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Original research article

Clinical characteristics, risk factors and outcomes in patients with severe COVID-19 registered in the ISARIC WHO clinical characterisation protocol: a prospective, multinational, multicentre, observational study

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TITLE: Clinical Characteristics, Risk Factors and Outcomes in Patients with Severe COVID-19 Registered in the ISARIC WHO Clinical Characterisation Protocol: A Prospective, Multinational, Multicentre, Observational Study.

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Take home message: Countries and hospitals need to identify strategies to increase their ICU capacity (i.e., trained personnel, ICU beds and monitoring systems) to treat patients presenting to the hospital with severe COVID-19 rather than provide such care outside of the ICU

ABSTRACT

Due to the large number of patients with severe COVID-19, many were treated outside of the traditional walls of the ICU, and in many cases, by personnel who were not trained in critical care. The clinical characteristics and the relative impact of caring for severe COVID-19 patients outside of the ICU is unknown.

This was a multinational, multicentre, prospective cohort study embedded in the ISARIC WHO COVID-19 platform. Severe COVID-19 patients were identified as those admitted to an ICU and/or those treated with one of the following treatments: invasive or non-invasive mechanical ventilation, high-flow nasal cannula, inotropes, and vasopressors. A logistic Generalised Additive Model was used to compare clinical outcomes among patients admitted and not to the ICU.

A total of 40440 patients from 43 countries and six continents were included in this analysis. Severe COVID-19 patients were frequently male (62.9%), older adults (median [IQR], 67 years [55, 78]), and with at least one comorbidity (63.2%). The overall median (IQR) length of hospital stay was 10 days (5-19) and was longer in patients admitted to an ICU than in those that were cared for outside of ICU (12 [6-23] vs. 8 [4-15] days, $p<0.0001$). The 28-day fatality ratio was lower in ICU-admitted patients (30.7% [5797/18831] vs. 39.0% [7532/19295], $p<0.0001$). Patients admitted to an ICU had a significantly lower probability of death than those who were not (adjusted OR:0.70, 95%CI: 0.65-0.75, $p<0.0001$).

Patients with severe COVID-19 admitted to an ICU had significantly lower 28-day fatality ratio than those cared for outside of an ICU.

BACKGROUND

The clinical presentation of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection varies from asymptomatic individuals to severe respiratory failure.[1] Severely ill patients may require advanced respiratory support (e.g., invasive, non-invasive mechanical ventilation, or high flow nasal cannula) or extra-respiratory support (e.g., vasopressors, inotropes or renal replacement therapy).[2] Severe COVID-19, defined as requiring ICU admission or advance ventilatory support, occurs in 15% to 30% of hospitalized individuals, with in-hospital fatality ratios ranging from 30% to 70%, depending on various factors including patients' age, comorbidities, and access to medical interventions.[3, 4] High-quality supportive care remains the standard of care for these patients.[5, 6]

During the SARS-CoV-2 pandemic, many international healthcare systems became overwhelmed, requiring medical interventions traditionally restricted to delivery in an ICU by specially trained personnel to be delivered in other hospital areas, sometimes by healthcare workers without equivalent training.[7] Thus, invasive and non-invasive mechanical ventilation, high-flow nasal cannulas (HFNC), and treatment with inotropes or vasopressors, have been used outside of the ICU due to the acute surge in cases and lack of ICU capacity.[8] Several strategies have been proposed, to rapidly train non-ICU personnel and to optimize resources during the pandemic.[9] However, the impact of these strategies is unknown.

Most studies describing the clinical characteristics and outcomes of COVID-19 patients admitted to the ICU are limited to a few centres within a single country and have not evaluated the impact of ICU-level treatment on clinical outcomes.[1, 10, 11] Moreover, available studies have not evaluated the outcomes of severely ill patients cared for outside of the ICU environment.[1, 10, 11] Moreover, there is a growing concern about whether available data characterizing patients with severe COVID-19 are generalizable to other regions of the world and whether severe COVID-19 patients can safely be cared for outside of an ICU.[12] Here, we describe a global population of patients with severe COVID-19, both those with and without ICU admissions during their hospital stay. We also describe outcomes in patients with severe COVID-19 inside and outside of the ICU to determine the potential impact of ICU admission.

