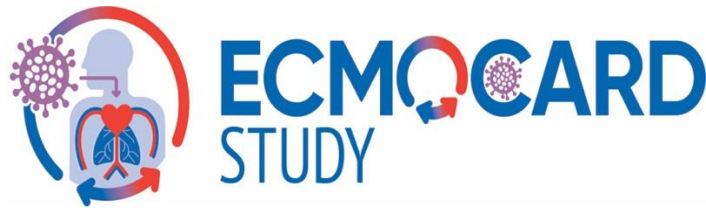




# ExtraCorporeal Membrane Oxygenation for 2019 novel Coronavirus Acute Respiratory Disease



**v. 1.2.6**

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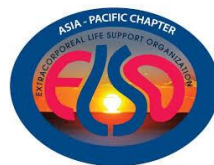
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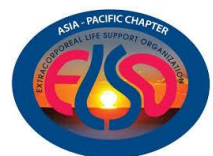


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## Summary

<b>Scientific Title</b>	ExtraCorporeal Membrane Oxygenation for 2019 novel Coronavirus Acute Respiratory Disease (ECMOCARD)
<b>Study Design</b>	Prospective/Retrospective multi-centre short period incidence observational study of patients in participating hospitals and intensive care units (ICUs) with 2019 novel coronavirus (COVID-19).
<b>The Collaborative</b>	<b>In response to the COVID-19 outbreak and to assist in pandemic planning both locally and globally, a research collaborative has been assembled.</b> The collaborative consists of investigators from the Asia-Pacific extracorporeal life support organization (APELSO) in collaboration with centres within the SPRINT-SARI and ISARIC Network. In Australia, this study will be also complemented through collaboration with the “National registry on the treatment and outcomes of patients requiring ECMO” (EXCEL Registry).
<b>Study Aim and Objectives</b>	To describe clinical features; severity of pulmonary dysfunction; incidence of ICU admission and use of mechanical ventilation and ECMO; ECMO technical characteristics; duration of ECMO; complications; and survival of patients with COVID-19.
<b>Inclusions/Exclusions</b>	All patients admitted to ICU with lab-confirmed COVID-19 infection by real-time PCR and/or next-generation sequencing will be included. Patients receiving mechanical ventilation or ECMO for other concomitant causes will be excluded.
<b>Consent</b>	Given the negligible risk associated with this study and the timely nature in which the data needs to be collected, a waiver of consent is sought.
<b>Study Setting</b>	International multi-centre study, conducted in all collaborating hospitals/ICU-based research networks in Asia, Australia and New Zealand, Europe and North America.
<b>Sample Size</b>	All patients with confirmed COVID-19 infection admitted to ICUs at the collaborative centres
<b>Study Start Date</b>	From the commencement of COVID-19 global epidemic
<b>Study Duration</b>	Until completion of COVID-19 global epidemic, as judged by the World Health Organization
<b>Data collection processes</b>	Patients will be studied from time of ICU admission until hospital discharge or up to 28 days post ICU admission, whichever occurs later. All clinical information will only be recorded if taken as part of routine clinical practice at each site. Only re-identifiable data will be submitted centrally (REDCap hosted at Oxford University for International centres and at Monash University for Australian centres). A specific ECMOCARD Case Report Form (CRF) will be used by participating sites to collect a minimum data set of ICU, mechanical ventilation and ECMO data. Data for ECMOCARD and SPRINT SARI observational study will be concomitantly collected. In Australia, patients concomitantly included into the EXCEL registry, EXCEL data will be requested to complement ECMOCARD data and reduce daily workload.

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## Introduction

The ExtraCorporeal Membrane Oxygenation for 2019 novel Coronavirus Acute Respiratory Disease (ECMOCARD Trial) will be carried out within the network and web-based case collection forms of the ISARIC consortium's SPRINT-SARI study and in Australian and New Zealand centres, upon conclusion of the epidemics, potentially complemented through the study "A comprehensive national registry on the treatment and outcomes of patients requiring ECMO" (EXCEL Registry).

