Long-term impAct in inTEnsive caRe survivors oF CORonavirus disease-19

The AFTERCOR Study

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Summary

Scientific Title	Long-term impAct in inTEnsive caRe survivors oF CORonavirus disease 19 (The AFTERCOR study)
Study Design	Prospective multi-centre longitudinal observational study of intensive care unit survivors of coronavirus disease 2019 (COVID-19).
The Collaborative	The collaborative consists of international investigators across 6 continents who have previously cooperated to achieve goals of the ECMOCARD study during the 2020 SARS-CoV-2 pandemic.
Study Aim and Objectives	To describe following discharge from the intensive care unit recovery up to two years of the following aspects/functions: 1. Health-related quality of life 2. Dynamics of organs dysfunction and recovery 3. Pulmonary function
Inclusions/Exclusions	Inclusion Criteria 1. Laboratory-confirmed COVID-19 infection by real-time PCR 2. Written informed consent from the patient at the time of discharge from the ICU 3. Previous enrolment into the ECMOCARD observational study 4. Aged ≥18 years 5. Discharge from an intensive care unit Exclusion Criteria 1. Pregnancy at time of infection 2. Patients unable to complete long-term follow-up, due to logistical problems 3. Patient paralysed due to pre-existing neurological condition before being admitted to hospital for COVID-19 4. History of pulmonary resection 5. Previous pulmonary transplant

	6. Documented advanced neurologic disorder for which the patient is unable to carry out 6-min walk test 7. Documented psychiatric disease for which the patient is unable to carry out interview
Consent	Informed consent will be obtained directly from the patient, upon ICU discharge. If the patient is unable to provide a consent form upon admission, informed consent will be obtained by his/her next of kin and then will be obtained from the patient at the first follow-up, at 3 months following ICU discharge.
Study Setting	International multi-centre longitudinal study, conducted in hospitals of the ECMOCARD network
Sample Size	We aim at including 500 patients
Study Start Date	15th September 2020
Study Duration	31st December 2024
Data collection processes	Patients will be studied from time of ICU discharge up to 2 years thereafter. Follow-up visits will be scheduled at 3, 6, 12, 18 and 24-month post-ICU discharge. Per each patient, we will use the 10-digit number previously provided by the ECMOCARD study to identify ECMOCARD patients who will be also enrolled into the AFTERCOR study and followed up for two years. The Research Coordinator will compile an enrolment log including the patient's name, contact information (phone number), age, hospital identification number and the unique ECMOCARD study number, which will also be used for the AFTERCOR study. At each follow-up visit we will assess 1) Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36); 2) Montreal Cognitive Assessment; 3) Dynamics of organs dysfunction and recovery; 4) St. George's Respiratory Questionnaire; 5) Pulmonary function testing; 6) Chest radiography; 7) 6-minute-walk test with continuous oximetry and 8) Patient Health Questionnaire 9 (PHQ-9). In patients who performed a Chest CT-scan during their ICU stay, a Chest CT-scan will be carried out at 6 months. Finally, in patients who performed an echocardiography during their ICU stay, a transthoracic echocardiography will be carried out at 3, 12 and 24 months. The pulmonary function tests, arterial blood gas analysis, chest x-ray, the echocardiography and the 6 minute walking test will be performed at every follow-up visit or until normalization of the test results. If a result is deemed to be in the

	normal range for this patient, the test will not be repeated during the following visits.

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Introduction

In January 2020, members of the Asian-Pacific Extracorporeal Life Support Organization designed The ExtraCorporeal Membrane Oxygenation for 2019 novel Coronavirus Acute Respiratory Disease (ECMOCARD Study, www.ecmocard.org), which was carried out within the network and web-based case collection forms of the ISARIC consortium's SPRINT-SARI study and in collaboration with the Monash University to collect data "A comprehensive national registry on the treatment and outcomes of patients requiring ECMO" (EXCEL Registry). *The ECMOCARD study was designed to characterize COVID-19 patients admitted to the intensive care unit (ICU), irrespective of the use of extracorporeal membrane oxygenation (ECMO)*. The ECMOCARD study follow-up was up to 28 days post ICU admission or hospital discharge, whichever occurred later. Thus, the ECMOCARD study will not provide information on the long-term recovery or complications of COVID-19 patients admitted into the ICU.

Coronaviruses

Coronaviruses are a family of enveloped, single-stranded, positive-strand RNA viruses classified within the Nidoviraes. Coronaviruses may infect mammals and birds, triggering respiratory, enteric, hepatic, and neurologic diseases[1]. Six coronavirus species are known to cause human disease. The coronaviruses 229E, OC43, NL63, and HKU1 are prevalent worldwide and most commonly cause only marginal respiratory symptoms. Two other strains, the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have originated from animal to human transmission and have caused more serious, sometimes fatal, respiratory illnesses. In previous years, SARS-CoV[2,3] and MERS-CoV[4,5], have caused serious respiratory infections, with mortality rates of 10% for SARS-CoV[6] and 37% for MERS-CoV[7].

2019 Novel Coronavirus (COVID-19)

In late December 2019, in Wuhan, Hubei, China, a new respiratory syndrome emerged with clinical signs resembling viral pneumonia and person-to-person transmission[8]. Prompt diagnostic methods, through deep sequencing analysis from lower respiratory tract samples, corroborated emergence of a novel coronavirus, namely the 2019 novel coronavirus (COVID-19).

In particular, Na Zhu and collaborators[9] were able to isolate the virus from bronchoalveolar lavage (BAL) from patients with pneumonia of unknown cause, who were in Wuhan on December 21, 2019 or later, and who had been present at the Huanan Seafood Market. RNA extracted from BAL fluid from the patients was used as a template to clone and sequence a genome using a combination of Illumina sequencing and nanopore sequencing. More than 20,000 viral reads from individual specimens were obtained, and most contigs matched to the genome from lineage B of the genus betacoronavirus — showing more than 85% identity with a bat SARS-like CoV (bat-SL-CoVZC45, MG772933.1) genome. Virus isolation from the clinical specimens was performed with human airway epithelial cells and Vero E6 and Huh-7 cell lines. 2019-nCoV–infected human airway epithelial cultures were examined with light microscopy and with transmission electron microscopy 6 days after inoculation. Cytopathic effects were observed 96 hours after inoculation on surface layers of human airway epithelial cells and lack of cilium beating was seen with light microcopy. Through transmission electron microscopy, the authors were able to image the COVID-19 particles, that generally appeared spherical, of 60 to 140 nm, with some pleomorphism and distinctive spikes, about 9 to 12 nm (Fig. 1), and gave virions the appearance of a solar corona. This morphology corroborated the Coronaviridae family.

Figure 1

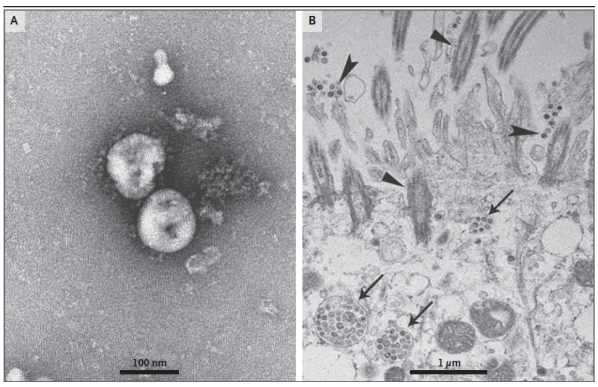

Figure 1: A: COVID-19 particles are depicted. B: COVID-19 in human airway epithelium, as reported in previous publicaition[9].

Investigators carried out inclusive phylogenetic analysis that showed that COVID-19 falls into the genus betacoronavirus, which includes coronaviruses as SARS-CoV, bat SARS-like CoV, and others from humans, bats, and other wild animals.

Thus far, more than 130 million confirmed cases, including health-care workers, have been identified worldwide, and several exported cases have been confirmed in other provinces in China, Thailand[10], Japan[11], South Korea[12], Singapore[13], Germany, Italy[14], France, Iran[15], USA[16] and many other countries[17]. An early case report in 41 patients with laboratory-confirmed COVID-19 infection in Wuhan has been reported[18]. The median age of the patients was 49 years and mostly men (73%). Among those, 32% were admitted to the ICU because they required high-flow nasal cannula or higher-level oxygen support measures to correct hypoxaemia. Less than half had underlying diseases, including diabetes (20%), hypertension (15%), and cardiovascular diseases (15%). On admission, 98% of the patients had bilateral multiple lobular and subsegmental areas of consolidation (Fig 2)[19].