METHODS

The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) - World Health Organization (WHO) Clinical Characterization Protocol for Severe Emerging Infections provided a framework for prospective observational data collection on hospitalised patients. The protocol, case report forms, consent forms and study information are available in the online supplement and in the ISARIC website (https://isaric.tghn.org). This is a standardized protocol for investigating severe acute infections of pathogens of public health interest with tiered data collection tailored to a range of resource settings. Investigators from 43 countries collected prospective data using the ISARIC CRF built on Research Electronic Data Capture (REDCap, version 8.11.11, Vanderbilt University, Nashville, Tenn.) hosted by the University of Oxford. Other investigators collected data on a variety of locally-hosted data systems and submitted data for centralised mapping to the ISARIC dataset. All investigators retain full rights to their data.

This observational study required no change to clinical management and permitted patient enrolment in other research projects. The ISARIC-WHO Clinical Characterisation Protocol was approved by the World Health Organization Ethics Review Committee (RPC571 and RPC572). Local ethics approval was obtained for each participating country and site according to local requirements.

Study population

Hospital-admitted patients included in the ISARIC database between January 17th and December 31st, 2020; this analysis was limited to those with laboratory-confirmed SARS-CoV-2 infection detected by reverse transcription polymerase chain reaction (rtPCR) in a respiratory sample analysed according to the sites' local diagnostic methods and protocols and classified as severe COVID-19. We used a modified WHO severity criteria[5] to categorize severe COVID-19 using the following criteria: patients treated with invasive or non-invasive mechanical ventilation, those treated with HFNC, and/or patients treated with vasopressors or inotropes; and/or patients treated within the ICU. Patients in whom more than 30% of the required clinical data variables were missing were excluded from the analysis.

Outcomes

The primary outcome of this analysis was 28-day fatality ratio (from hospital admission date). The secondary outcomes were 90-day fatality ratio and hospital length-of-stay (LOS).

Variables and measurement

Variables used in this analysis were age, sex, ethnicity (i.e., White, Black, Latino, Asian, Arab, other), symptoms, comorbidities, vital signs on admission, systemic complications, date of hospital admission, date of ICU admission, date of death, the requirement of advanced ventilatory support, treatment with vasopressors or inotropes, country of recruitment and its income classification according to the World Bank (https://data.worldbank.org/country). All the variables are listed in the study protocol and the online supplement. To study fatality ratios, only patients with a reported date of death were classified as dead. Patients that were still admitted at the point of data extraction were not included in the denominator to calculate the fatality ratio or other clinical outcomes. Only patients with a reported hospital discharge were included in calculating the hospital length of stay. All study variables were predefined in the ISARIC study protocol and case report form completion guide available online (https://isaric.tghn.org). The number of COVID-19 cases per million were obtained from the website Our World in Data (https://ourworldindata.org/coronavirus, access on April 12, 2021).

Study definitions

The complete definitions of all variables were predetermined in the study protocol and are available in the online supplement. However, some definitions are provided here.

ICU admission: Patients admited to an intensive care, intensive therapy, intermediate care, or high dependency unit. This variable was collected independent of treatments received and was reported by each centre. *High-flow nasal cannula:* Respiratory support continuously applied through large-bore nasal prongs using a gas flow heated and humidified at initial flow greater of 20 L/min (or up to 80 litres per minute) and a fraction of inspirated oxygen of up to 1.0.

Statistical methods

Data were converted to Study Data Tabulation Model (version 1.7, Clinical Data Interchange Standards Consortium, Austin, Tex.) to integrate data collected on locally hosted databases with data collected on the ISARIC database. A bivariate analysis was initially carried out to compare the quantitative variables according to their distribution by other factors. If data were normally distributed, the Student's t-test was applied for independent samples; if the variable data were not normally distributed, Mann Whitney's U test was used. Categorical variables were compared by a Chi-square test. Variables were analysed by age, sex, date of hospital admission, and ICU admission. A logistic Generalised Additive Model (GAM) was fitted to assess the association of being admitted to the ICU with 28-day fatality ratio, adjusting for demographics (i.e., sex, and number of comorbidities), age treated as a non-linear continuous measure using a cubic spline, physiological variables on admission (i.e., heart rate, respiratory rate and blood pressure [systolic and diastolic blood pressure]) advance ventilatory support (i.e., HFNC, Non-invasive mechanical ventilation or Invasive Mechanical Ventilation), treatment with vasopressors or inotropes, the development of acute respiratory distress syndrome during hospital stay, month of admission, countries' income classification and new cases per million people per country at the moment of hospital admission.

