X	X	X	X	X	X	X
Study Discharge Form (incl. mortality)	X	X	X	X	X	X	X	X	X	X

Visits may be conducted by phone or video interview/email/mail

Items in BLUE are administered by RA using CRFs, Items in RED are direct patient/caregivers facing questionnaires/surveys.

Items in PURPLE can be for participants to fill out directly or administered/ filled out by RA.

NOTE: Other visit time points may be done for clinical purposes or for additional sample collection.

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A parallel cohort of family caregivers will be followed as well. Caregiver participants who's family member has agreed to the study extension will also be offered an optional extension period from 18-36 months.

Figure 4.1.3.2 The CANCOV Data Collection Schedule CAREGIVER COHORT for HOSPITALIZED ICU COHORT (following the RECOVER program schedule)

Data Collected COVID19+ CAREGIVER	Collection Time Points to 3 years after critical illness									
	In Hospital		Follow Up							
	ICU	7 days post ICU	1 month	3 months	6 months	12 months	18 months	24 months	30 months	36 months
Caregiver Eligibility Checklist	X	X	X	X						
Informed consent documentation	X	X	X	X						
<b>SITE INFO &amp; CONTACT INFORMATION</b>	X									
Study Visit	X	X	X	X	X	X	X	X	X	X
Caregiver Profile	X	X	X							
Caregiving Questionnaire			X							
<b>SOCIODEMOGRAPHICS, COMORBIDITIES &amp; MEDICATIONS</b>			X PR-1	X PR-1a	X PR-1a	X PR-1a	X PR-1a	X PR-1a	X PR-1a	X PR-1a
<b>QUALITY OF LIFE / MENTAL HEALTH</b>										
<ul style="list-style-type: none"> <li>• RAND 36-Item Short Form Health Survey 1.0 (SF-36v1)</li> <li>• CD Resilience Risk Scale (CD-RISC)</li> <li>• Post-traumatic Stress Disorder Checklist-5 (PCL-5)</li> <li>• Patient Health Questionnaire-9 (PHQ-9)</li> <li>• General Anxiety Disorder (GAD-7)</li> <li>• Caregiver Assistance Scales (CAS)</li> <li>• Caregiving Impact Scale (CIS)</li> <li>• Personal Gain Scale</li> <li>• Pearlin's Mastery Scale</li> <li>• Medical Outcomes Study Social Support Scale (SS)</li> </ul>		X	X	X	X		X	X	X	X
Study Discharge Form	X	X	X	X	X	X	X	X	X	X

Visits may be conducted by phone or video interview/email/mail

Items in BLUE are administered by RA using CRFs.

Items in RED are direct patient/caregivers facing questionnaires/surveys.

Items in PURPLE can be for participants to fill out directly or administered/ filled out by RA.

NOTE: Other visit time points may be done for clinical purposes or for additional sample collection.

#### 4.1.4 Blood Samples:

We will collect 35-45 ml (approximately 2-3 tablespoons) of blood in total, at each study time point (as shown above for the different cohorts). These will be used for the multi-omic, immunological, serological, inflammatory markers and coagulation studies. [At some sites, we will be collecting peripheral blood mononuclear cells (PBMCs). This tube will need to be processed as soon as possible (max of 24 hours) and can only be done in certain laboratories.

Blood will be collected from the arm by trained personnel with proper PPE use, in conjunction with usual clinical blood draw where possible, to limit exposure of staff to the patient and limit patient participant discomfort.

If participants are unable to attend at study centre for blood sample collection, a contract is in place with LifeLabs Ontario to arrange the collection, processing and shipping of de-identified samples to UHN for storage/analysis. A sample collection kit will be sent to participants with an information page on how to have research blood samples collected. A similar process may be undertaken in other provinces.

If a residual clinical blood sample is available, we will ask the lab for the sample.

### **4.1.5 Nasopharyngeal, nasal and oral swab sample collection:**

The majority of nasopharyngeal, oral and nasal swabs are tested at Mount Sinai Hospital in Ontario. If consent is obtained, we will ask for viral genome data. If the viral swab has not been sequenced, we will ensure that it does get sequenced. This data will be accessed with participants' consent.

## 4.2 PATIENT OUTCOME MEASURES

Demographics and clinical data will be collected from all patients, and will include: age, sex, gender, SES, pre-existing conditions (diabetes, lung disease, cardiac conditions etc), burden of comorbid illnesses by Charlson and Elixhauser Comorbidity Score<sup>28,29</sup> and the BORG Dyspnea Scale, current medications including complementary and alternative medicine use, smoking and vaping history, weight, height, obesity (BMI>30), functional status prior to current illness, Functional Independence Measure (FIM or acuteFIM), 6-minute walk test (6MWT), Clinical Frailty Scale (CFS) score, Rockwood Rapid Geriatric Assessment, Reintegration to Normal Living Index (RNLI), Traumatization of Hospitalization survey, Stigma Scale for infectious disease, and Medical Research Council Score (MRC) for muscle strength measured at different time points according to above data collection schedule. Below is a list of the various measures (not all of them will be used for all cohorts at all time points):

### **Functional Independence Measure (FIM):**

This is a measure of self-care, sphincter control, mobility, locomotion, communication, social and cognitive skills that has been validated and standardized in spinal cord and stroke populations. A higher FIM score (scale 0-126) connotes better function in these domains<sup>33</sup>. The acuteFIM is a subscale of the FIM and adapted to patients in hospital<sup>34</sup>. The FIM can only be administered by individuals who have been trained and certified.

### **Six Minute Walking Test (6MWT) with oximetry:**

Subjects walk as far as they can in six minutes while receiving maximum encouragement. It is simple to execute, inexpensive, standardized and gives a tangible measure of functional exercise capacity. It has been validated in survivors of critical illness<sup>35</sup>. The 6MWT will be conducted according to American Thoracic Society standards.