Figure 2

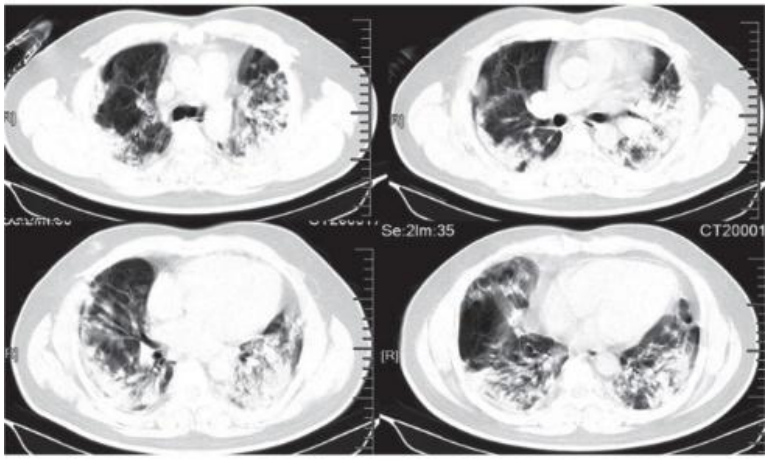

Figure 2 Caption: Transverse chest CT images from a 40-year-old man showing bilateral multiple lobular and subsegmental areas of consolidation on day 15 after symptom onset. Transverse chest CT images from a 53-year-old woman showing bilateral ground-glass opacity and subsegmental areas of consolidation on day 8 after symptom onset, adapted from[18]

Importantly, acute respiratory distress syndrome (ARDS) developed in 29% of the patients, while acute cardiac injury in 12%, and secondary infection in 10%. Invasive mechanical ventilation was required in 10% of those patients, ***and two of them (5%) had refractory hypoxaemia and received extracorporeal membrane oxygenation (ECMO)***.

In a later retrospective report by Wang and collaborators[20], clinical characteristics of 138 patients with COVID-19 infection were described. Those patients were admitted at Zhongnan

Hospital of Wuhan University in Wuhan, China, from January 1 to January 28, 2020. The median age was 56 years and clinical signs of the infection comprised fever (98.6%), fatigue (69.6%), and dry cough (59.4%). ICU admission was required in 26.1% of the patients for acute respiratory distress syndrome (61.1%), arrhythmia (44.4%), and shock (30.6%). Among these patients, 11.1% received high-flow oxygen therapy, 41.7% non-invasive ventilation, and 47.2% invasive ventilation. During the period of follow-up, overall mortality was 4.3%. Interestingly, a very small number of COVID-19 cases have been described in children and it seems that the spectrum of illness is limited in the paediatric population[21].

In later reports from developed countries, such as Italy, pressure on healthcare systems and ICUs was highly emphasized[14,22–24] and strategic plans to avoid collapse of regional healthcare systems described. Interestingly, in-vitro investigations confirmed that SARS-CoV-2 presented similar aerosol and surface stability to that of SARS-CoV-1[25], this controverts the rapid spread of this novel SARS coronavirus, in comparison with previous ones. Thus, rather than due to intrinsic characteristics of the virus, the rapid spread of the infection worldwide could be related to several asymptomatic SARS-CoV-2 carriers[26], especially younger patients, who might have contributed to the exponentially increase number of cases worldwide. In addition, as demonstrated in previous studies[27], high viral loads are present in respiratory secretions of patients with or without COVID-19, which could also facilitate the spread of the infection. Ultimately, many healthcare systems in Europe faced an abrupt exponential increase in patients infected by SARS-CoV-2 and, accordingly to aforementioned figures, several patients developed COVID-19 concurrently, rapidly overcoming capabilities of healthcare facilities and ICU resources. In particular, in several countries, the need for ventilators and personal protective equipment reached a critical point[28].

The ECMOCARD Study

After initial outbreaks of SARS-CoV-2 worldwide, many investigators became aware that the paucity of data on pathophysiology and predictors of severity and outcome were intensifying the clinical burden of the Covid-19 pandemic. As reported above, Chinese reports corroborated that patients who progressed to need for intensive care represented a group with mortality in excess of 50% in many countries. ***The ECMOCARD project was developed in mid-January by APELSO investigators and was designed to collect information across the Asia Pacific region on***

COVID 19 patients, from ventilatory support strategies, up to ECMO and anti-viral therapies. As the outbreaks spread globally, the involvement of international sites in the ECMOCARD project has grown exponentially. As of late March 2020, there were 47 countries with almost 300 participating sites involved in ECMOCARD across 6 continents (Fig 3). Major companies, such as Amazon and IBM are collaborating with the ECMOCARD group to facilitate data collection and Artificial Intelligence assisted decision support.

Figure 3

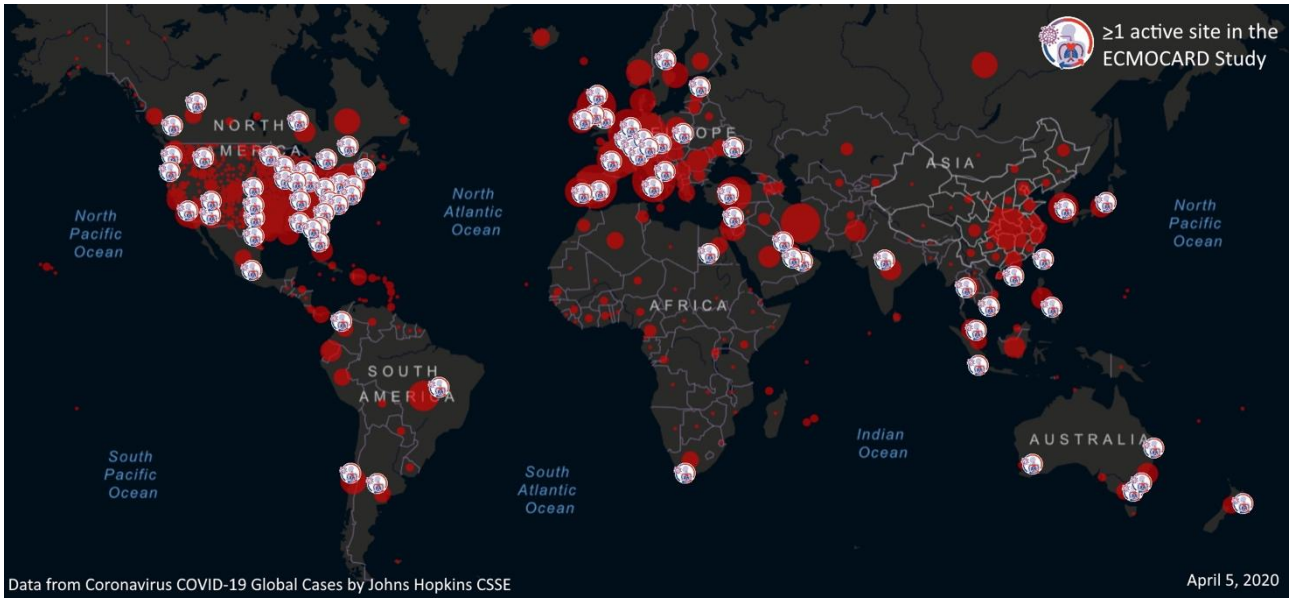

Figure 3 Caption: Global outbreaks by SARS-CoV-2 and ECMOCARD collaborative centers

Long-term impact of critical care illness and ARDS

Following discharge from the intensive care unit, critically ill patients often present various degrees of physical and neurological impairments, irrespective of the specific diagnosis or severity of illness upon admission. Critical illnesses can cause a large variety of damage to multiple organs, and often recovery requires prolonged post-ICU care. In particular, comprehensive evidence has been published on the long-term deleterious effects of ARDS in patients who survived the acute phase[29]. In an interesting study by Davidson and collaborators[30], ARDS survivors were matched with controls with similar severity and found that ARDS was independently associated with reduced pulmonary function and overall physical function. Herridge et al. studied 109 ARDS survivors up to 5 years from ICU discharge. Physical and neuropsychological disorders were

consistent between 2 and 5 years of follow-up, with incomplete recovery even after 5 years. ARDS patients returned to work within 2 years, but healthcare costs per patient remained substantially increased. Fan and collaborators studied more than 200 patients post-acute lung injury, who were admitted to the ICU with an average APACHE II score of 26 and were followed up for physical disability up to 2 years post discharge[31]. Although evidence of weakness decreased over time, when physical function was compared with matched population norms, 6-min walk distance test and (6MWD) and Medical Outcomes Short-Form 36 Health Survey (SF-36) were compromised at all follow-up times (range, 52–69% of predicted), up to 2 years post discharge. Long-term impact in the subpopulation of ARDS patients undergoing ECMO was evaluated by Grasselli et al.[32] Importantly, mortality rate was 44 and 41% in the ECMO and non-ECMO group, respectively. Among survivors, pulmonary function was almost normal after 1 year, but quality of life and post-traumatic stress disorder was higher in the group not receiving ECMO.