### International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC)

The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) was formed in 2011, in response to global recognition of the unmet need for timely and effective clinical research during outbreaks of emerging infectious disease with epidemic or pandemic potential. ISARIC represents a new paradigm for effective, coordinated, and timely collaborative clinical research during rapidly emerging threats to public health. It is collaboration among clinicians, clinical researchers, epidemiologists, ethicists, statisticians, laboratory-based clinicians, basic scientists, and public health experts. The mission of ISARIC is to develop operational readiness and to co-ordinate the conduct of essential clinical research to characterise and respond to new epidemic or pandemic infectious disease threats, thereby informing and guiding evidence-based optimal management. ISARIC is facilitating the coordination of SPRINT-SARI, which supports ISARIC's goal of improving the effectiveness of clinical researching globally during a pandemic by:

1. Establishing protocols, with standardised definitions and study methods, for conducting time-critical research during outbreaks of emerging infectious diseases;
2. Coordinating a large number of globally diversified hospitals and/or ICU-based networks with pre-existing ethics, administrative, regulatory and logistics in place, sufficient to implement study protocols, especially including regions where this type of clinical research has traditionally not been performed;
3. Identifying and solving barriers to pandemic research, including those identified in SPRINT-SARI;
4. Studying SARI globally, providing evidence on SARI microbiology, treatment and outcome in both resource-rich and resource-poor settings;
5. Allowing ISARIC to evaluate its research capacity and capabilities; and

6. Assisting ISARIC to maintain network stakeholders during inter-pandemic periods.

### Short PeRIod IncideNce sTudy of Severe Acute Respiratory Infection (SPRINT-SARI)

Severe acute respiratory infection (SARI) continues to be of major relevance to public health worldwide. In the last 10 years there have been multiple SARI outbreaks around the world. The 2009 H1N1 pandemic was estimated to result in more than 200,000 respiratory deaths globally<sup>1-3</sup>. The World Health Organization (WHO) defines SARI as an acute respiratory infection of recent onset (within 10 days) requiring hospitalisation, manifested by fever ( $\geq 38^{\circ}\text{C}$ ) or a history of fever and cough<sup>4-6</sup>. There is international consensus that it is important to undertake observational studies of patients with SARI as an essential component of pandemic and epidemic research preparedness. The primary aim of the SPRINT-SARI study was to establish a research response capability for future epidemics / pandemics through a global SARI observational study. The secondary aim of this study was to describe the clinical epidemiology and microbiology profiles of patients with SARI. The tertiary aim of this study was to assess the Ethics, Administrative, Regulatory and Logistic (EARL) barriers to conducting pandemic research on a global level. SPRINT-SARI was designed as a multi-centre, prospective, short period incidence observational study of patients in participating hospitals and intensive care units (ICUs) with SARI. The study period was planned to occur, in both Northern and Southern hemispheric winters. The study period comprised a 5 to 7-day cohort study in which patients meeting a SARI case-definition, who are newly admitted to the hospitals/ICUs at participating sites, will be included in the study. The study was planned to be conducted in 20 to 40-hospital/ ICU-based research networks globally. All clinical information and sample data were planned to only be recorded if taken as part of the routine clinical practice at each site and only fully anonymised and re-identifiable data will be submitted centrally. The primary outcome of SPRINT-SARI was to test the feasibility of conducting a global study of SARI.

#### Secondary Outcomes:

1. Incidence of SARI
2. Disease severity and risk factors for severe disease due to SARI
3. Case Fatality Proportion of SARI
4. Duration of ICU/hospital stay due to SARI
5. Microbiology of SARI, including variability in testing



6. Treatments received during hospitalization for SARI
7. Evaluate impact on incidence of alternative case-definitions of SARI
8. Evaluate the operational characteristics of this study, including CRF, Completion Guidelines, and entry criteria to provide information by which iterative improvement in study design can be achieved.
9. Explore the feasibility of extrapolation of results obtained at participating sites to population levels

## Coronaviruses

Coronaviruses are a family of enveloped, single-stranded, positive-strand RNA viruses classified within the Nidovirales. Coronaviruses may infect mammals and birds, triggering respiratory, enteric, hepatic, and neurologic diseases<sup>7</sup>. 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<sup>8,9</sup> and MERS-CoV<sup>10,11</sup>, have caused serious respiratory infections, with mortality rates of 10% for SARS-CoV<sup>12</sup> and 37% for MERS-CoV<sup>13</sup>.