### **Pulmonary Function Testing (spirometry)**

These are non-invasive measures of lung volume, capacity, rates of flow, and gas exchange through a mouthpiece connected to a spirometer and are used for screening and diagnosis of lung disorders. These tests will be conducted according to American Thoracic Society standards. For non-hospitalized and hospitalized non-ICU participants, spirometry will be conducted only if clinically indicated.

### **Medical Research Council (MRC) Score for Muscle Strength:**

This score measures level of muscle strength in proximal and distal muscle groups on a scale from 0-5 where 0 indicates no muscle flexion, and 5 indicates full muscle function against gravity and against resistance. Muscle strength in the upper extremities (arm, forearm, wrist) and lower extremities (leg, knee, foot) will be tested.

### **Medical Outcomes Study Short Form -36 Questionnaire (SF-36):**

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The self-administered SF-36 evaluates eight health concepts: physical functioning, role functioning-physical, bodily pain, general health, vitality, social functioning, role functioning-emotional, and mental health<sup>36</sup>. Previous studies have used this instrument in survivors of critical illness and it takes approximately 15 minutes to complete<sup>37</sup>.

#### **Patient Health Questionnaire (PHQ-9):**

The PHQ-9 is a validated, multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression. It incorporates DSM-IV depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool. The PHQ-9 is brief and useful in clinical practice. The PHQ-9 is completed by the patient in minutes and is rapidly scored by the clinician. The PHQ-9 can also be administered repeatedly, which can reflect improvement or worsening of depression in response to treatment<sup>38</sup>.

#### **General Anxiety Assessment Form (GAD-7):**

The GAD-7 is a valid and efficient tool for screening for generalized anxiety disorder and assessing its severity in clinical practice and research. It is easy-to-use, self-administered patient questionnaire that can be completed in minutes<sup>39</sup>.

#### **PCL-5 Trauma Score:**

The PCL-5 is a validated, reliable, 20-item self-report measure that assesses the 20 DSM-5 symptoms of Post-Traumatic Stress Disorder (PTSD). It takes approximately 5-10 minutes to complete<sup>40</sup>.

#### **Connor-Davidson Resiliency Scale (CD-RISC):**

The CD-RISC-10 is a validated, reliable 10-item measure that assesses resilience or how well one is equipped to bounce back after stressful events, tragedy, or trauma. The CD-RISC-10 scale is comprised of ten of the original 25 items from the CD-RISC25 scale. Total scores range from 0-40<sup>41</sup>.

The CD-RISC-2 is a shorter version with 2 questions and captures the essence of the whole instrument and will be used in the non-hospitalized cohort and the hospitalized non-ICU cohort.

#### **Reintegration to Normal Living Index (RNLI):**

This short self-administered assessment tool will determine the degree to which participants reintegrate into normal social activities such as recreation, mobility in the community and interaction in family or other relationships<sup>42,43</sup>. This tool has been validated in community living adults with mobility limitations<sup>44,45</sup>.

#### **BORG Dyspnea scale:**

This short assessment tool assesses perceived exertion using a 10 point scale as assessed by the patient's experience.<sup>46</sup>

#### **Clinical Frailty Scale Score (CFS):**

The CFS is a reliable and validated scale shown to be a strong predictor of institutionalization and mortality in older and also critically ill patients across differing age groups<sup>47,48</sup>.

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### **Rapid Geriatric Assessment:**

The Rapid Geriatric Assessment (RGA) is a tool developed to quickly identify four geriatric syndromes including frailty, sarcopenia, anorexia of aging and cognitive dysfunction and takes less than 4 minutes to administer. The components of the RGA are the **FRAIL** for frailty, **SARC-F** for sarcopenia, **SNAQ** for anorexia of aging and the **Rapid Cognitive Screen** which is derived from the St. Louis University Mental Status Examination. All the screening tools have been validated in multiple continents and are available in up to 30 languages.

### **Stigma Scale (SS)**

There is no COVID-19 specific validated stigma scale. We are modifying a short stigma scale that has been validated to assess enacted and internalized stigma and psychological distress in patients with tuberculosis<sup>49</sup>. We will be testing this modified scale out in a subgroup of patients prior to using it in our wider cohorts.

### **Hospital mortality, 1-year mortality:**

The determinants of hospital mortality and 1-year outcome will inform risk stratification and outcome.

### **Pattern and Cost of Post-hospital discharge Healthcare Utilization (Resources and Costs):**

Data collection will be similar to that done for the ARDS and SARS outcomes studies and as detailed previously<sup>8,50</sup>.

### **For the outpatient cohort:**

Health services use after enrollment including hospitalization, emergency department visits, outpatient contact with physicians including virtual visits and phone calls.

To ensure standardization of all outcome measures, only those trained according to the standard operating procedures will administer the testing/questionnaires.

## 4.3. CAREGIVER OUTCOME MEASURES

The following quantitative information will be collected:

1. Dependent variables: The same HRQoL and resilience questionnaires described above will be used to assess for all family caregiver outcomes: SF-36<sup>36</sup>, PCL-5<sup>40</sup>, and CD-RISC<sup>41</sup>. In the family caregivers of HOSPITALIZED ICU COHORT, mental health outcomes using PHQ-9<sup>38</sup>, GAD-7<sup>39</sup> will also be collected as well as sociodemographics, healthcare utilization and comorbidities.

2. Independent variables: Additional outcome measures specific to family caregivers include: assessment of social support by **Medical Outcomes Study Social Support Scale (SS)**<sup>51</sup>; participation in valued activities will be assessed by the **Care-giving Impact Scale (CIS)**<sup>52,53</sup>; level of care provided to the ICU survivor in terms of activities of daily living, instrumental activities and medical care will be evaluated by the **Care-giving Assistance Scale (CAS)**<sup>52,53</sup>; caregivers' sense of control over life will be assessed by **Pearlin's Mastery Scale**<sup>54</sup>; personal development as a result of providing care will be assessed by the **Personal Gain Scale**<sup>55</sup>; and sociodemographic characteristics of the caregiver will be obtained.

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These measures have demonstrated good psychometric properties and have been used in previous care-giving studies in ARDS<sup>8</sup> and RECOVER Program I caregivers<sup>13</sup>.