To date no data are available on the long-term effects of COVID-19 post-ICU admission. Nevertheless, evidence from previous investigations on the 2003 SARS outbreak may indicate that COVID-19 could substantially affect quality of life of survivors. In an interesting study by Hui and collaborators[33], 110 SARS survivors (64% healthcare workers) were studied at Hong Kong after 3 and 6 months from symptoms onset. At 6 months 30% of the patients still had abnormal chest radiographs and between 3 and 22% had impairment in specific pulmonary function tests. Overall quality of life was still impaired at 6 months after disease onset. In another cohort of 94 patients who survived SARS, pulmonary function and health status was assessed at one year[34]. A various range of pulmonary function abnormalities were detected in 37% of the patients. Importantly, the health status, as measured through the St. George Respiratory Questionnaire (SGRQ), was still significantly worse compared with the healthy population after 1 year. Likewise, Li Ts and collaborators studied 59 critically-ill SARS patients (mean age 47 years old) up to 1 year[35]. Mortality was 24% at hospital discharge and at 1 year. Respiratory function improved throughout the period of assessment, but patients aged over 40 years had significant impairment in the quality of life even at 12 months.

As for the latest outbreak by MERS in 2012, Batawi and collaborators appraised quality of life of MERS survivors who required hospitalization in Saudi Arabia during 2016-2017. They used

the SF-36 to assess 8 quality of life domains. Importantly, MERS survivors of critical illness reported lower quality of life than survivors of less severe illness, emphasizing substantial impact of MERS and resulting admission to the ICU.

In conclusion, evidence from previous outbreaks of SARI and MERS substantiate an important impact of coronaviruses that cause critical respiratory diseases. To date it is unknown the long-term impact that COVID-19 may have on survivors and long-term studies are needed to address these unexplored fields.

Objectives

Hypothesis

Long-term impact of COVID-19 on neurological, pulmonary, renal, liver function and health-related quality of life is unknown. We theorise that COVID-19 patients admitted to the ICU could have various degrees of organ dysfunctions up to 2 years post ICU discharge, which could result in an impaired quality of life.

Aims

This is a multi-centre international study in survivors of COVID-19, who required admission to the intensive care unit to achieve following aims:

1. Health-related quality of life as measured through:
    a. Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)
    b. Patient Health Questionnaire-9
2. Dynamics of organs dysfunction and recovery
    a. Cardiac injury markers and transthoracic echocardiography
    b. Kidney injury markers
    c. Liver injury markers
    d. Cognitive outcome (Montreal Cognitive Assessment)
3. Recovery of pulmonary function, as measured through
    a. St. George's Respiratory Questionnaire
    b. Pulmonary function testing
    c. Chest radiography
    d. Chest CT-scan following 6 months from ICU discharge
    e. 6-minute-walk test with continuous oximetry.

Materials and Methods

Study Design

This is an international multi-centre, prospective observational study of patients who have been infected by SARS-CoV-2, developed COVID-19 and were admitted to an ICU. The study will

be conducted at Australian and international hospitals collaborating within the ECMOCARD network. Patients will be studied from time of ICU discharge up to 24 months. Information will be collected on demographics, co-existing illnesses before ICU admission, severity of illness during ICU admission and post-ICU quality of life and organ dysfunction/recovery.

Research centres

This is a collaborative effort among collaborative centres of the ECMOCARD study network.

Study Population

We plan to recruit 500 consecutive patients with COVID-19 infection admitted to the ICU, in 10-20 participating international centres, who meet the inclusion criteria with no-exclusion criteria at the participating sites. It is anticipated that each participating Institution could contribute between 2 up to 50 patients, with attrition allowance of 100 patients. Each site's recruitment will be determined by the incidence of the disease during the study period, and their ability to collect the required data throughout the long-term study period.

Inclusion Criteria

1. Clinically suspected or laboratory-confirmed COVID-19 infection by real-time PCR
2. Admission to an intensive care unit for COVID-19 and discharge
3. Written informed consent from the patient at the time of discharge from the ICU (APPENDIX A)
4. Previous enrolment into the COVID-19 Critical Care Consortium observational study
5. Aged ≥18 years

Exclusion Criteria

1. Pregnancy
2. Patients unable to complete long-term follow-up, due to logistical problems
3. Patient paralysed before being admitted to hospital for COVID-19 (e.g. stroke, neuromuscular disorders)

4. History of pulmonary resection
5. Previous pulmonary transplant
6. Documented advanced neurologic disorder for which the patient is unable to carry out 6-min walk test
7. Documented psychiatric disease for which the patient is unable to carry out interview

Co-enrolment

This is an observational longitudinal study in patients previously enrolled into the ECMOCARD observational study. Co-enrolment with other studies including interventional clinical trials is accepted.

Ethics

Guiding Principles

The Chief Investigators and study management team are responsible for ensuring the study is performed in accordance with the protocol. This study is to be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964, most recently amended in October 2013), and the most recent, relevant ethical conduct of research guidelines published in the country of the participating site. The Principal Investigator at each site is responsible for maintenance of a securely held enrolment log linking the patient hospital record number and the study number as per their countries research guidelines.

Comply with all local requirements

National or regional Coordinators in their defined location will be responsible for clarifying the requirements for ethics approval. It is the responsibility of the site Chief Investigator and Research Coordinator to ensure ethics approval has been granted prior to commencing the study and all local requirements are addressed. Each participating site will require ethics approval for this protocol, data collection, and any other study documents relevant to their region. When possible, each participating study site will be supported by the AFTERCOR, Project Officer with

their application. The Principal Investigator will produce progress reports, and any other required documentation for the local independent Ethics Committee in accordance with their guidelines. It is the responsibility of the Chief Investigator at each participating hospital to keep an up to date record of all correspondence and applicable documentation with the local Independent Ethics Committee. We will be collecting data on the requirements and the time frame for approvals in each participating network region.

Confidentiality of patient data

No identifying data will be entered into the central database. Participants' names and phone numbers will be collected, and confidentiality of information in medical records will be preserved locally by the site Research Coordinator. The confidentiality of the participant will be maintained unless disclosure is to comply with the law.

Informed consent

Only in patients who meet the inclusion/exclusion criteria, informed consent will be obtained directly from the patient, upon ICU discharge. If the patient is unable to provide a consent form upon admission, informed consent will be obtained by his/her next of kin and then will be obtained from the patient at the first follow-up, at 3 months following ICU discharge.

Data Collection Methods

As detailed in following paragraphs, we will use ECMOCARD data collected on patient demographics, ethnicity, presence of predefined comorbidities, severity of critical illness, clinical course during ICU stay and antiviral and antibiotic medications. Then, patients' clinical status will be followed-up at 3, 6, 12, 18 and 24-month post ICU-discharge. In order to evaluate the health-related quality of life prior to the admission to the ICU, upon the first visit at 3 months post-ICU discharge, we will ask the patient to complete an additional Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and St. George's respiratory questionnaire (SGRQ), based on his/her recollection of his/her clinical status before admission to the ICU.