## 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<sup>14</sup>. 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<sup>15</sup> 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 microscopy (Fig. 1).

**Figure 1**

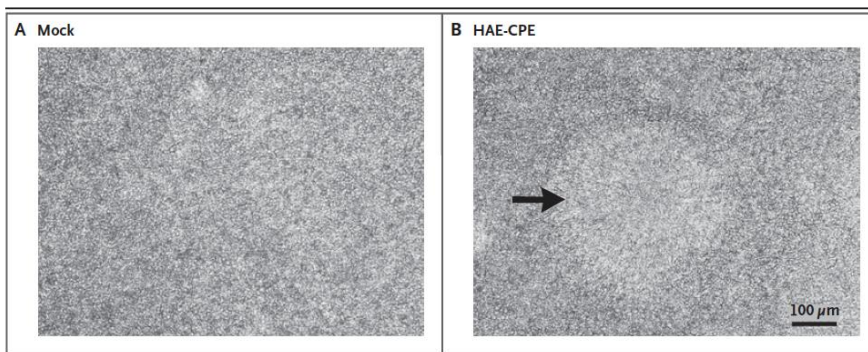


Figure 1: Cytopathic effect of the novel coronavirus, as reported in previous publication<sup>15</sup>

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. 3), and gave virions the appearance of a solar corona. This morphology corroborated the Coronaviridae family.

**Figure 2**

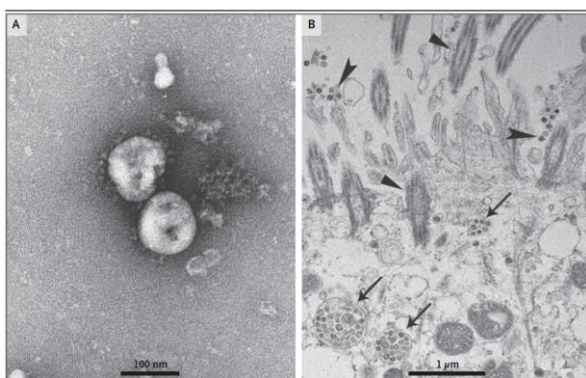


Figure 2: A: COVID-19 particles are depicted. B: COVID-19 in human airway epithelium, as reported in previous publication<sup>15</sup>.

Finally, 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 111,000 confirmed cases, including health-care workers, have been identified worldwide, and several exported cases have been confirmed in other provinces in China, Thailand<sup>16</sup>, Japan<sup>17</sup>, South Korea<sup>18</sup>, Germany, Italy<sup>19</sup>, France, Iran<sup>20</sup>, USA<sup>21</sup> and many other countries<sup>22</sup>. An early case report in 41 patients with laboratory-confirmed COVID-19 infection in Wuhan has been reported<sup>23</sup>. 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 (Figure 3)<sup>24</sup>.

**Figure 3**

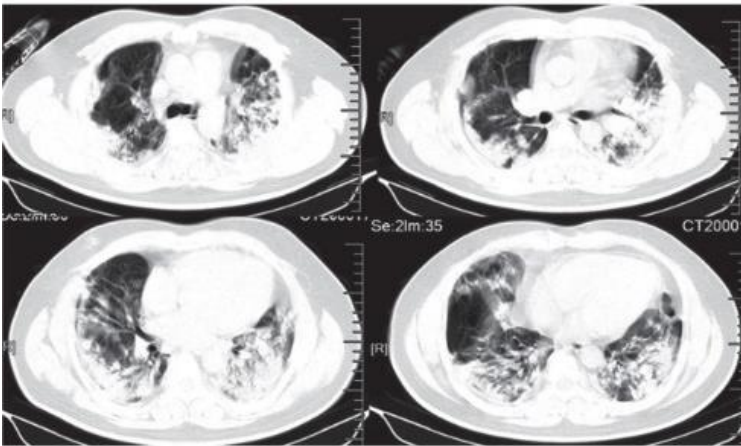


Figure 3 Caption: Transverse chest CT images from a 40-year-old man showing bilateral multiple lobular and subsegmental areas of consolidation on day 15 after symptom onset. Transverse chest CT images from a 53-year-old woman showing bilateral ground-glass opacity and subsegmental areas of consolidation on day 8 after symptom onset, adapted from<sup>23</sup>