#### **4.4 BLOOD SAMPLE PROCESSING**

Blood samples will only be handled by trained staff in laboratories that are certified to handle viral exposure safely. Each site will have a best practice blood collection/banking/shipping protocol established prior to initiating blood collection. For example, the PRESERVE study (COVID-19 biobank) is collecting bloods on inpatients at the UHN sites. Most sites are processing and storing samples and shipping them in batches to UHN for longer term central storage.

Genomic DNA will be extracted and sequenced on the NovaSeq6000 to an average depth of 30X to determine host genetic variants that are associated with severe COVID-19 disease using a candidate gene approach while enabling future genome-wide association studies. Whole genome sequencing will be conducted (see section 6.1.2 for details).

Viral genomes isolated from nasopharyngeal, nasal and oral swabs and sequenced as part of the Canadian COVID Genomics Network (**CanCOGeN**), the Genome Canada national SARS-CoV-2 virus sequencing initiative, with established funding, will be accessed and linked to CANCOV participants' data.

Epigenomics/transcriptomic profile will be obtained by extracting total cellular RNA and DNA from whole blood for the subsequent analysis of genetics, by the polymerase chain reaction (following reverse transcription), by microarray analyses and DNA methylation analysis. Since both epigenetic (DNA methylation [DNAm] patterns) and RNA transcriptional patterns are dynamic – collecting samples at different days (timed samples) will further allow us to understand changes over time to determine which changes may be associated with “good” (e.g. recovery) versus “bad” (e.g. MV/ICU admission/death) outcomes. This will represent a novel linkage between genetic, transcriptional, cellular, and metabolic signatures of disease and clinical post-infection recovery trajectories.

T/B cell receptor sequencing will be performed. To enable a high-resolution map of T/B-cell clonality and dynamics over time, we will profile T/B-cell repertoire in the 3 serial blood samples from patients during and after resolution of COVID infection. Illumina-compatible next-generation sequencing libraries will be constructed from DNA from white blood cells.

Various immunological and inflammatory biomarkers, including cytokines and MIF, will be tested. Total antibody levels will be assessed on one of the Health Canada approved immunoassays (e.g. Elecsys Anti-SARS-CoV-2 assay by Roche). Antibody characterization (isotype, antigen target and viral neutralization ability) will also be performed, including antibody neutralization assay, intracellular cytokine staining assays and T-Cell receptor profiling. Special coagulation tests will also be performed.

Only de-identified samples will be sent out of UHN to research partners for analysis. All regulatory data/material transfer agreements, contracts, and ethics approvals will be in place prior to samples leaving UHN.

**4.5 DURATION OF STUDY PARTICIPATION AND EXPECTED FREQUENCY OF STUDY VISITS**

As the study has progressed, we have seen that a number of patient participants have extended illness post COVID-19 exposure. There is increased interest in the following these patients for longer periods to characterize symptomology and recovery. We have therefore constructed an extension consent to allow follow up of study patients at 18, 24, 30 and 36 month follow up.

**NON-HOSPITALIZED COHORT:**

Study participants are expected to be followed in the study for 12 months, but they are free to leave at any point in the study. They will have study visits (virtual or in person visits) at baseline, 7 days, 1 month, 3 months, 6 months and 12 months. For consenting participants, we will extend study participation to 18, 24, 30 and 36 months. Each virtual visit will take 20-50 minutes to complete and in-person visits will take 1 ½ to 2 hours to complete.

**HOSPITALIZED NON-ICU COHORT:**

Study participants will enter the cohort at the time of hospital admission and will be followed while they are in the hospital (baseline to discharge, depending on their health status) and at 1, 3, 6 and 12 months after discharge or at the time of death. Patients will be offered participation in the study extension from 18-36 months. If they decline, patients will leave the cohort at one year.. Each virtual visit will take 20-50 minutes to complete. The in-person visits will take about 2 hours to complete.

A parallel cohort of family caregivers will be recruited, and will be followed up at 1, 3, 6 and 12 months after the patient has been discharged from the hospital. Caregivers will leave the study at one year or at the time of patient's death. Each study time point will take approximately 30 minutes to complete. Caregivers of study patients who agree to the 36 months extension will also be offered an extension to study participation up to 36 months.

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Patients who have been admitted to the GIM wards of participating centres, but who were discharged prior to study start up at their centre will be approached for participation in the outpatient follow up portion of the study. These patients will have follow up visits at 1, 3, 6, and 12 months post discharge and be offered participation in the extension from 18-36 months. However, depending on the time between discharge and consent, some visits may be missed. For patient participants who joined the study at their 6 month post discharge/diagnosis date, we will offer an additional study visit time-point.

### **HOSPITALIZED ICU COHORT:**

Study patients will enter the cohort at the time of ICU admission and/or MV (day 1) and will be followed up at 7 days and at 1, 3, 6, and 12 months after discharge from the ICU or at the time of death. Patients will be offered participation in the study extension from 18-36 months. If they decline, patients will leave the cohort at one year.

The 7-day assessment and questionnaires will be conducted in those patients who fulfill capacity on the ward and will take 40 to 50 minutes to complete. Each follow up visit (for all patient arms) will take 2 hours to complete. The follow up questionnaires/surveys (described previously) will take 40 minutes to complete.

Patients who have been admitted to the ICU wards of participating centres, but who were discharged prior to study start up at their centre will be approached for participation in the follow up portion of the study. These patients will have follow up visits at 1, 3, 6, and 12 months post discharge and be offered participation in the extension from 18-36 months. Patients who joined the study at the 6 month time point will be asked to attend an additional 8-9 month study visit for sample and information collection.

A parallel cohort of family caregivers will be recruited and followed up at 7 days and at 1, 3, 6, and 12 months after the patient has been discharged from the ICU. Caregivers will leave the study at one year or at the time of the patient's death. Caregivers of study patients who agree to the 36 months extension will also be offered an extension to study participation up to 36 months.