Data collection

Based on previous data collection for the ECMOCARD study, each site has been identified via a 3-digit network code, a 3-digit site code, and each patient has been assigned a 4-digit sequential patient code making up the patient ID number at time of originally enrolment in ECMOCARD. The site code was obtained by registering on the eCRF, data management system upon initial collaboration with ECMOCARD. Thus, patient numbers have been assigned sequentially for each site beginning with 0001. The full patient identification number will therefore be a 10-digit number, with the format of the following: network code - site code – individual patient code [_][_][_]-[_][_][_]-[_][_][_][_](eg. 001-012-0001). ***We will use the 10-digit number previously provided by the ECMOCARD study to identify ECMOCARD patients who will be also enrolled into the AFTERCOR study and followed up for two years. Access to the data entry system will be protected by username and password.*** Username and password will be assigned by the University of Queensland during the registration process of the AFTERCOR study for individual Research Coordinators or Site Investigators. All electronic data transfer between study site and database will be username and password protected. Each centre will maintain a trial file including a protocol, ethics approval documentation, and paper CRFs. ***The Research Coordinator will compile an enrolment log including the patient's name, contact information (phone number), age, hospital identification number and the unique ECMOCARD study number, which will also be used for the AFTERCOR study. Subsequent data will be identified by the unique study number only. A participant list will be used in each study site to match identifier codes in the database to individual patients in order to record clinical outcomes and supply any missing data points. The Participant List will be maintained locally and will not to be transferred to any other location. The enrolment log and study data will be kept separately.***

The AFTERCOR data collection forms will be also made available at all participating sites as a paper CRF. The AFTERCOR CRF will be available in a variety of languages and will be translated into languages appropriate for all participating sites. The translation of the paper and electronic CRFs from English into the required language will be the responsibility of the national lead investigators and collaborators of the Critical Care Research Group and checked for consistency by an appropriate investigator in the relevant country. All data will be collected by trained staff

at each study site and these individuals will enter all required data described in the protocol into the CRFs directly from the source data. Trained staff at sites with the IT capabilities can enter all required data directly into the protected online database, known as the eCRF; paper CRFs are the alternative option for direct data entry with subsequent transcription, upon completion, into the eCRF. ***Information recorded in the CRF and eCRF should accurately reflect the participants' examinations carried out at each follow-up visit.*** The Research Coordinator or Site Investigator will have the ability to choose the process they use to enter data into the eCRF, where data may be entered at one time or intermittently. If used, the original paper based CRF will be stored within a locked office in each study site. The intent of this process is to improve the quality of the clinical study by providing prompt feedback to the Investigators on the progress of the submitted data and to enhance the ability to collect early safety information in a more timely fashion to fully comply with the intent of GCP requirements. ***Data will be entered into an online eCRF database managed by the University of Queensland.*** In Countries unable to upload data on a centralised database the right to retain a local database on a national server is available with aggregated completely anonymised data exported centrally for analysis.

Screening log

No screening log will be maintained.

Data quality

Several procedures to ensure data quality and protocol standardisation will help to minimise bias. These include:

1. Online meetings for all research coordinators will be held to ensure consistency in procedures;
2. A detailed data dictionary will define the data to be collected on the case report form;
3. Quality checks will be built into the data management system and there will be quality checks of critical data points entered into the CRFs to ensure standardization and validity of the data collected;

An achievable data set will be fundamental to the success of the study. We have identified the key data points whilst not discouraging centres from participating through an excessive burden of data collection. Data queries may be generated, depending on resource availability. Any information that is not available for the investigator will not be considered as missing. No assumptions will be made for missing data. We will examine whether missing data is associated with patient characteristics such as age and comorbidity.

Data management

Data entry and data management will be coordinated by the AFTERCOR steering committee, including programming and data management support. On behalf of the management committee, University of Queensland will act as custodian of the data. The management committee of the trial will take responsibility for the content and integrity of any data. Participating institutions will adhere to the research and data sharing policies of AFTERCOR, Sample and Data Sharing Policy, Version 0201.1.1. ***Clinical investigators contributing to the research efforts will be given full recognition for their efforts and will be given the opportunity to access data. Ownership of any data transferred to the eCRF will be retained by the site that contributed it.*** All analysis of pooled data will be undertaken with the explicit agreement of each site who contributed. AFTERCOR management committee will retain the right to use all pooled data for scientific and other purposes. All members of the study group will have the right to access the pooled data for research purposes provided the research proposal has been reviewed and deemed satisfactory by the management committee following publication of the primary manuscript. Individual patient data provided by participating sites will remain the property of the respective institution. Of note, a data management plan will be developed to address researchers' intentions related to generation, collection, access, use, analysis, disclosure, storage, retention, disposal, sharing and re-use of data and information, the risks associated with these activities and any strategies for minimising those risks.

Monitoring

Data monitoring will be conducted on a randomly selected subset (up to 5%) of cases, through discussion with the local site investigator to discuss data collection techniques. Direct site visits will not be feasible, given the scope of the study.

ECMOCARD Previously Collected Parameters

The following parameters, previously collected for the ECMOCARD study will be used to describe baseline clinical status, upon ICU discharge and enrolment into AFTERCOR.

Demographics and Medical History prior to ICU admission

1. Demographics
2. Comorbidities

ICU admission/stay

1. Duration of hospital stay
2. Duration of ICU stay
3. Duration of invasive mechanical ventilation
4. Duration of ECMO
5. Last blood gases prior to ICU discharge
6. Need of haemodialysis upon ICU discharge
7. Use of vasoactive drugs during ICU stay
8. Use of cardiac-assist devices during ICU stay
9. Acute physiology and chronic health evaluation (APACHE II) score upon ICU admission
10. Sequential organ failure assessment (SOFA) score upon ICU admission
11. Use of anti-viral treatment during ICU stay
12. Use of antibiotics during ICU stay
13. Use of prone position during ICU stay
14. Use of neuromuscular blockade during ICU stay
15. Use of inhaled nitric oxide during ICU stay
16. Most common ventilatory mode during invasive mechanical ventilation

a) Average tidal volume (ml/Kg of ideal body weight) during invasive mechanical ventilation
b) Average positive end-expiratory pressure during invasive mechanical ventilation
c) Average airway plateau pressure during invasive mechanical ventilation

17. Haemoglobin upon ICU discharge
18. White blood cells upon ICU discharge
19. AST upon ICU discharge
20. ALT upon ICU discharge
21. Creatinine upon ICU discharge
22. Infectious complications during ICU stay
23. Haemorrhagic complications during ICU stay
24. Transfused blood during ECMO
25. Transfused plasma during ECMO
26. Transfused platelets during ECMO
27. Transfused cryoprecipitates during ECMO

Pre-Admission clinical status

After 3 months from ICU discharge, we will determine patient's clinical frailty score[36] before ICU admission, through recollection of his/her clinical status by the patient and/or relatives, as reported in the questionaries in the APPENDIX A.

Post-ICU assessments

In the following sections, we describe parameters that will be assessed and recorded at 3, 6, 12, 18 and 24 months after ICU discharge (Figure 1 and 2):

Health-related quality of life

We will measure, at each follow up visit, the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), using the original SF-36 stemmed from the Medical Outcome Study[37],

which was conducted by the RAND Corporation (APPENDIX B). The SF-36 is a 36-item patient-reported questionnaire to appraise health-related quality of life[38]. The SF-36 comprises eight multiple-item domains to appraise the following aspects:

1. Physical functioning (10 items)
2. Bodily pain (2 items)
3. Role limitations due to physical health problems (4 items)
4. Role limitations due to personal or emotional problems (4 items)
5. Emotional well-being (5 items)
6. Social functioning (2 items)
7. Physical energy/fatigue (4 items)
8. General health perceptions (5 items).

Scores for each domain range from 0 to 100, with a higher score defining a more favourable health state. Scores for each aspect can range from 0 (worst) to 100 (best).

Additionally, we will screen for symptoms of depression through the Patient Health Questionnaire-9 (PHQ-9), which is a self-administered diagnostic instrument. It consists of 10 questions and scores each of the nine DSM-IV criteria as 0 (not at all) to 3 (nearly every day). This screening tool has been validated for the use in primary care.

Dynamics of kidney, liver and neurological injury and recovery

We will measure at each follow-up visit, the following parameters:

1. Full blood count
2. Creatinine
3. eGFR
4. AST and ALT
5. gGT and GLDH, bilirubin
6. Need of haemodialysis since the last follow-up visit
7. Hospital admissions for neurological decompensation since ICU discharge or last follow-up visit
8. Hospital admissions for cardiac failure since ICU discharge or last follow-up visit

9. Hospital admissions for renal failure since ICU discharge or last follow-up visit
10. Hospital admissions for liver failure since ICU discharge or last follow-up visit

Neurological injury and recovery

We will measure at each follow-up visit (Figure 1 and 2) the Montreal Cognitive Assessment Score[39], as shown in the APPENDIX B to assess cognitive impairment and recovery.

Cardiac injury and recovery

We will measure at each follow-up visit (Figure 1 and 2) pro-BNP and in patients who underwent an echocardiography during the ICU stay, we will perform a transthoracic echocardiography at 3, 12 and 24 months post ICU discharge.