To further assess the non-linear associations of age, calendar time, and per-capita number of COVID-19 cases within a country with fatality ratio, a logistic GAM was fitted using 28-day fatality ratio as a dichotomous outcome. Further non-linear terms for age, comorbidities, calendar day, and COVID-19 cases per million in the affected country were modelled as cubic splines. A sensitivity analysis was constructed using the above GAM and excluding patients enrolled in the United Kingdom (the majority of paints included in the analysis were registered at this country) to control for the centre effect. A further sensitivity analysis was constructed by excluding all patients identified as admitted to ICU without any other advanced ventilator support or vasopressor. All data processing and statistical analysis were performed using Python version 4.0 with the following data packages: Pandas version 1.2.4, Tidyverse version 1.3.0, Bioconductor version 3.12. Moreover, we also used R version 4.0.4, and SPSS 27 for Mac.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of this manuscript. The corresponding author (LFR) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

A total of 149504 patients with rtPCR-confirmed SARS-CoV-2 infection were screened for the study. After applying the enrolment criteria, 40440 severe COVID-19 patients fulfilled the inclusion criteria and were included in the analysis (**Figure 1**). Patients were enrolled in 6 continents and 43 countries. The majority of patients were enrolled in high-income countries (88.9%, 35956/40440); however, 4472 patients were enrolled in upper-middle-income and lower-middle-income countries (**Figure 2, Table 1**). Importantly, 85.2% of patients were enrolled in Europe (**Figure 2, Table 1**).

Demographic and clinical characteristics

Most of the patients were male (62.9%, 25459/40440), with a median (interquartile range [IQR]) age of 67 (IQR 55-78) years. The race of patients was most frequently recorded as White (53.0%, 21460/40440), followed by Asian (7.6%, 3080/40440), Black (4.0%, 1631/40440), and Latino (1.0%, 425/40440). At least one comorbidity was reported in 63.2% (25591/40440) of patients (**Table 1**); the most frequently identified comorbidity was chronic arterial hypertension (29.5%, 11910/40404), followed by chronic cardiac disease (20.2%, 8161/40440), chronic pulmonary diseases (12.0%, 4848/40440), obesity (11.4%, 4623/40440), and chronic kidney disease (10.3%, 4151/40440). ICU patients were younger (61 years [50-70] vs. 75 years [62-84], $p<0.0001$), more frequently male (67.7% [13571/20044] vs. 58.4% [11930/20396], $p<0.0001$), and with fewer comorbidities (median [IQR], 1 [0-2] vs. 2 [0-4], $p<0.0001$) than non-ICU patients (**Table 1**).

Regarding symptoms on the day of hospital admission, the most frequently reported were shortness of breath (59.2%, 23955/40440), fever (52.2%, 21115/40440), dry cough (52.1%, 21065/40440) and fatigue/malaise (30.6%, 12391/40440). About physiological parameters on hospital admission, the median (IQR) temperature was 37.3^{o}C (36.7-38.2); patients were

tachycardic on admission (median [IQR], 93 [81-108] beats per minute), and tachypnoeic on admission (median [IQR], 24 [20-28] breaths per minute) (**Table 1**). Other differences were observed in the physiological variables among patients admitted and not admitted to the ICU (**Table 1**).

In-hospital treatments and systemic complications

The most frequently administered treatments were systemic antibiotics (87.3%, 35316/40440), systemic corticosteroids (28.3%, 11435/40440), and antivirals (19.8%, 8025/40440). Among the whole cohort, 62.9% (25433/40440) of patients were treated with HFNC, 38.4% (15522/40440) with non-invasive mechanical ventilation and 40.7% (16542/40440) were treated with inotropes or vasopressors (**Table 2, Supplementary Figure 1 and 2**). Invasive mechanical ventilation was more frequently applied in ICU compared to non-ICU patients (59.6% [11957/20044] vs. 2.5% [505/19891], $p<0.0001$), in contrast, non-ICU patients were more frequently treated with HFNC (81.1% [16542/19819] vs. 44.4% [8891/20044], $p<0.0001$) (**Table 2**). Moreover, patients admitted to the ICU were more frequently treated with prone positioning (36.9% [7390/20044] vs. 2.1% [277/20396], $p<0.0001$), systemic corticosteroids (38.1% [7627/20044] vs. 18.7% [3808/20396], $p<0.0001$) and haemodialysis (14.7% [2953/20044] vs. 1.2% [238/20396], $p<0.0001$) than non-ICU patients (**Table 2**).