Caregivers will complete surveys at day 7 after ICU discharge of their family member, (ICU patients only) and at the same follow up times as outlined for patients (above). The questionnaires/surveys will take 40 minutes to complete.

## **5.0 Selection of Subjects**

### **5.1 INCLUSION CRITERIA**

#### **Patient:**

1. > 16 years of age
2. COVID-19+ test
3. Individuals who are suspected to have had COVID-19 infection but who have not had a positive test will be offered serological screening through CANCOV. If their results are positive for COVID-19 antibodies, they will be invited to participate in the CANCOV study.

#### **Caregiver:**

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1. Family caregivers of hospitalized COVID-19+ patients who are participating in the study. Family caregivers are defined as the family member or friend who is responsible for providing and/or coordinating all the COVID-19 survivors' post-hospital care without financial compensation. They will be included if they are able to read and speak English and are over the age of 18 years.

### **5.2 EXCLUSION CRITERIA**

1. Anticipated death or withdrawal of life sustaining treatment within 48 hours.
2. Catastrophic neurological injury in the opinion of the attending physician (e.g. Grade V SAH or massive CVA).
3. Patient unlikely to comply with follow-up.
4. Physician refusal (only for hospitalized patients).
5. Patient or SDM (substitute decision maker) refuses consent.
6. No next of kin or SDM available (if patient unable to provide consent).

## **6.0 Statistics**

### **6.1 PRIMARY ANALYSIS OF PATIENT OUTCOMES:**

We will determine the association between baseline sociodemographic/clinical/multi-omic biomarker characteristics as outlined in 4.1 to clinical and functional short- and long-term outcomes as outlined in 4.2. Multiple linear regression will be used for continuous outcomes and logistic regression for dichotomous outcomes.<sup>56</sup>

#### **6.1.1 Secondary Analyses:**

We will determine the association between functional impairment (FIM, CFS, 6MWD, MRC) on day 7 in hospitalized non-ICU patients on the GIM ward and hospitalized ICU patients on day 7 after ICU discharge and baseline characteristics outlined in 4.2.1. In addition, we will explore the relationship between baseline characteristics and the FIM score, distance walked in 6 minutes, Physical Component Score and Mental Component Score of the SF-36, hospital mortality and mortality, all at 1, 2 and 3 years after hospital/ICU discharge. Multiple linear regression will be used for continuous outcomes and logistic regression for dichotomous outcomes.<sup>56</sup>

Other secondary analyses will include:

Dependent variables will be the maximum FIM, maximum distance walked in 6 minutes, highest SF-36 score, total post index hospitalization costs, GAD7, PHQ9, PCL5, CD-RISC scores, hospital mortality and overall mortality, all at 1, 2 and 3 years after ICU discharge. The independent variables will include sex, premorbid disease, baseline characteristics outlined in 4.2.1, highest APACHE II score during ICU admission, highest MODS score during ICU admission and the number of failed organ systems documented during the ICU admission. Multiple linear or logistic regression will be used, as appropriate. In addition, we will use Cox proportional-hazards modelling to examine the relationship between actual survival time and FIM, age and Charlson comorbidity and Elixhauser scores. Other secondary analyses will include the examination of associations between these same variables and the binary outcomes ICU and 1-year mortality through use of multiple logistic regression.

#### **6.1.2 Blood Sample Analyses:**

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Host genetic profiling: Genomic DNA primary analysis in COVID-19 patients at candidate genes in the ACE2/serine protease pathway (ACE2 receptor protein: GRCh38.p13, Serine proteases PRSS, TMPRSS, KLK etc) will identify variants in these genes that contribute to severe disease among patients with COVID-19 infections. Whole genome sequencing of the samples will enable our contribution to larger Canadian COVID-19 host genome sequencing efforts, such as those initiated by the CFI-MSI funded Canadian genome sequencing infrastructure (CGeN HostSeq Databank) and other international efforts with which CGeN is collaborating. (<https://www.sciencemag.org/news/2020/03/how-sick-will-coronavirus-make-you-answer-may-be-your-genes>).

To correlate genomic and serological data, analysis of covariance will be used to test whether pathogenic variation in different genes is associated with differences in antibody titer, adjusting for covariates (e.g. age, ancestry, comorbidities). Analyses will be stratified by sex, and results will be disaggregated by sex. Genome-wide association (GWAS) will occur iteratively as new data becomes available through CanCOGeN using a variety of packages depending on outcome measures and custom methodology (VikNGS) for rare and common variants.

Epigenomic/transcriptomic profiling: analysis of changes in DNA methylation in patients with COVID-19 will determine: (i) differences between “sick” vs “not-sick” COVID-19 patients; (ii) differences in DNAm that lead to changes in RNA; (iii) differences that are modifiable by treatment (e.g. ARBS); (iv) differences that may change over time (days 0/1; 3/4; and day 7, and convalescent samples).

Immunologic profiling: a rapid-detection biomarker-based test for clinicians have been developed by Dr. Yeung’s childhood arthritis group to predict risk for poor outcome and enable rapid selection of targeted biologic therapies. These models can be repurposed to form a predictive tool for early identification of those who will develop COVID-19-related macrophage activation syndrome (MAS), which is associated with poor outcomes. Work by our team has already established that patients and treatment responses can be stratified by integrating biologic and clinical data. The pipeline for testing, including biologic assays (custom gene transcription and cytokine panels) and analytical framework (computational and machine learning algorithms), are all in place and running. We plan to transfer these models for use in COVID-19 infections.

We will assess immunity by measuring antibody isotype, titer, antigen targets, and viral neutralization ability in acute samples and at 6 months and 1-year post-diagnosis, and we will perform T/B-cell receptor sequencing. Genetic variation will be assessed by host genome and virus sequencing. Physiological response will be characterized by biochemistry and hematology laboratory parameters as well as patient characteristics obtained from the charts (age, sex, race/ethnicity, symptoms, outcome, comorbidities, treatment). Immunity, genetic variation, viral variation, physiological/biochemical response and patient characteristics will be correlated with clinical outcomes.