Dynamics of pulmonary injury and recovery

We will measure at each follow-up visit (Figure 1 and 2) the following parameters:

1. Arterial blood gases test *will be carried out until partial pressure of oxygen and carbon dioxide achieve values ≥75 and ≤ 42 mmHg, respectively*.
2. Admissions for respiratory failure since ICU discharge or last follow-up visit
3. Respiratory infections since ICU discharge or last follow-up visit

Pulmonary imaging

We will measure at each follow-up visit a chest radiography (Figure 1 and 2) *until the chest radiography is reported as normal by a fully-trained radiologist*. In addition, only in patients who underwent a Chest CT-scan during their ICU stay, during the second visit at 6-month post-ICU discharge, a pulmonary computed tomography will be carried out.

St. George's Respiratory Questionnaire

St. George's respiratory questionnaire (SFRQ) (APPENDIX B) measures quality of life associated with chronic respiratory diseases and it has been used in various reports of long-term impact of ARDS[30,34,40,41]. The SGRQ results are grouped into 3 domains (symptoms, activity, and impacts). Total score ranges from 0 to 100 with a lower score indicating better pulmonary-specific quality of life. A 4-point change in the SGRQ has been determined to be a clinically meaningful difference[30,42].

Pulmonary function testing

We will measure basic spirometry parameters at each follow up visit, pre and post bronchodilation, according to the standards of the American Thoracic Society[43]. *As reported above, in case in the previous follow up partial pressure of oxygen and carbon dioxide be ≥75 or ≤ 42 mmHg, respectively, breathing room air, (Figure 1), we will not repeat pulmonary function tests*. Conversely, in case partial pressure of oxygen and carbon dioxide be consistently <75 or > 42 mmHg, respectively, breathing room air, we will extend assessments as follows:

1) Body plethysmography

2) Airway resistance

3) Gas exchange

6-minute-walk test with continuous oximetry

A standardized 6-minute-walk test will be carried out in duplicate at each follow-up visit post ICU discharge following recommendation from the European Respiratory Society[44]. *Of note, in case patients will achieve minimal normal reference values, as computed by predictive equations below, the test will not be repeated in the following follow up.*

Predictive equation for males: 6MWD(m) = 867 – (5.71 age, yrs) + (1.03 height, cm)

Predictive equation for females: 6MWD(m) = 525 – (2.86 age, yrs) + (2.71 height, cm) – (6.22 BMI).

The 6-minute-walk-test provides an objective measure of cardiopulmonary and musculoskeletal functions. The distance walked in 6 minutes will be computed. In addition, arterial oxygen saturation will be continuously monitored and recorded during testing.

Power calculation

We did not use a formal sample size calculation to arrive at a figure of 500 patients. This is because this is not a hypothesis testing study, and hence we have no primary outcome on which to base a sample size. Instead this is an observational study that will examine multiple research questions. A target of 500 patients will give good power to detect differences between groups, for example it gives a 90% power to detect a standardized difference of 0.33 between two equally sized groups (using a two-sided alpha of 0.05).

Data Analysis

Summary statistics will be used to describe the sample characteristics at ICU discharge. Plots will be used to summarise outcomes over time for both individual patients and averages by groups. Multivariable regression analyses will be used to examine associations between baseline characteristics and severity variables upon admission and discharge in the ICU, and how these impact outcomes at 3, 6, 12, 18 and 24 months after ICU discharge. The residuals of the models will be checked for multi-modality, skew and outliers. Models will also be checked for collinearity and influential values. We will use Kaplan-Meier methods to appraise survival probabilities from the date of discharge from the ICU. Statistical significance will be set at $p<0.05$.

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Regulation, Ethics and Governance

The Protocol, and any following amendment to the original protocol, will be potentially translated to the main language of the collaborative institution and submitted for the approval of each institutional review board (IRB). All protocols of the study will require approval by each institutional review board, before enrolment of patients.

Each Principal Investigator will be responsible for the oversight of relevant local Governance review and approval, as per their individual institution requirements. The Principal Investigator will ensure that their study team possess adequate training and appropriate qualifications to conduct the trial in line with the principles of Good Clinical Practice (GCP) and their local laws and regulations.

Conflict of interest

The investigators who developed this study protocol DO NOT have any significant financial or personal interest that would reasonably appear to be affected by the proposed research activities.

Data collection and Site Monitoring plan

Data Collection

Data will be collected in dedicated electronic forms and/or hard copies as provided by the AFTERCOR study organization. A custom-designed electronic case report form will be developed in REDcap and will be hosted at the University of Queensland, Australia. Hard copies and electronic data will be kept for at least 7 years following the conclusion of the study. Each investigator will be responsible to collect and preserve data obtained at his/her collaborative institution.

Site Monitoring

All investigators of the study will meet every 6 months, to monitor the quality of the data collected and prepare future publications

Compensations

No compensation will be offered to collaborating institutions.

Data Access

All essential documentation of the AFTERCOR will be stored in an Investigator Study File (ISF), which will be held by the University of Queensland. On completion of the study, this information will be archived by the investigators of the Critical Care Research Group, Chermside, Australia. Following the publication of the primary and secondary outcomes, additional analyses could be undergone on the data collected. In the event of publications arising from these analyses, those responsible will need to provide the Chief Investigator with a copy of the manuscript for approval prior to submission.

Feasibility

This is a multi-centre study performed within the ECMOCARD network of clinical research institutions. The study will be conducted in centres that have collaborated for the recruitment of intensive care unit patients into ECMOCARD and with broad experience in critical illnesses and post-ICU complications. In summary, the ECMOCARD international network of collaborators provides ideal conditions to perform reported study.

Dissemination and Publication

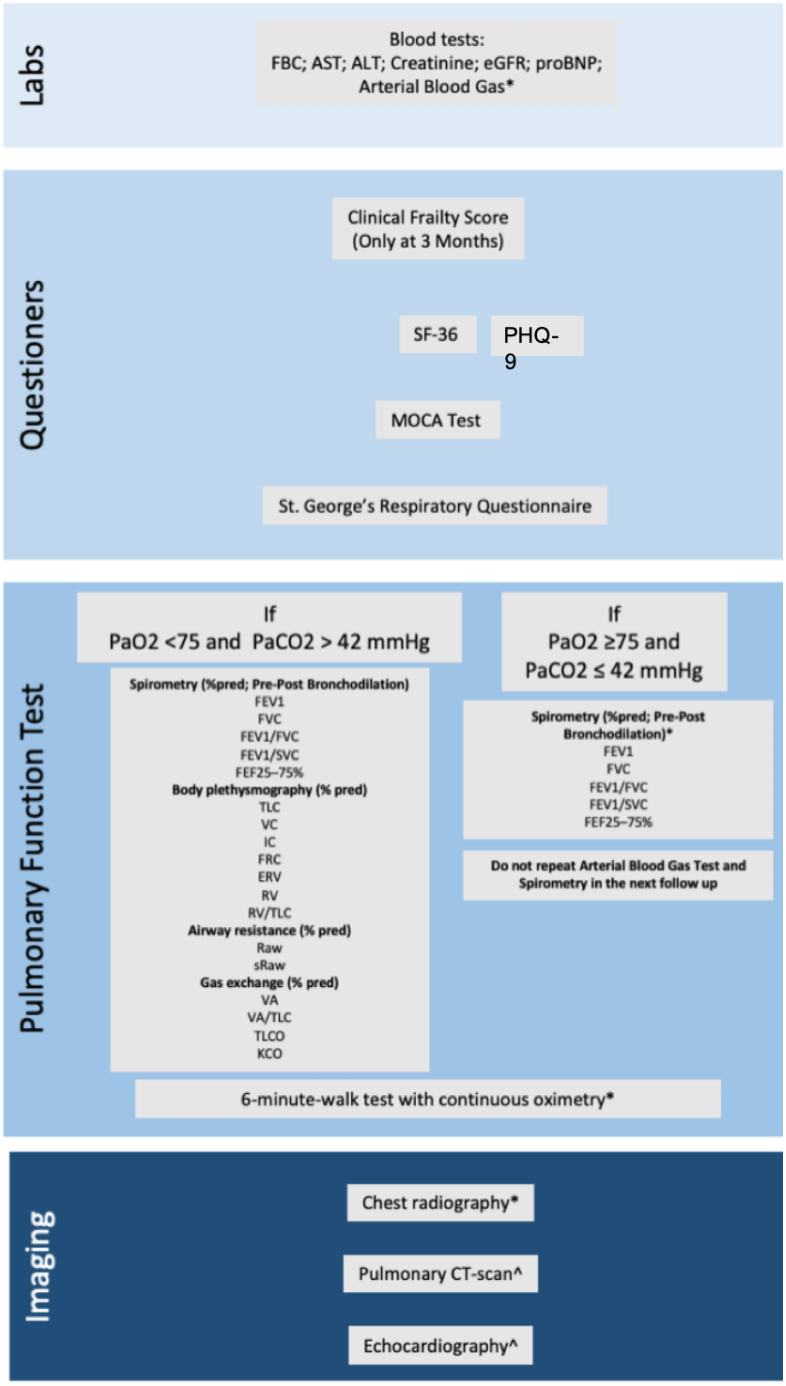
Publication policy

Ownership of the data arising from the study resides with the study teams. After the study, results will be analysed and tabulated and a study report will be prepared. This report will be made available to the study collaborators and the relevant IRBs. The study findings will be presented at national and international meetings. We plan to publish our study findings in a high-quality peer reviewed journal.