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<sup>25</sup>, 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%). Interestingly, lymphopenia occurred in 70.3% of the patients, prolonged prothrombin time 58%, and elevated lactate dehydrogenase 39.9%. 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% noninvasive ventilation, and 47.2% invasive ventilation. **ECMO support was needed in 11% of the patients admitted to the ICU.** During the period of follow-up, overall mortality was 4.3%.

## Objectives

### Hypothesis

We hypothesize that a significant percentage of patients with COVID-19 infection will require admission to the intensive care unit, mechanical ventilation and ECMO for refractory hypoxemia

### Aims

This is a multi-centre international study in patients with COVID-19 who require admission to the intensive care unit, mechanical ventilation and/or ECMO to characterize the following features:

1. Incidence of ICU admission, use of mechanical ventilation and ECMO
2. Risk factors
3. Clinical features
4. Severity of respiratory failure
5. Need for non-invasive and invasive mechanical ventilation and ECMO
6. Settings of invasive mechanical ventilation
7. ECMO technical characteristics
8. Duration of ECMO
9. Complications
10. ICU survival
11. Hospital survival.
12. Requirements and the time frame for approvals in each participating network region

## Materials and Methods

### Study Design

This is an international multi-centre, prospective/retrospective observational study of patients in participating hospitals and ICUs with COVID-19 infection. The study will be conducted at 20 to 90 hospital networks globally and will aim to recruit as many patients as possible. The aim is to recruit all eligible patients at each study location and there is no maximum number of patients that can be recruited from any one site. Patients will be studied from time of ICU admission up to 28 days or until hospital discharge, whichever occurs later. Information will be collected on demographics, co-existing illnesses, severity of illness, source and type of clinical specimens (upper

versus lower respiratory tract and collection date), results of microbiological tests. ECMOCARD will specifically focus on collecting data of mechanical ventilation and ECMO and administration of other major therapies (including vasoactive therapies, hypoxaemia rescue therapies, and dialysis), administration of antibiotics and antivirals (and adjunctive therapies, e.g. immunomodulators, corticosteroids) and outcomes at ICU (if applicable), hospital discharge and 28 days.

### Research centres

This is a collaborative effort among investigators of the Asia-Pacific extracorporeal life support organization (APELSO) in collaboration with centres within the SPRINT-SARI and ISARIC Network.

### Study Population

We plan to recruit as many patients as possible of the patients with COVID-19 infection admitted to the ICU, in as many locations as possible, who meet the inclusion criteria with no-exclusion criteria at the participating sites. It is anticipated that each participating Institution could contribute between 5 and 50 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.

### Inclusion Criteria

1. Laboratory-confirmed COVID-19 infection by real-time PCR and/or next-generation sequencing
2. Admission to an intensive care unit

### Exclusion Criteria

1. Patients treated with mechanical ventilation for other concomitant causes
2. Patients treated with ECMO for other concomitant causes

### Co-enrolment

This is an 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 Co-ordinators 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 Co-ordinator 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 and data collection of the ECMOCARD and ISARIC SPRINT-SARI CRF (RAPID, CORE, SUPPLEMENTARY TO CORE, DAILY and EPIDEMIOLOGY) and any other study documents relevant to their region. When possible, each participating study site will be supported by the ECMOCARD, 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 will not be collected, and confidentiality of information in medical records will be preserved. The confidentiality of the participant will be maintained unless disclosure is to comply with the law. To adhere to international ethical review board requirements and facilitate global ECMOCARD and