Recently we have identified individuals with a negative COVID-19 test that have been reporting symptoms very similar to those of COVID-19 patients. We would like to investigate whether changes in blood tests seen in patients with a positive COVID-19 test, are different from people with a negative COVID-19 test. To explore this, will be asking participants who are part of the screening arm for CANCOV, to provide optional additional samples so the above analyses can be run in parallel with our COVID-19 positive cohort.

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### 6.2. ANALYSIS OF CAREGIVER OUTCOMES

To identify changes in caregiver outcomes over time and determine factors associated with these outcomes, hierarchical linear modelling for longitudinal data<sup>57</sup> will be used. Mixed effects modelling will be used as it accounts for the underlying heterogeneity between and within participants (i.e., intercepts and slopes are allowed to vary across participants). This approach will help to identify changes in the dependent variables over time as well as identify factors associated with the dependent variables. The model will consider illness factors (e.g. COVID-19 ICU survivor functional abilities, comorbid conditions, walking ability, anxiety, depression, PTSD, resilience, stigma, and quality of life) and caregiver factors (e.g., care-giving assistance, impact on caregiver lifestyle) on caregiver outcomes. These analyses will identify aspects of the illness and care-giving situation that place family caregivers at higher risk for experiencing emotional distress and poor HRQoL.

### 6.3.GEMINI LINKAGE

We will use established GEMINI methods to collect patient-level clinical and administrative hospital data for all patients admitted to a general medicine, medical subspecialty (e.g. cardiology, respirology), or ICU service at the 30 largest hospitals in Ontario. This mix of academic and community hospitals from all regions accounts for ~70% of acute medical and ICU inpatient beds in Ontario. We will capture all patients hospitalized for COVID-19 at these hospitals (projected n=6,700 patients over the pandemic). GEMINI can currently collect: laboratory results (including COVID-19 tests), radiology reports, blood transfusions, in-hospital medications, vital signs, patient room/transfers, attending physicians, and clinical notes. GEMINI also collects patient demographics, diagnoses, procedures, residence in long-term care, and other data reported to the Canadian Institute for Health Information Discharge Abstract Database and National Ambulatory Care Reporting System. GEMINI data were previously updated annually, but this has been accelerated to respond to COVID-19. The first GEMINI COVID-19 data extraction from 7 hospitals will be complete by the end of May, enabling immediate analytics upon announcement of funding for this grant. The GEMINI COVID Lab will add isolation precautions orders and patient code status orders. Data will be updated every 1-3 months, depending on each hospital's capabilities. These data will be linked through existing data sharing agreements to longitudinal data from ICES, allowing comprehensive assessment of: a) COVID test status for all patients (including pre- and post-hospital PCR results) and case demographic data (e.g. occupation of infected patients from the integrated Public Health Information System); b) pre- and post-hospital healthcare use (e.g. physician and emergency department visits); and c) post-hospital outcomes (e.g. readmission and mortality). We will explore equity considerations through linkages to sociodemographic data. ICES administrative datasets are now rapidly available (monthly) to respond to COVID-19. Data will be deidentified and held securely in a cloud-based, high performance computing environment (letter of support from HPC4Health) that already houses both GEMINI and ICES data to facilitate seamless remote access for scientists with sufficient capacity for advanced modeling and machine learning (ML).

### 6.4 ICES LINKAGE

We will link the CANCOV dataset with the Institute for Clinical Evaluative Sciences (ICES) to understand the continuum of illness after COVID-19 infection and the patient/caregiver pre-ICU health status trajectory. The Canadian Institute for Health Information (CIHI) contains demographic, administrative

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and clinical data for all acute care discharges and day surgery in Ontario and other Canadian provinces, with the exception of Quebec. This "Discharge Abstract Database" (DAD) has existed since 1979 and is populated by trained and monitored data-abstractors using standardized and validated abstraction formats. The DAD contains information on administrative admission and discharge data, patient demographics, up to 25 diagnoses (and derived calculations of the Charlson comorbidity index), interventions, ICU admission and discharge data (and ICU type), episodes of MV, blood product transfusion, and various assigned values such as case mix groups and resource intensity weighting. Provincial Health Information is housed at ICES in Ontario and is routinely linked with a high degree of accuracy to other administrative datasets. ICES is a prescribed entity under section 44 of the Personal Health Information Protection Act, S.O. 2004, c. 3 Schedule. A (PHIPA) and O. Reg. 329/04 section 18(3), which meets the statutory requirements of section 45 of PHIPA ("Prescribed Entity"). Linkage Plan: GEMINI and RECOVER Program ICES collaborators will identify all patients to have been admitted to an acute care GIM ward or intensive care unit ("SCU" or special care unit) in given years and link records for eligible patients in CANCOV to several other population-based administrative datasets to ascertain prior and subsequent emergency department visits (via National Ambulatory Care Reporting System (NACRS)) and death (via provincial Registered Persons Database) during the study period. Healthcare costs data can also be derived from linkages to utilization data on physician services (via Ontario Health Insurance Plan (OHIP and other provincial health insurance plan databases)), medication use (via Ontario (ODB) and other provincial Drug Benefit database ), home care (via Home Care Reporting System (HCRS)), long-term care (via Complex Continuing Care Reporting System CCRS), and rehabilitation hospitalization (via National Rehabilitation Reporting System NRS)). At ICES, this will allow a multi-year "look-back" of CANCOV patients who have suffered critical illness, and a multi-year (depending upon the date of critical illness) "follow-up" period, to determine subsequent interactions with the health care system, resource use and long-term outcomes. Ontario has a specific hospital-based patient case-costing program, and in addition, a recently validated "getcost" macro program at ICES allows for determination of costs of care divided along all in-patient and out-patient services, including acute hospitalizations (DAD), same day surgery and ER visits (NACRS), ambulatory care visits, rehabilitation hospitalization (NRS), complex continuing care and long-term care (CCRS), mental health, home care, primary and specialist care (OHIP), pharmaceuticals for those over 65 years (ODB) and laboratory testing.