Systemic complications were reported in the majority of patients (64.4%, 26068/40440); 19.6% (7928/28182) of patients developed ARDS, being more frequent in patients admitted to the ICU (28.7% [5747/20044] vs. 10.5% [2181/20396], $p<0.0001$). Moreover, acute kidney injury was documented more frequently in ICU admitted patients (20.1% [4030/20044] vs. 12.4% [2536/20396]). Bacterial pneumonia was more frequent in patients admitted to the ICU (12.9% [2591/20044] vs. 10.3% [2104/20396], $p<0.0001$). Other systemic complications are reported in **Table 3**.

Clinical outcomes

The overall 28-day fatality ratio in our cohort was 34.9% (13329/38126) and 37.7% (14394/38126) for 90-day fatality ratio (**Figure 1, Table 1, Supplementary Figure 5**). The 28-day fatality ratio was 30.7% (5797/18831) in patients admitted to the ICU and 39.0%

(7532/19295) in patients cared for exclusively outside the ICU. The 90-day fatality ratio was 33.7% (6358/18831) in those admitted to ICU and 41.6% (8036/19295) in those cared for outside the ICU. The median (IQR) overall hospital length of stay (LOS) was 10 days (5-19), which was longer in ICU patients (12 days [6-23] vs. 8 days [4-15], $p<0.0001$) when compared to non-ICU patients (**Table 1**). Finally, the hospital LOS in survivors was 11 (5-21) days, and it was longer in ICU admitted patients (13 [6-27] vs. 9 [5-17], $p<0.0001$).

A biphasic distribution of the number of cases and deaths was identified, with a peak between April and May and October and November 2020 (**Supplementary Figure 3 and 4**). Patients older than 65 years were frequently diagnosed with severe COVID-19 and had a higher fatality ratio (**Supplementary Figures 3 and 4**). A clear relationship between age and the probability of death was observed (**Figure 4 and Supplementary Figure 5**). Over the study period, fatality ratio in patients with severe COVID-19 decreased over time, being higher during April and lower by the end of August (**Figure 4 and Supplementary Figure 5**).

Association of ICU admission with 28-day and 90-day fatality ratios

After adjusting for confounding variables (i.e., age, number of comorbidities, sex, presence of ARDS, treatments [inotropes, vasopressors, HFNC, invasive and non-invasive mechanical ventilation], country's income classification, number of new cases per day in the relevant country and, physiological variables on hospital admission [heart rate, respiratory rate, systolic or diastolic blood pressure, and temperature]), patients admitted to the ICU had a lower risk of 28-day fatality ratio (OR:0.70, 95%CI: 0.65-0.75, $p<0.0001$) (**Table 4**) and 90-day fatality ratio (OR:0.69, 95%CI: 0.64-0.74, $p<0.0001$) (**Supplementary Table 1 and Supplementary Figure 5**). Patients enrolled later in the pandemic (i.e., after the first peak in May-June 2020) were also less likely to die regardless of ICU admission (OR:0.98, 95%CI: 0.96-0.99, $p<0.0001$). Previously documented risk factors for death, including age, sex, prior comorbidities, and ARDS, were confirmed in our study (**Table 4**).

To test these results, we performed a sensitivity analysis with ethnicity (**Supplementary Table 3**), patients enrolment in the United Kingdom, sex, and age revealed a similar protective effect of ICU admission on 28-day and 90-day fatality ratios (**Table 4, Figures 4, Supplementary Figure 5**). Then, we performed a supplementary sensitivity analysis to control for centre effect by removing patients enrolled in the United Kingdom, finding lower fatality

ratios in patients admitted to the ICU (**Supplementary Table 2**). Finally, we removed patients who were admitted to ICU who did not need advance ventilatory support (**n=2716, Supplementary Figure 1**), confirming that patients admitted to the ICU had lower likelihood of dying.