SPRINT-SARI ISARIC data polling/sharing the CLiRes Data Management System will convert all dates entered (DD/MM/YYYY) into the eCRF into a re-identifiable format (D1, D2) at a system level. The original entered data (DD/MM/YYYY) will only be accessible by the site Research Co-ordinator and the site Principal Investigator using their unique database account details. ***In Australia, re-identifiable data will be entered into a central REDCap database hosted by Monash University and harmonised with the SPRINT-SARI study.***

#### Rule of Transfer

It is proposed that if a patient is transferred from a facility participating in ECMOCARD and SPRINT-SARI to another facility that is also participating, the patient's previously allocated patient ID number will be documented in the CRF completed by the receiving hospital at time of admission. All sites participating in SPRINT-SARI will be asked to include a ECMOCARD and SPRINT-SARI study information sheet in the patients transferring documents, notifying the new hospital of the patient's inclusion in ECMOCARD and SPRINT-SARI, the patients re-identifiable participation number, the contact details of the Principle Investigator of ECMOCARD and SPRINT-SARI in the country and the ECMOCARD and SPRINT-SARI coordinating centre. If you are unsure if a patient has previously been enrolled in ECMOCARD and SPRINT-SARI please check to see if the patients transferring hospital and ward/unit are included in the participating sites list on the ECMOCARD and SPRINT-SARI website ([www.sprintsari.org](http://www.sprintsari.org)). Please use the patients existing ECMOCARD and SPRINT-SARI participant number at the new hospital when entering data into the paper and/or eCRF. Sites will not have access to any data collected outside their hospital; it is the responsibility of each hospital to enter data pertaining to their component of the patient's hospital admission. If a patient is transferred to a non-participating hospital, there will be no further data collection.

#### International waiver of informed consent

It is expected that this study will not require individual patient consent. This study is in effect a large-scale clinical audit, as all data is already recorded as part of routine clinical care, therefore justifying participant enrolment using a waiver of consent. Waiver of consent may be available for studies that submit only re-identifiable information and where involvement in the research carries no more than low risk. Any location that deems individual consent necessary can use potential forms reported in the Appendix A. In particular, only in patients who meet the inclusion/exclusion criteria,



informed consent will be obtained directly from the patient, either before the study or retrospectively in case the patient is unconscious at the time of enrolment. If the patient is unable to provide a consent form upon admission, informed consent will be obtained by his/her next of kin.

## Informed Consent in Australia

In Australia all patients admitted to the ICU and meeting all inclusion and no exclusion criteria will be included in ECMOCARD observational study. Their hospital data will be included under a waiver of consent, in line with the National Statement (chapter 2.3) and the NHMRC *Ethical Considerations in Quality Assurance and Evaluation Activities, 2014*.

Data for ECMOCARD and SPRINT SARI observational study will be concomitantly collected. In addition, to minimise workload for site staff, whenever possible, EXCEL data will be requested to complement ECMOCARD data. SPRINT-SARI and EXCEL have both been approved to recruit patients under a waiver of consent. Yet, it is important to emphasize that ethics approval certificate for Project 202/16 has the following special condition: “A waiver of the requirement for consent was granted for the collection and use of identifiable information during relevant epidemics and pandemics. An opt-out approach will be used at all other times.”

## Data Collection

### ISARIC Data Collection Methods

As detailed in following paragraphs, we will collect data prospectively or retrospectively on patient demographics including age, sex, height, weight, and ethnicity, as well as the presence of predefined comorbidities. **General data will be collected from each site using the SPRINT-SARI data tool, namely the WHO and ISARIC NOVEL CORONAVIRUS (nCoV) ACUTE RESPIRATORY INFECTION CLINICAL CHARACTERISATION (<https://isaric.tghn.org/novel-coronavirus/>).** This CRF comprises three CRF tiers. The sites research capacity will determine which CRF or combinations of CRFs that are to be completed, at the site’s discretion. The CRF was assembled by ISARIC members on the basis of the WHO natural history protocol, INFINITE (ANZICS), MOSAIC and others<sup>5,26</sup>. The CRF was assembled to be a basic CRF with the aims of avoiding data duplication, and with the intention of being user friendly and applicable in all settings, regardless of the resources available<sup>27</sup>. The CRF has