#### **6.5 SAMPLE SIZE**

We will prospectively recruit 1000 COVID-19+ non-hospitalized and 1000 hospitalized COVID-19+ patients on a competitive enrollment basis. We will enroll 500 caregivers within the hospitalized patient cohort. We will enroll 1000 patients infected with COVID-19 anticipating that 900 will still be alive and in the study at the 1-year follow up based on current COVID-19 mortality data. This will provide a sample of approximately 500 family caregivers. Based on current projections of the number of COVID-19 cases in Canada, we estimate that Ontario, Quebec, British Columbia and Alberta will have another 30,000 new cases of COVID-19 infections and participating hospitals will admit approximately 6,000 COVID-19 positive patients in the study period. In the planned sample of 1000 hospitalized patients, 30-40% are expected to experience a poor short-term outcome defined as ICU admission and/or MV.

### **8.0 Quality Control and Quality Assurance Procedures**

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Site investigators will take responsibility for the conduct of the Ontario COVID-19 Prospective Cohort Study (CANCOV). Site investigators will supervise the day-to-day operation of the project, and are responsible for ensuring that ICH-GCP guidelines are followed and study personnel are qualified and trained on the study protocol and procedures.

### **8.1. STEERING COMMITTEE**

The **CANCOV** Steering Committee members will be responsible for overseeing the conduct of the trial, for upholding or modifying study procedures as needed, addressing challenges with protocol implementation, formulating the analysis plan, reviewing and interpreting the data, and preparing the manuscript. This will be achieved through meetings (in-person or by conference call) at least quarterly. All committees will report directly to the Steering Committee. Members of the steering committee will include representation from across medical and interdisciplinary specialties, as well as patient and caregiver.

### **8.2 DATA MONITORING COMMITTEE**

Members of the **CANCOV** research team from the University Health Network and the University of Toronto will monitor the data. Members will review the first five completed charts from each site as well as a random sample of 10% of completed data thereafter. Monitoring will ensure protocol compliance, proper study management, and timely completion of study procedures. The committee will meet weekly to discuss and monitor ongoing study-related activities. The group will be responsible for:

- conducting monthly meetings with all participating site Co-Investigators and Research Coordinators
- conducting site initiation, monitoring visits and site close-up
- ensuring data collection is complete at the specified time
- creating monthly Newsletters with real time tracking of recruitment rates and data collection

Quality Control and Assurance will also be performed independently by the Biostatistics Research Unit (BRU) at UHN.

## **9.0 Ethics**

### **9.1 CONSENT PROCESS**

We have constructed the consent documents to allow patient participants to choose different levels of participation. The rationale is to decrease patient burden as much as possible. We anticipate most patients will participate in the entire study follow up period.

**NON-HOSPITALIZED COHORT:** If the potential participant does not have the capacity to provide informed consent, (limited capacity due to cognitive impairment etc), the substitute decision maker (SDM) will be contacted. A copy of the consent document will be sent to the SDM by email (or paper mail) for them to review prior to the consent discussion. We wish to include patients in this study who may require an SDM for reasons other than COVID-19 illness. Excluding participants that lack capacity due to dementia, etc, may produce selection bias and exclude information on this population. As the

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CANCOV study is observational in nature and has low risk, we don't feel it is unreasonable to include this population.

We anticipate that, due to the increased risk of contagion, study visits including the consenting visit may be done virtually using a smartphone, tablet, computer etc. so that verbal consent will be obtained and documented. The process will be as above. If the patient comes for the in-person 1-month visit, we will obtain in person signed consent.

**HOSPITALIZED NON-ICU COHORT:** Potential patients will be identified by the study investigator(s), a member of the research team (coordinators or assistants) and/or by GIM staff members (MDs, bedside nurse, and/or allied health professionals). A team member within the patients' circle of care (GIM staff) will approach the patient (if capacity is assessed as sufficient to understand and provide informed consent), to inform them of the study and asked if they would like to learn more about it. If the patient, (or when required the SDM), states their interest in the study, they will be provided with a paper copy of the consent document to keep and review, and the research team will be advised to reach out as soon as possible. In order to limit the use of personal protective equipment, the research team will correspond with GIM patients using a smartphone, tablet, computer etc. If the patient does not have a device, a tablet will be provided to the patient for their use during the inpatient portion of their study participation.

Once a member of the research team (coordinator/assistants/Investigator) is able to communicate with the patient, the patient's capacity to consent will be assessed and documented as per the revised Aid to Capacity Evaluation. If capacity is found to be sufficient to understand the informed consent process, then the consent form will be reviewed.

If the research staff finds the patient does not have the capacity to provide informed consent, (patient currently too ill to participate, limited capacity due to dementia, etc), they will contact the SDM on file. A copy of the consent document will be sent to the SDM by email (or paper mail) for them to review prior to the consent discussion.

If a patient has no capacity to give consent and the SDM/Family caregiver cannot be found and/or reached, they will not be enrolled in the study. If at a later date they are able to provide consent, they may be approached again for participation.

When consent is obtained from the SDM/family caregiver, the patient's capacity for first-person consent will be assessed during the hospital stay or at the first study follow-up visit. The research team will explain the study and inform the patient they were consented by their SDM. The patient will be invited to give written informed consent to continue participation. If the patient chooses to withdraw from the study, no further investigations or data will be collected. Serum collected to that point will be destroyed.

We have constructed the consent documents to allow patient participants to choose levels of participation. The rationale is to decrease patient burden as much as possible. We anticipate most patients will participate in the entire study follow up period.

### **CANCOV Protocol v1.3**

**HOSPITALIZED ICU COHORT:** Critically ill patients will likely be intubated and sedated. Potential patients will be identified by the study investigator(s), a member of the research team (coordinators or assistants) and/or by staff members (MDs, and allied health professionals) of the ICU. After a potential patient is identified, a member of the research team (coordinator/assistants/Investigator) will review the ICU flowsheet and contact the ICU team (e.g. MD, bedside nurse, allied health) to ascertain patient capacity. The patient's capacity to consent will be assessed and documented as per the revised Aid to Capacity Evaluation. If they are able to consent, the bedside nurse will witness the consenting process. Consent will be obtained only if all parties believe that the patient has capacity.