DISCUSSION

This analysis describes the clinical characteristics, symptoms, and outcomes from the largest prospective, multinational cohort of hospitalised patients with severe COVID-19. Worse clinical outcomes were seen in older, male, obese, patients with comorbidities and those who developed ARDS. Fatality ratios in patients hospitalised with severe COVID-19 changed over time, being higher during the initial weeks of the pandemic's first wave. Finally, we identified that severe COVID-19 patients admitted to ICU had lower 28-day and 90-day fatality ratios, independent of age, disease severity, number of comorbidities, countries' income classification, healthcare system saturation (i.e., number of new cases per day), and treatments received when compared with patients that were cared for outside of ICU.

Previous studies have found that around 30% of patients infected with SARS-CoV-2 can develop severe disease requiring admission to an ICU or advanced ventilatory support, such as invasive, non-invasive mechanical ventilation, or HFNC.[10, 13-16] Our study found that 32% of patients that required hospital admission developed severe COVID-19, which is in alignment with prior published data. Regarding the clinical characteristics of patients with severe COVID-19, Grasselli G *et al.[11]* reported that 82% of patients hospitalised in the Italian hospitals were male, with a median age of 63 years old, and frequently have several comorbidities. Xie J *et al.[10]* reported that severely ill patients in China had a median age of 63 years old; 65% were male and had a past medical history of cardiovascular diseases, specifically hypertension. Moreover, several studies have also confirmed the associations between age, sex and comorbidities and severe COVID-19 disease.[2, 3, 17, 18] Our findings are in concordance with our results, where the median admission age was 67.5 years old, and the majority of patients were male. We also found that most of patients who developed severe COVID-19 had at least

one comorbidity, with hypertension, chronic cardiac diseases, and chronic pulmonary diseases being most frequent.

During the pandemic, several pharmacological and non-pharmacological interventions have been used to treat patients with COVID-19.[5, 6, 19] The primary approach was to identify effective treatments by repurposing antiviral agents, immunomodulatory drugs, and medications with theoretical antiviral properties. However, this approach led to excessive use of interventions without evidence-based support, and the data supporting these interventions are controversial.[12, 20] To date, the only medications that have been consistently demonstrated to reduce fatality ratios in COVID-19 patients requiring oxygen supplementation are corticosteroids, specifically dexamethasone.[21, 22] In our study, patients received several medications and non-pharmacological interventions. Notably, we found that most patients were treated with systemic antibiotics and many other interventions, as reported previously in other studies.[23] This high antibiotic usage in patients with severe COVID-19 is concerning, because bacterial coinfection was not frequent in our cohort. Moreover, it is essential to highlight that only 28.3% of patients were treated with systemic corticosteroids, being more frequently used in patients admitted to the ICU. This might be explained by the fact that the RECOVERY trial results were published six months after the beginning of the pandemic,[22, 24] and pre-pandemic data did not support the use of corticosteroids by many international guidelines in patients with severe viral pneumonia.[25, 26]

The COVID-19 pandemic has brought unprecedented challenges to healthcare systems around the world.[27] In many countries, ICU capacity was overwhelmed, requiring severely ill patients to be treated in non-ICU settings.[8, 9] Other studies have evaluated the utility of using non-invasive respiratory support in the general wards, showing that this treatment can be safely delivered outside of the ICU,[8] although outcomes were not compared with similar patients treated in an ICU. We found that treating patients in the ICU was associated with a lower fatality ratio after adjusting for a number of possible confounders, including the severity of illness. There is an important selection bias of patients admitted to ICU because clinicians tend to admit patients with a better survival probability. However, our results build on previous work that personnel trained in ICU care, and the presence of a higher nurse-to-patient ratio may significantly impact the fatality ratio in severely ill patients more than access to specific organ support interventions.[28]

An interpretation regarding why the fatality ratio is different among patients admitted and not to the ICU is required. These data are novel and have not been reported previously in patients with severe COVID-19. However, in Hong Kong, during the SARS 2003 pandemic, it was reported that expanding ICU settings was associated with higher fatality ratios.[29] Intensive care is often defined by the nurse-to-patient ratio and monitoring by trained staff, which may be a determinant of our findings.[30] Notably, we do not have information regarding personnel training, the monitoring systems used, or the staff ratios caring for these patients.