previously been used in Singapore, New Zealand, Saudi Arabia, Vietnam, and North America and adapted by a working group for the purposes of this study with ISARIC approval to all changes made. In 2020, with the emergence of the COVID-19 epidemics, the ISARIC CRF eCRF were modified in order to characterize patients with this infection. In addition, Chief Investigators of the ECMOCARD trial further improved the ISARIC CRF eCRF to specifically describe COVID-19 patients admitted to the ICU and undergoing mechanical ventilation and ECMO.

**GENERAL ISARIC CRF**

Tier	Site Resource Level	CRFs completed for each patient
Tier 0	Sites that do not have the resources to collect Tier 1	<ul style="list-style-type: none"> <li>• Rapid CRF</li> </ul>
Tier 1	Sites that do not have the resources to collect additional daily data outlined in Tier 2	<ul style="list-style-type: none"> <li>• Core CRF; and</li> <li>• Daily CRF (day 1 only).</li> </ul>
Tier 2	Sites with available resources to complete forms	<ul style="list-style-type: none"> <li>• Core CRF;</li> <li>• Daily CRF, day 1 &amp; 2:                             <ul style="list-style-type: none"> <li>○ hospital admission; and</li> <li>○ Daily CRF, day 1 &amp; 2 of ICU admission (if applicable).</li> </ul> </li> </ul>
Tier 3	Optional additional CRFs, sites can choose to complete Tier 3 CRFs according to their scientific interests	<ul style="list-style-type: none"> <li>• Epidemiology CRF.</li> </ul>

ECMOCARD Data Collection Methods

Streamlined data-collection instruments and procedures will be used in an attempt to minimise the work in study centres. Data will be collected from each site using the SPRINT-SARI data tool, namely the WHO and ISARIC NOVEL CORONAVIRUS (nCoV) ACUTE RESPIRATORY INFECTION CLINICAL CHARACTERISATION (<https://isaric.tghn.org/novel-coronavirus/>). As mentioned above, ISARIC CRF comprises three CRF Tiers. The sites research capacity will determine which CRF or combinations of CRFs that are to be completed, at the site’s discretion. To achieve ECMOCARD goals, collaborators will initially collect data to the general Tier 1 of the ISARIC CRF. Then, investigators will purposely collect data to the ECMOCARD tiers. Specifically we will collect data on

the timing of ICU admission, endotracheal intubation, ECMO commencement in relation to presumed onset of symptoms and hospital admission. We will investigate whether the ECMO treatment was commenced in the participating hospital or whether the patient was retrieved and transferred while receiving ECMO from a referral centre. We will also collect administration of antiviral and antibiotic medications. Severity of illness before endotracheal intubation and before ECMO will be investigated by respiratory rate, severity of hypoxemia, hypercapnia, non-pulmonary vital organ support, ventilator settings, and use of rescue ARDS therapies in the 12 hours before ECMO commencement. Finally, duration of mechanical ventilation, ECMO, ICU and hospital stay, ICU and hospital mortality will be documented. In patients who died during hospital admission, we characterized the mode of death from a list of predefined options. ***Of note, In Australian centres, patients enrolled into the study “A comprehensive national registry on the treatment and outcomes of patients requiring ECMO) (EXCEL Study) will be identified by the ECMOCARD eCRF. Likewise, in the EXCEL study eCRF, a specific question will be added to identify patients enrolled in the ECMOCARD. Thus, we will complement ECMOCARD CRF with data collected through the EXCEL study.***