If the patient doesn't have capacity, then the SDM will be approached for consent. Within the patients' circle of care, a team member will approach the patient or SDM, inform them of the study, and ask them if they would like to learn more about it. If the patient (or SDM), states their interest in the study, then a member of the research team will contact them to explain the study in full, and to ensure eligibility/ absence of exclusion criteria and review consent with the patient/SDM. Consent must be obtained within 72 hours of ICU admission, meaning the patient or SDM will have at minimum 24 hours to consider participation in the study.

**CAREGIVER COHORT:** Family caregivers of hospitalized patients participating in the study will be approached for the caregiver portion of the study. If they are interested and are able to consent, study staff will discuss the study and obtain consent via phone / email / paper version.

### **9.3 DESCRIPTION OF PROCEDURE FOR INFORMED CONSENT FROM RESEARCH PARTICIPANTS**

A member of the research team (coordinators or assistants) will obtain informed consent. The research team member will explain to the patient, or SDM, and the patient's family caregiver in lay terms the evidence that supports the study as well as the procedures, the risks and benefits, voluntary participation and the confidentiality of the study. Consenting participants will be informed that care will not be affected in any way should they decide to refuse participation or withdraw from the trial. All questions will be answered. Once the patient, or his/her SDM/the patient's family caregiver decide to give informed consent, this will be obtained verbally. An opportunity will be given to speak with the investigator if the patient/ SDM/patient's caregiver wish.

The consent process and form will outline to the participant exactly how they can remove their data and samples from the study, should they change their mind regarding study participation. Participants will be informed that they may refuse any of the testing and/or questionnaire completion used in this study at the time of the data collection. They will be informed that if tests and analysis have already been done on their data/sample, it will not be possible to withdraw those results. However, no further testing will be done. A copy of the consent form will be given to each study participant to take home with them for future reference and contact.

Review and approval of the study and any amendment to it must be obtained by the Institution Research Ethics Board before any study related procedures commence - apart from changes/amendments necessary to eliminate immediate hazard to the study participants.

### **10.0 Data/Sample Handling and Record Keeping**

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### **10.1 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

Study personnel including data managers, research associates, principal investigators/applicants, co-investigators/applicants and all collaborators on the granting applications will have access to the study related documents (protocol, consent, Case Report Forms (CRF) and source data/documents (patient chart/electronic patient record). Each site will have full access to their data. All study data will be de-identified. Only those in the **CANCOV** core group and trained research staff at the provincial applicant's institutional site-UHN (Co-PIs Cheung and Herridge, and the 2 project managers) will have access to all identifiable information. Access to primary data may be requested by the UHN sponsor for data monitoring purposes.

All paper files will be kept secured in locked cabinets located in office areas accessible by study personnel within each participating site. Subjects are identified by a unique study number. A separate enrollment log is kept linking individuals. Each site will maintain a master linking log, and only the site will have access to this.

### **10.2 BLOOD SAMPLE HANDING, STORAGE, AND MANAGEMENT**

Blood samples will be stored in a container that does not have any personal identifying information at the participating site. These will be shipped to and centrally stored at the UHN COVID-19 Biobank and only biobank staff have access to this area.

CANCOV investigators and research partners analyzing blood samples will only be allowed access to de-identified samples once all regulatory data/material transfer agreements and ethics considerations are finalized. In order to ensure every precaution will be taken in order to protect sample quality and participant confidentiality, we have formalized a Data Access and Publication (DAP) process for review and regulatory oversight of this process.

### **10.3 DATABASE MANAGEMENT**

Data files will be stored on a secured electronic data capture system with privacy and security settings that meet or exceed industry standards. The Toronto Health Economics and Technology Assessment (THETA) Collaborative team has developed, updates and maintains the online data collection tool (REDCap). The CANCOV team have worked collaboratively with THETA to create this tool. Standardized data that are electronically captured through REDCap<sup>®</sup> will sit in a secure private cloud environment such as the HPC4Health platform. There will be linkage to data collected in GEMINI in the neutral zone of HPC4Health. GEMINI data collection is governed by separate ethics approvals at the various participating institutions.

CANCOV investigators, academic and commercial partners who are conducting analyses on CANCOV blood samples as well as those from the Canadian Critical Care Research Group, will be granted access to corresponding de-identified CANCOV data. To date, these include Hospital for Sick Children, Toronto, Ontario who will receive data to run the genetic analysis (The Centre for Applied Genomics), Sinai Health System who will run the serological assays, The Thrombosis & Atherosclerosis Research Institute (TaARI), who will run the coagulation studies, and Dr. Marvin Fritzler who will run the immunologic

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biomarkers and cytokine assays. All data sharing will be formalized by contractual data and material sharing agreements.

The **CANCOV group** at UHN will govern, maintain and manage the servers and retain ownership of all data therein. The data will be protected by the University Health Network firewall, with exclusive access to **CANCOV** staff.

As CANCOV has received funding from a number of Federal government groups (CIHR, CITF), we have been tasked with sharing data with other federally funded organizations, such as CGen/CanCoGen and CITF. De-identified data and sample analysis results will be shared with CITF. Data may also be shared with approved research groups in Canada and internationally. The CANCOV DAP committee will review access requests from academic and commercial research groups with ethics approved protocols. Any shared data will be de-identified or anonymized. All data sharing will be formalized by contractual data and material sharing agreements.

The data on the CANCOV Database will be stored for 20 years, or, until it is no longer useful for research.

The THETA collaborative has advised that study data will exist in the UHN REDCAP backup server until they are cleaned. The THETA Collaborative is working in conjunction with a UHN REDCap<sup>®</sup> governance working group to determine the duration for back-up before pruning.

All records and documents pertaining to the **CANCOV** study will be retained by the study trial site at UHN for at least 10 years after the completion of the study.