Authorship policy

Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org). Authorship of parallel studies conducted outside of the main trial will be according to the individuals involved in the study but must acknowledge the contribution of the involved investigators.

Figure 1

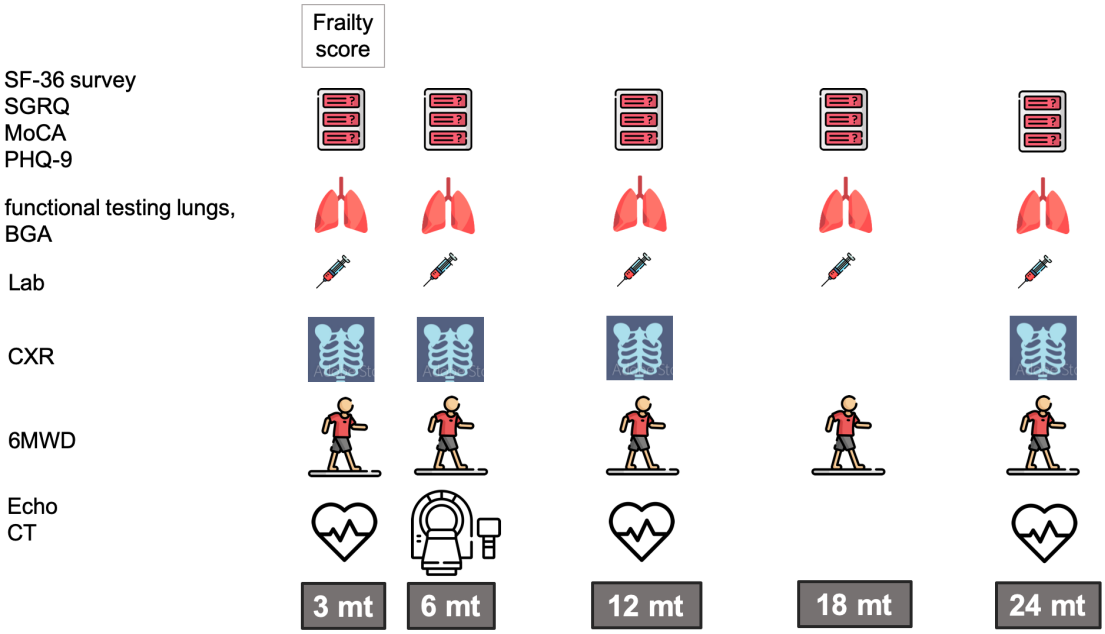


Planned assessments

Figure 1 caption: FBC, full blood count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; N-terminal (NT)-pro hormone brain natriuretic peptide; SF-36, 36-item short form survey; MOCA, Montreal cognitive assessment; PaO2, arterial partial pressure of oxygen; PaCO2, arterial partial pressure of carbon dioxide; FEV1: forced expiratory volume in 1 s; FVC: forced expiratory volume; SVC: slow vital capacity; FEF25–75%: forced expiratory flow between 25 and 75% of FVC; TLC: total lung capacity; VC: vital capacity;

IC: inspiratory capacity; FRC: functional residual capacity; ERV: expiratory reserve volume; RV: residual volume; Raw: airway resistance; sRaw: specific airway resistance; VA: accessible alveolar volume; TLCO: transfer factor of the lung for carbon monoxide; KCO: transfer coefficient of the lung for carbon monoxide. CT, computed tomography; * We will perform these tests until normalization; ^Only in patients who underwent CT-scan/echocardiography during ICU admission.

Figure 2



Timeline of assessments

Figure 2 caption: SF-36, 36-item short form survey; SGRQ, St George Respiratory Questionnaire; MOCA, Montreal cognitive ass
PHQ-9, Patient Health Questionnaire-9; BGA, Blood Gas Analysis; Lab, Laboratory Analysis; CXR, Chest X-Ray; 6MWD, 6 minute
Test; Echo, Echocardiography; CT, Computertomography

APPENDIX A: INFORMED CONSENT

Retrospective patient Information Sheet

Centre No. _____

City, Country _____

PATIENT INFORMATION SHEET

Version 1.2.0 – June 20, 2020

Title of project: **Long-term impAct in inTEnsive caRe survivors oF CORonavirus disease-19**

Local Investigator: [name and telephone number]:_____

You were recently admitted to the intensive care unit for Coronavirus Disease 2019 (COVID-19). We would like to ask you permission to collect your clinical data after discharge from the intensive care unit for an observational research study and to understand the burden of COVID-19 after discharge. Before you decide to participate to this study and to allow us to use your data, it is important for you to understand why the research is being done and what it is involving. Please read the following information carefully and, if you wish, discuss further with your relatives or friends. Ask us if there is anything that is unclear or if you would like more information. Thank you for reading this.

1) What is the purpose of the study?

In late December 2019, a new coronavirus causing severe respiratory infection has been discovered. The infection originated from Wuhan, Hubei, China, and spread worldwide. The infection is caused by a coronavirus named 2019 novel coronavirus (2019-nCOv) and caused a disease named COVID-19. Patients with COVID-19 often required intensive care, because they were too sick to be managed in a normal medical ward. Given that COVID-19 is a novel disease

not fully defined and investigated, medical doctors are uncertain how to treat this disease. In addition, the long-term effects of COVID-19 in patients who have been discharged from the intensive care unit is completely unknown. Thus, we designed this study to primarily assess the burden of COVID-19 in patients who have recovered from the acute disease and who have been discharged from the intensive care unit. This trial has been designed by highly specialized doctors in the field of Intensive Care Medicine, Respiratory Medicine and with great experience in clinical studies. This is an international study, which comprises many hospitals in Australia, Europe, North America, South America, Asia and Africa, involving patients who were previously admitted into the intensive care units. This study has been reviewed and approved by the Research Ethics Committee of your hospital.

2) Why have I been chosen?

You have been chosen because you have been infected by 2019-nCOv and developed COVID-19 and during the course of the infection you were admitted to an intensive care unit. Hence, we would like to inclusively examine your recovery post discharge from the intensive care unit to understand the long-term effects of COVID-19.

3) Do I have to take part?

It is up to you to decide whether you could be available to be examined by the investigators following discharge from the intensive care unit. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you will receive in the future from any hospital. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form, a copy of the consent form will be also given to you.

4) What will happen to me if I take part?

As part of the study, after you are discharged by the intensive care unit, we will contact you and schedule various hospital visits – after 3, 6, 12, 18 and 24 months from the intensive care unit discharge – with a medical doctor and investigators who are collaborating with this study. During these visits we will perform the following assessments:

Blood tests: It is a procedure in which a sample is taken of your venous blood to get information about your health and to assess the effects of COVID-19 to your heart, kidneys and liver

Arterial blood gas test: A blood gas test requires the collection of a small sample of arterial blood. Arterial blood can be obtained from an artery in your wrist.

Quality of life questionaries: We will ask you to complete 3 forms to assess the recovery and your quality of life post-COVID-19 infection. Completion of these tests will take approximately 2 hours.

Pulmonary Spirometry: The test usually takes about 15 minutes. During the procedure a doctor or a nurse will place a clip on your nose to keep both nostrils closed and they will place a cup-like breathing mask around your mouth. Afterward, the doctor will instruct you to take a deep breath in, hold your breath for a few seconds, and then exhale as hard as you can into the breathing mask. You will repeat this test at least three times to make sure that your results are consistent. Your doctor will also give you an inhaled medication known as a bronchodilator to open up your lungs after the first round of tests. They'll then ask you to wait 15 minutes before doing another set of measurements.

Body Plethysmography: A respiratory care technician will perform this test. You will sit or stand in a small, airtight chamber that is partially or completely see-through and may resemble a phone booth. Like in the spirometry, the technician will put clips on your nose to shut off air to your nostrils. They you will be asked to breathe or pant against a mouthpiece when it is both opened and closed. This will provide your doctor with important measurements, including the amount of air left in your lungs when you breathe out normally, which is called functional residual capacity (FRC); how much air is left when you breathe out as much as possible, or residual capacity (RC). The test usually takes three minutes to perform. This test may include a tracer gas such as carbon dioxide in the air you breathe during the test to evaluate the capability of your lungs to exchange gases.