Our study has strengths and limitations that are important to acknowledge. First, the ISARIC COVID-19 dataset is composed mainly of patients enrolled in high-income countries. However, this is a large prospectively collected cohort of patients enrolled in more than 40 countries worldwide, strengthening these results' generalizability. We performed a sensitivity analysis which showed no difference across income groupings. Secondly, the decision not to admit a patient to the ICU may be based on several factors, including treatment restriction orders and the clinician's estimation of surviving; however, this information is not easily collected and was not available in our dataset. Not having these data limits the conclusions we may draw about the impact of ICU admission on clinical outcomes as it is a residual selection bias. Third, the definitions of what constituted an ICU varies per country and centre. We assumed that similar treatment and care were offered to all COVID-19 patients upon ICU admission. Notably, the identified protective effect of ICU admission was consistent in the entire cohort, even after sensitivity analyses. Forth, several variants have emerged during the pandemic in different parts of the world. These variants have different disease severity, and vaccines might have different protective effects, affecting overall mortality. However, we did not have information regarding the virus identified, and thus, we did not control for this, which is an important limitation. However, we control for admission date, which might indirectly control for these variables that appeared worldwide over the pandemic. Fifth, oxygen saturation and blood arterial gases are frequently used to determine severity and guide treatment in patients with COVID-19. However, in our study, we do not have these data in all patients, which is a limitation we need to recognize. Importantly, we have vital signs and systemic complications that allowed us to assess disease severity. Finally, as our study included patients from several countries and centres with high caseloads and resourced limitations, the analysis was limited by missing data, possibly biasing the ultimate results.

CONCLUSIONS

More than 30% of hospitalised SARS CoV-2-infected patients develop severe COVID-19 with high fatality ratios. These patients frequently require advanced supportive treatments, which has imposed an unprecedented burden on healthcare systems worldwide. Providing high-quality care to severely ill patients is a complex endeavour that requires trained personnel, a designated setting, monitoring equipment, and specialized management. The results presented in this study warrant caution about treating severely ill patients outside of an ICU and encourage hospitals to find strategies for severely ill patients to be treated in an ICU by personnel trained for the role.

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Data sharing

The dataset is available through the Infectious disease Data Observatory website (https://www.iddo.org).

Potential Conflict of interest: In the attached document.

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TABLES

Table 1. Baseline characteristics of patients with confirmed SARS-CoV-2 infection that developed severe COVID-19 stratified by patients admitted to the Intensive Care Unit (ICU).