### **Data collection**

Both the SPRINT-SARI ISARIC and ECMOCARD CRF will be made available at all participating sites as a paper CRF. The SPRINT-SARI ISARIC and ECMOCARD CRFs 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 should accurately reflect the participants' medical/hospital notes. 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 from countries outside Australia will be entered into an online eCRF database managed by the Oxford University Clinical Research Unit, Vietnam (OUCRU) for the SPRINT-SARI ISARIC and ECMOCARD tiers. Data from Australia will be entered into an online eCRF database managed by Monash University, and will be complemented with data from SPRINT SARI observational study (ALFRED HREC Reference 202/16) and EXCEL (ALFRED HREC Reference 534/18)).** 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. Each site will be identified via a 3-digit network code, a 3-digit site code, and each patient will be assigned a 4-digit sequential patient code making up the patient ID number at time of originally enrolment in SPRINT- SARI. The site-code will be specified as to whether it is an ICU, hospital ward, or other facility. The site code is obtained by registering on the eCRF, data management system. Patient numbers should be assigned sequentially for each site beginning with 0001. In the case of a single site recruiting patients on different wards, or where it is otherwise difficult to assign sequential numbers, it is acceptable to assign numbers in blocks. Alpha characters can also be used (e.g. Intensive Care Unit will assign A001 onwards, in-patient ward will assign B001 onwards). **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).** The register of patient names and study numbers will not leave the participating hospital. Access to the data entry system will be protected by username and password. Username and password will be assigned during the registration process 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. 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 is maintained locally and is not to be transferred to any other location. The Research Coordinator will compile an enrolment log

including the patient's name, age, hospital identification number and unique study number. Subsequent data will be identified by the unique study number only. The enrolment log and study data will be kept separately.

### 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.

### Data management

Data entry and data management will be coordinated by ISARIC and ECMOCARD steering committee, including programming and data management support. On behalf of the management committee, ANZIC-RC and ISARIC will act as custodian of the data. The management committee of the trial will take responsibility for the content and integrity of any data. There will be periodic assessments of data burden to ensure that the infrastructure is organized to handle large amounts of incoming data in small time periods. SPRINT-SARI and ECMOCARD will adhere to the research and data sharing policies of ISARIC, Sample and Data Sharing Policy, Version 4, 21 July 2014. ***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.*** Networks will retain the right to request raw data for all sites included in their network for research purposes, provided that the research proposal has been reviewed and approved by the management committee, ISARIC and ECMOCARD following publication of the primary manuscript. All analysis of pooled data will be undertaken with the explicit agreement of each site who contributed. ISARIC and ECMOCARD 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. Only summary data will be presented publicly. 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.

## Collected Parameters

The following parameters will be assessed and recorded. All the mandatory variables to be assessed are highlighted in red:

### Demographics and Medical History

1. Personal Data
2. Medical History
3. Smoking habits
4. Chronic alcohol abuse
5. Intravenous drug abuse
6. Immuno-competency status



#### COVID-19 infection

1. Date of first signs of infection
2. Date of hospital admission
3. Date of ICU admission
4. Date of invasive mechanical ventilation
5. Blood gases before commencement of invasive mechanical ventilation
6. Use of continuous renal replacement therapy before commencement of invasive mechanical ventilation
7. Use of vasoactive drugs before commencement of invasive mechanical ventilation
8. Use of cardiac-assist devices before commencement of invasive mechanical ventilation
9. Acute physiology and chronic health evaluation (APACHE II) score upon ICU admission
10. Use of anti-viral treatment
11. Use of antibiotics

#### Clinical parameters upon commencement of invasive mechanical ventilation

1. Date of invasive mechanical ventilation commencement
2. Use of prone position
3. Use of neuromuscular blockade
4. Use of recruitment manoeuvres
5. Use of inhaled nitric oxide
6. Use of bicarbonate
7. Blood gases
8. Ventilatory mode
9. Inspiratory fraction of oxygen
10. Respiratory rate
11. Tidal volume (ml/Kg of ideal body weight)
12. Positive end-expiratory pressure
13. Airway plateau pressure