Chest X-ray: During the procedure, your body is positioned between a machine that produces the X-rays and a plate that creates the image digitally or with X-ray film. You may be asked to move into different positions in order to take views from both the front and the side of your chest. During the front view, you stand against the plate, hold your arms up or to the sides and roll your shoulders forward. The X-ray technician may ask you to take a deep breath and hold it for several seconds. Holding your breath after inhaling helps your heart and lungs show up more clearly on the image. During the side views, you turn and place one shoulder on the plate and raise your hands over your

head. Again, you may be asked to take a deep breath and hold it. If you have trouble standing, you may be able to have the exam while seated or lying down.

Chest computed tomography scan (only one time after 6 months from the intensive care discharge and only if you underwent this test during your initial admission to the hospital for COVID-19): Chest CT scan is a more detailed type of chest x ray. This painless imaging test takes many detailed pictures, called slices, of your lungs and the inside of your chest. Computers can combine these pictures to create three-dimensional (3D) models to help show the size, shape, and position of your lungs and structures in your chest. Chest CT scan will be done in the radiology department. The CT scanner is a large, tunnel-like machine that has a table. You will lie still on the table and the table will slide into the scanner. You will hear soft buzzing or clicking sounds when you are inside the scanner and the scanner is taking pictures. You will be able to hear from and talk to the technician performing the test while you are inside the scanner.

Transthoracic echocardiography: The test will take less than an hour. During the procedure you will need to undress from the waist up. The technician will attach electrodes to your body. Then, the technician will move an ultrasound transducer back and forth on your chest to record the sound waves of your heart as an image. You may be asked to breathe or move in a certain way.

5) What do I have to do?

You do not have to do anything yourself throughout this 2-year study, we will arrange all hospital visits and we will sort every appointment related to this study on your behalf. The medical doctor and investigators will keep you informed at all times.

6) What are the possible risks and benefits of taking part?

Risks of this study are minimal given that we will only perform non-invasive assessments. Nevertheless, risks associated with each test are detailed below:

Blood tests: The main risks of blood tests are discomfort and bruising at the site where the needle goes in. These complications usually are minor and go away shortly after the tests are done

Arterial blood gas test: The main risks of blood tests are discomfort and bruising at the site where the needle goes in. These complications usually are minor and go away shortly after the tests are done. Yet, it is important to emphasize that the needle for arterial blood gas test is thinner than needles for standard blood test.

Quality of life questionaries: No risks

*Pulmonary Spirometry: F*ew complications can occur during or after a spirometry test. You may feel a bit dizzy or have some shortness of breath immediately after performing the test. In very rare cases, the test may trigger severe breathing problems.

Body Plethysmography: The main risks associated with lung plethysmography include dizziness, light-headedness, shortness of breath and anxiety, if you are uncomfortable in tight spaces.

Chest X-ray: A chest X-ray is a painless, non-invasive procedure with marginal risks. X-rays use a small amount of radiation, about the same levels that occur naturally in the environment. The lowest possible amount of radiation needed to produce the image will be used during the assessment. Importantly, chest X-rays will be performed protecting the abdomen from radiation.

Chest computed tomography scan: There is always a slight chance of cancer from excessive exposure to radiation. Hence we will perform chest computed tomography scan only one time after 6 months from the intensive care discharge and only if you underwent this test during your initial admission to the hospital for COVID-19. We will not use contrast media; hence you will not have any risk of allergic reaction to contrast media

Transthoracic echocardiography: There are no known risks from a transthoracic echocardiography. However, during the test the technician may have to press hard on your chest with the transducer and you may feel brief discomfort.

7) Will my taking part be kept confidential?

All information that has been collected about you during the course of the research study will be kept strictly confidential. Your identifying details will be held in a secure environment and only accessed by the research team for the purposes of follow up.

8) What will happen to the results of the research study?

The study is estimated to take around two years and six months.. It is hoped to be finished by May 2024. If you would like a copy of the published results, please contact the Principal Local Investigator.

Contact for further information

If you would like further information, please feel free to contact _____, the leading investigator of the study at this site.

Patient Consent Form

Centre No. _____
City, Country _____

PATIENT CONSENT FORM

Version 1.2.0 – June 20, 2020

Title of project: **Long-term impAct in inTEnsive caRe survivors oF CORonavirus disease-19**

Local Investigator: [name and telephone number]:_____

I,……(Full Name and Surname) acknowledge and certify that:

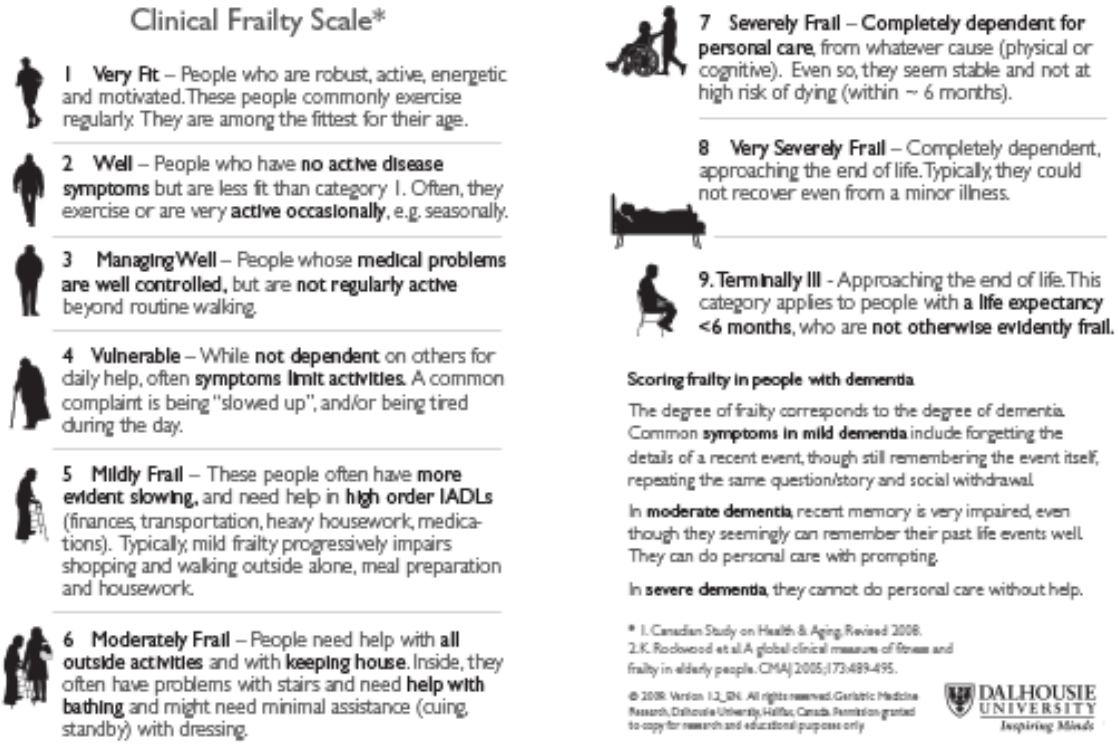
1. I confirm that I have read and understand the information sheet dated _____ for the above study and have had the opportunity to ask questions
2. I understand that my participation is voluntary and that I am free to withdraw my consent at any time, without giving any reason and without my medical care or legal rights being affected
3. I understand that sections of my medical notes and results from various tests may be looked at by responsible individuals involved with the study. I give permission for these individuals to have access to my records
4. I give permission for my personal identifying information to be collected, stored and used by the study office to enable follow up my health status. This is on the understanding that any information will be treated with the strictest security and confidentiality
5. I give permission for my local investigator to contacted me to have updates on my health status and schedule follow up visits
6. I agree to take part in the above study

Name of patient	Date	Signature
_____	_____	_____
Name of person taking consent (if not Principal Local Investigator)	Date	Signature
_____	_____	_____
Name of Principal Local Investigator	Date	Signature
_____	_____	_____

1 copy for patient, 1 for Principal Local Investigator, 1 to be kept with hospital notes

APPENDIX B: QUESTIONNAIRS

Clinical Frailty score



Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house.** Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail – Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging. Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

DALHOUSIE UNIVERSITY Inspiring Minds

SF-36 Questionnaire

Today's date:____/_____/_____ **ID No:__ __ __ __ __ __**

First name:_____ Surname: _____

SF-36 Questionnaire

This questionnaire asks for your views about your health. For ALL questions, please tick, cross or colour the circle that most closely matches your response. There are no right or wrong answers. Please answer ALL questions.