### **11.0 Study Timeline**

We plan to begin study recruitment in June 2020 and completion of patient accrual by no later than June 2021. We will complete 12 month follow-up by December 2022. The study extension up to 36 months will be completed by December 2026.

### **12.0 Contribution**

The Canadian COVID-19 Prospective Cohort Study (CANCOV) provides a platform to coordinate, collaborate, and synchronize the recruitment, follow-up and biospecimen / data collection of various CIHR and CITF funded COVID-19 studies. It will provide a detailed characterization of the physical, functional, neuropsychological, pattern of healthcare utilization and recovery trajectories after severe illness and how these intersect with outcomes in family caregivers. The novel contribution to the international literature is the linkage of the multi-omic, immunologic and inflammatory biomarkers, serologic and coagulation studies to detailed high quality, longitudinal, multi-system curated phenotypic data.

With reducing numbers of new COVID-19 cases, CANCOV offers a pragmatic approach that will limit the burden to patients, limit exposure and spread to research personnel, and reduce the duplication of efforts and cost, while providing an interprovincial synergized platform that centralizes all COVID-19

### **CANCOV Protocol v1.3**

related data for Canadian researchers. CANCOV also provides a mechanism to avoid the development of silos of small and large datasets, so that the full value of investments in COVID19 research in Canada (investments that have been made in important but independent regional and pan-Canadian research studies that each have distinct areas of focus and on specific phases of disease) can be realized.

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## APPENDIX – CANCOV Investigators

Co-lead Principal Investigator	Cheung, Angela M
Co-lead Principal Investigator	Herridge, Margaret
<b>ONTARIO INVESTIGATORS</b>	
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Co-Principal Investigator	Batt, Jane
Co-Principal Investigator	Stelfox, Tom
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<b>NOVA SCOTIA INVESTIGATORS</b>	
Co-Investigator	Nabha Shetty, Nova Scotia Health
<b>MANITOBA INVESTIGATORS</b>	
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Co-Investigator	Olafson, Kendiss, University of Manitoba
<b>SASKATCHEWAN INVESTIGATORS</b>	
Co-Investigator	Moisey, Lesley
<b>GEMINI list of collaborators</b>	<b>Appendix</b>
<b>RECOVER list of collaborators</b>	<b>Appendix</b>

## APPENDIX - GEMINI INVESTIGATORS AND SITES

Site	Site Investigator(s)	Role on the COVID-19 Action Initiative
St. Michael's Hospital	<b>Fahad Razak</b> MD, MSc, St. Michael's Hospital, Department of Medicine, University of Toronto.	Co-Primary Investigator
	<b>Amol Verma</b> MD, MPhil, St. Michael's Hospital, Department of Medicine, University of Toronto.	Co-Primary Investigator
Toronto General & Toronto Western	<b>Tom MacMillan</b> MD, University Health Network, Department of Medicine, University of Toronto	Co-Primary Investigator
	<b>Lauren Lapointe-Shaw</b> MD, Dept. of Medicine, University of Toronto	Co-Investigator
Mount Sinai Hospital	<b>Janice Kwan</b> MD, MPH, Department of Medicine, Mount Sinai Hospital; Dept. of Medicine, University of Toronto	Co-Investigator
	<b>Mike Fralick</b> MD, SM, Mount Sinai Hospital	Co-Investigator
Credit Valley & Mississauga Trillium Hospitals	<b>Terence Tang</b> MD, Trillium Health Partners, Department of Medicine, University of Toronto	Co-Investigator
Sunnybrook Hospital	<b>Adina Weinerman</b> MD, MHSc, Sunnybrook Health Sciences Centre, Department of Medicine, University of Toronto.	Co-Investigator
<b>Sites currently in the process of approval</b>	Hamilton Health Sciences, William Osler Health System, London Health Sciences, St. Joseph's Health Centre, Thunder Bay Regional Health Sciences Centre	

## APPENDIX - RECOVER INVESTIGATORS AND SITES

Site	Site Investigator(s)	Role on the COVID-19 Action Initiative
UHN – TGH	Margaret Herridge	Co-Lead PI
UHN – TGH/TWH:	Niall Ferguson	Collaborator
UHN – TWH	Victoria McCredie	Collaborator
UHN - TGH MSICU	Vincent Lo	Collaborator
UHN - TGH MSICU	Stacey Burns	Collaborator
UHN - TGH MSICU	Lorenzo del Sorbo and Ewan Goligher;	Collaborator
UHN - TGH CVICU/CICU	Matteo Parotto	Collaborator
	Patrick Lawler	Co-Investigator
UHN - Pyschiatry:	Susan Abbey and Adrienne Tan	Collaborator
UHN - TGH Pyschiatry Nursing	Sarah Greenwood	Collaborator
UHN - TGH Neuromuscular Clinic	Hans Katzberg	Collaborator
UHN - TGH Clinical Operations Director	Linda Flockhart	Collaborator
UHN - TGH Lung Transplant	Dmitry Rozenberg	Collaborator
UHN Biostatistic Research Unit	Ella Huszti	Collaborator
	George Tomlinson	Co-Primary Investigator
UHN - TGHRI Scientific Associate	Priscila Robles	Collaborator
UHN Toronto Rehab Institute	John Flannery and Mark Bayley	Collaborator
TGHC - Grace	Jake Tran, Raphael Rush and John Ruth	Collaborator
UofT – IHPME	Lusine Abrahamyan and Murray Krahn	Collaborator
UofT Occupational Therapy	Jill Cameron	Collaborator
UofT Physical Therapy	Sunita Mathur	Collaborator
SickKids/Implementation Science	Melanie Barwick	Collaborator
Sinai Health System ICU	Sangeeta Mehta, Laveena Munshi and Michael Detsky	Collaborator
St. Michael's Hospital	Jan Friedrich, Karen Burns, John C Marshall and Laurent	Collaborator
	Jane Batt	Co-Investigator
	Claudia Dos Santos	Co-Primary Investigator
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