#### Daily assessment of clinical parameters during invasive mechanical ventilation

1. Date of assessment
2. Use of prone position

3. Use of neuromuscular blockade
4. Use of recruitment manoeuvres
5. Use of inhaled nitric oxide
6. Blood gases
7. Ventilatory mode
8. Inspiratory fraction of oxygen
9. Respiratory rate
10. Tidal volume (ml/Kg of ideal body weight)
11. Positive end-expiratory pressure
12. Airway plateau pressure
13. Haemoglobin
14. White blood cells
15. AST
16. ALT
17. Lactate
18. Creatinine
19. Use of continuous renal replacement therapy
20. Use of vasoactive drugs
21. Use of anticoagulants
22. Transfused blood products
23. Infectious complications
24. Haemorrhagic complications

#### Clinical features before commencement of ECMO

1. Date of ECMO commencement
2. Use of prone position
3. Use of neuromuscular blockade
4. Use of recruitment manoeuvres
5. Use of inhaled nitric oxide
6. Use of bicarbonate
7. Blood gases



8. Ventilatory mode
9. Inspiratory fraction of oxygen
10. Respiratory rate
11. Tidal volume (ml/Kg of ideal body weight)
12. Positive end-expiratory pressure
13. Airway plateau pressure

#### ECMO characteristics

1. Type and manufacturer of centrifugal blood pump driven circuit
2. Type and manufacturer of low-resistance oxygenator
3. Type of ECMO: venous-venous or venous-arterial
4. Peripheral access: femoral, jugular, both
5. ECMO blood flow rate day 0, and every 24 hours thereafter
6. ECMO gas flow rate day 0, and every 24 hours thereafter
7. Anticoagulation during ECMO
8. Frequency of ECMO circuit change
9. Ventilatory settings on ECMO
10. Vasoactive support on ECMO
11. Organ dysfunctions on ECMO

#### ECMO adverse effects

1. Transfused blood during ECMO
2. Transfused plasma during ECMO
3. Transfused platelets during ECMO
4. Transfused cryoprecipitates during ECMO
5. Type and source of infectious complications
6. Type and source of haemorrhagic complications
7. Other complications

#### Main outcomes

1. Date of ECMO discontinuation
2. Date of invasive mechanical ventilation discontinuation

3. Date of ICU Discharge
4. Date of Hospital Discharge
5. Mortality at 28 days
6. Main cause of death

## Data Analysis

The global analysis of ECMOCARD categorical variables will be described as proportions and will be compared using chi-square or Fisher's exact test. Continuous variables will be described as mean and standard deviation if normally distributed or median and inter-quartile range if not normally distributed. Comparisons of continuous variables will be performed using one-way ANOVA or Mann-Whitney test, as appropriate. A logistic regression model will be performed to assess independent association between prognostic factors and outcomes, taking into account the hierarchical nature of the data. Significance will be set at  $p < 0.05$ .

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## Regulation, Ethics and Governance

Protocol and any following amendment to the original protocol will be 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. Sites should apply for a waiver of consent to be granted given the negligible risk nature of the study and the need for rapid data collection to inform pandemic responses globally.

### Conflict of interest

The investigators of the APELSON network 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 SPRINT-SARI and ISARIC Organisations (APPENDIX B) and the ECMOCARD Steering Committee (APPENDIX C). A custom-designed electronic case report form has been developed in REDCAP and for all Australian centres will be hosted at Monash University, Melbourne, 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 in March 2020, 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 ECMOCARD will be stored in an Investigator Study File (ISF), which will be held by the Critical Care Research Group (CCRG), University of Queensland. On completion of the study, this information will be archived by the CCRG. 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 SPRINT-SARI, ISARIC and APELSON networks of clinical research institutions, during an emergent new respiratory infection caused by the new COVID-19 virus. The study will be conducted in intensive care units with broad experience in mechanical ventilation and ECMO. Further intra-mural and extra-mural collaborations beyond the SPRINT-SARI, ISARIC and APELSON networks will be potentially pursued to promptly achieve goals. In summary, the SPRINT-SARI, ISARIC and APELSON multidisciplinary and international research team 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. Data requested from SPRINT-SARI and EXCEL investigators will reside with their own 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. SPRINT-SARI and EXCEL studies will be fully acknowledged in all publications and presentations.

### Authorship policy

Authorship will be determined according to the internationally agreed criteria for authorship ([www.icmje.org](http://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.