1. In general, would you say your health is:	Poor ◯	Fair ◯	Good ◯	Very good ◯	Excellent ◯
2. Compared to one year ago, how would you rate your health general in now?	Much worse now than one year ago ◯	Somewhat worse than one year ago ◯	About the same as one year ago ◯	Somewhat better than one year ago ◯	Much better than one year ago ◯

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	No, not limited at all	Yes, limited a little	Yes, limited a lot
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	◯	◯	◯
b. Moderate activities, such as moving a table pushing a vacuum cleaner, bowling, or playing	◯	◯	◯
c. Lifting or carrying groceries	◯	◯	◯
d. Climbing several flights of stairs	◯	◯	◯
e. Climbing one flight of stairs	◯	◯	◯
f. Bending, kneeling or stooping	◯	◯	◯
g. Walking more than a mile	◯	◯	◯
h. Walking several blocks	◯	◯	◯
i. Walking one block	◯	◯	◯
j. Bathing or dressing yourself	◯	◯	◯

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other daily activities as a result of your physical health?					
	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Cut down on the amount of time you spent on work or other activities	◯	◯	◯	◯	◯
b. Accomplished less than you would like	◯	◯	◯	◯	◯
c. Were limited in the kind of work or other activities	◯	◯	◯	◯	◯
d. Had difficulty performing the work or other activities (e.g. it took extra effort)	◯	◯	◯	◯	◯
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?					
	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Cut down on the amount of time you spent on work or other activities	◯	◯	◯	◯	◯
b. Accomplished less than you would like	◯	◯	◯	◯	◯
c. Did work or other activities less carefully than usual	◯	◯	◯	◯	◯
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?					
	Not at all	Slightly	Moderately	Quite a bit	All of the time
7. How much bodily pain have you had during the past 4 weeks?					
None	Very mild	Mild	Moderate	Severe	Very severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?					
	Not at all	A liitle bit	Moderately	Quite a bit	Extremely
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...					
	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. did you feel full of life?	○	○	○	○	○
b. have you been very nervous?	○	○	○	○	○
c. have you felt so down in the dumps that nothing could cheer you up?	○	○	○	○	○
d. have you felt calm and peaceful?	○	○	○	○	○
e. did you have a lot of energy?	○	○	○	○	○
f. have you felt downhearted and depressed?	○	○	○	○	○
g. did you feel worn out?	○	○	○	○	○
h. have you been happy?	○	○	○	○	○
i. did you feel tired?	○	○	○	○	○
10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?					
	None of the time	A little of the time	Some of the time	Most of the time	All of the time
11. How TRUE or FALSE is each of the following statements for you?					
	Defintely false	Mostly false	Don't know	Mostly true	Definitely true
a. I seem to get sick a little easier than other people	○	○	○	○	○

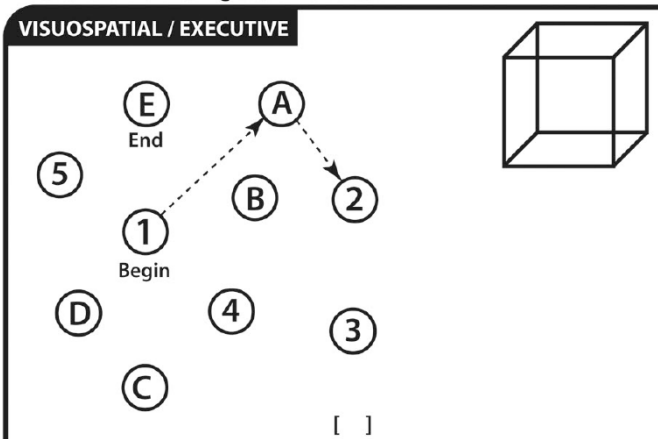
b. I am as healthy as anybody I know	○	○	○	○	○
c. I expect my health to get worse	○	○	○	○	○
d. My health is excellent	○	○	○	○	○

Montreal Cognitive Assessment

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube

[ ] [ ]

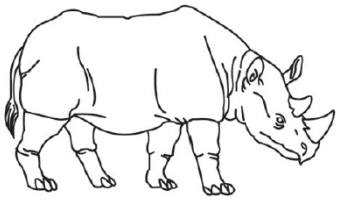
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

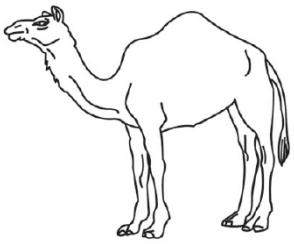
__/5

NAMING

[ ]



[ ]



[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2
__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B
__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**
__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ]
__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)
__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler
__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City
__/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

St. George's Respiratory Questionnaire

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE ORIGINAL ENGLISH VERSION

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have had over the past 3 months.

Please tick (✓) *one box for each question*:

	most days a week	several days a week	a few days a month	only with chest infections	not at all
1. Over the past 3 months, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 3 months, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 3 months, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 3 months, I have had attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 3 months how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) *one*:

- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✓) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 3 months, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✓) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day is good ☐
- every day is good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✓) *one:*

- No ☐
- Yes ☐

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your chest condition?

Please tick (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✓) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

Section 2

Questions about what activities usually make you feel breathless <u>these days</u>.

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

St. George's Respiratory Questionnaire
PART 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough hurts	☐	☐
My cough makes me tired	☐	☐
I am breathless when I talk	☐	☐
I am breathless when I bend over	☐	☐
My cough or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My medication does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My medication interferes with my life a lot	☐	☐

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

	Please tick (✓) in ***each box*** that applies to you ***because of your breathing***: True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
Jobs such as housework take a long time, or I have to stop for rests	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

	Please tick (✓) in ***each box*** that applies to you ***because of your chest trouble***: True	False
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

St. George's Respiratory Questionnaire

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog

Doing things at home or in the garden

Sexual intercourse

Going out to church, pub, club or place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

.....

.....

.....

.....

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐

It stops me doing one or two things I would like to do ☐

It stops me doing most of the things I would like to do ☐

It stops me doing everything I would like to do ☐

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

Patient Health Questionnaire-9 (PHQ-9)

	Not at all	Several days	More than half the days	Nearly every day
1. Over the *last 2 weeks,* how often have you been bothered by any of the following problems?				
a. Little interest or pleasure in doing things	☐	☐	☐	☐
b. Feeling down, depressed, or hopeless	☐	☐	☐	☐
c. Trouble falling/staying asleep, sleeping too much	☐	☐	☐	☐
d. Feeling tired or having little energy	☐	☐	☐	☐
e. Poor appetite or overeating	☐	☐	☐	☐
f. Feeling bad about yourself or that you are a failure or have let yourself or your family down	☐	☐	☐	☐
g. Trouble concentrating on things, such as reading the newspaper or watching television.	☐	☐	☐	☐
h. Moving or speaking so slowly that other people could have noticed. Or the opposite; being so fidgety or restless that you have been moving around a lot more than usual.	☐	☐	☐	☐
i. Thoughts that you would be better off dead or of hurting yourself in some way.	☐	☐	☐	☐
2. If you checked off any problem on this questionnaire so far, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all ☐	Somewhat difficult ☐	Very difficult ☐	Extremely difficult ☐

PHQ-9* Questionnaire for Depression Scoring and Interpretation Guide

For physician use only

Scoring:
Count the number (#) of boxes checked in a column. Multiply that number by the value indicated below, then add the subtotal to produce a total score. The possible range is 0-27. Use the table below to interpret the PHQ-9 score.

Not at all (#) _____ x 0 = _____
Several days (#) _____ x 1 = _____
More than half the days (#) _____ x 2 = _____
Nearly every day (#) _____ x 3 = _____

Total score: _____

Interpreting PHQ-9 Scores		Actions Based on PH9 Score	
		Score	**Action**
Minimal depression	0-4	< 4	The score suggests the patient may not need depression treatment
Mild depression	5-9		
Moderate depression	10-14	> 5 - 14	Physician uses clinical judgment about treatment, based on patient's duration of symptoms and functional impairment
Moderately severe depression	15-19		
Severe depression	20-27		
		> 15	Warrants treatment for depression, using antidepressant, psychotherapy and/or a combination of treatment.

* PHQ-9 is described in more detail at the McArthur Institute on Depression & Primary Care website www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/