		Patients admitted to the ICU		
Characteristic	**All** n=40440	**Yes** n=20044	**No** n=20396	***p** value*
Demographics				
Age, median (IQR)	67 (55, 78)	61 (50, 70)	75 (62, 84)	<0.0001
Female (%)	14939 (36.9)	6473 (32.2)	8466 (41.5)	<0.0001
Chronic comorbidities, n (%)				
Number of comorbidities, median (IQR)	2.0 (0.0-3.0)	1.0 (0.0-2.0)	2.0 (0.0-4.0)	<0.0001
Chronic arterial hypertension	11910 (29.5)	5712 (28.5)	6198 (30.4)	<0.0001
Chronic cardiac disease	8161 (20.2)	2493 (12.4)	5668 (27.8)	<0.0001
Chronic cardiac arrhythmia	38 (0.1)	34 (0.2)	4 (0.0)	<0.0001
Chronic pulmonary diseases	4848 (12.0)	1423 (7.1)	3425 (16.8)	<0.0001
Asthma	3920 (9.7)	1857 (9.3)	2063 (10.1)	<0.0001
Other chronic respiratory diseases	873 (2.2)	148 (0.7)	725 (3.6)	<0.0001
Chronic neurological disorder	2898 (7.2)	798 (4.0)	2100 (10.3)	<0.0001
Chronic rheumatic disorder	2736 (6.8)	794 (4.0)	1942 (9.5)	<0.0001
Chronic kidney disease	4151 (10.3)	1252 (6.2)	2899 (14.2)	<0.0001
Mild liver disease	413 (1.0)	187 (0.9)	226 (1.1)	0.08
Moderate or severe liver disease	454 (1.1)	163 (0.8)	291 (1.4)	<0.0001
Diabetes mellitus	9141 (22.6)	4343 (21.7)	4798 (23.5)	<0.0001
Chronic hematologic disorder	1069 (2.6)	354 (1.8)	715 (3.5)	<0.0001
Chronic immunosuppressive disorders	44 (0.1)	44 (0.2)	0 (0.0)	<0.0001
Chronic immunosuppressive medication	537 (1.3)	194 (1.0)	343 (1.7)	<0.0001
Cancer	680 (1.7)	197 (1.0)	483 (2.4)	<0.0001
Malignant neoplasm	2453 (6.1)	797 (4.0)	1656 (8.1)	<0.0001
Solid organ transplant recipient	192 (0.5)	76 (0.4)	116 (0.6)	0.006
AIDS/HIV	178 (0.4)	123 (0.6)	55 (0.3)	<0.0001
Asplenia	46 (0.1)	45 (0.2)	1 (0.0)	<0.0001
Dementia	2774 (6.9)	188 (0.9)	2586 (12.7)	<0.0001
Obesity	4623 (11.4)	2802 (14.0)	1821 (8.9)	<0.0001
Malnutrition	628 (1.6)	210 (1.0)	418 (2.0)	<0.0001
Symptoms on admission, n (%)				
Fever	21115 (52.2)	10578 (52.8)	10537 (51.7)	0.02
Abdominal pain	2386 (5.9)	1143 (5.7)	1243 (6.1)	0.09
Bleeding (haemorrhage)	463 (1.1)	173 (0.9)	290 (1.4)	<0.0001
Fatigue/malaise	12391 (30.6)	6317 (31.5)	6074 (29.8)	<0.0001
Shortness of breath	23955 (59.2)	11924 (59.5)	12031 (59.0)	0.30
Sore throat	2464 (6.1)	1619 (8.1)	845 (4.1)	<0.0001
Dry cough	21065 (52.1)	10230 (51.0)	10835 (53.1)	<0.0001
Cough - productive	6693 (16.6)	3132 (15.6)	3561 (17.5)	<0.0001
Cough - with haemoptysis	804 (2.0)	444 (2.2)	360 (1.8)	0.0001
Wheezing	2294 (5.7)	850 (4.2)	1444 (7.1)	<0.0001
Seizures	352 (0.9)	148 (0.7)	204 (1.0)	0.005
Altered consciousness/confusion	5964 (14.7)	1759 (8.8)	4205 (20.6)	<0.0001
Disturbance or loss of smell (anosmia)	1047 (2.6)	614 (3.1)	433 (2.1)	<0.0001
Disturbance or loss of taste (ageusia)	1275 (3.2)	631 (3.1)	644 (3.2)	0.95
Severe dehydration	1614 (4.0)	538 (2.7)	1076 (5.3)	<0.0001
Vomiting/nausea	5006 (12.4)	2469 (12.3)	2537 (12.4)	0.71
Diarrhoea	5335 (13.2)	2872 (14.3)	2463 (12.1)	<0.0001
Muscle aches (myalgia)	5562 (13.8)	3397 (16.9)	2165 (10.6)	<0.0001
Chest pain	3823 (9.5)	1951 (9.7)	1872 (9.2)	0.05
Headache	2918 (7.2)	1747 (8.7)	1171 (5.7)	<0.0001
Joint pain (arthralgia)	1495 (3.7)	739 (3.7)	756 (3.7)	0.91

Skin ulcers	419 (1.0)	77 (0.4)	342 (1.7)	<0.0001
Lower chest wall indrawing	528 (1.3)	334 (1.7)	194 (1.0)	<0.0001
Skin rash	304 (0.8)	140 (0.7)	164 (0.8)	0.24
Conjunctivitis	110 (0.3)	72 (0.4)	38 (0.2)	0.0001
Runny nose (rhinorrhoea)	927 (2.3)	665 (3.3)	262 (1.3)	<0.0001
Ear pain	95 (0.2)	49 (0.2)	46 (0.2)	0.69
Lymphadenopathy	170 (0.4)	59 (0.3)	111 (0.5)	<0.0001
Inability to walk	279 (0.7)	226 (1.1)	53 (0.3)	<0.0001
Anorexia	349 (0.9)	285 (1.4)	64 (0.3)	<0.0001
Asymptomatic	272 (0.7)	93 (0.5)	179 (0.9)	<0.0001
Physiological parameters on admission, median (IQR)				
Temperature, °centigrade	37.3 (36.7-38.2)	37.4 (36.7-38.3)	37.3 (36.6-38.1)	<0.0001
Heart rate, beats per minute	93 (8-108)	96 (84-110)	91 (79-105)	<0.0001
Respiratory rate, breaths per minute	24 (20-28)	24 (20-30)	22 (19-28)	<0.0001
Systolic blood pressure, mmHg	130 (114-145)	130 (115-144)	130 (114-146)	0.02
Diastolic blood pressure, mmHg	74 (65-83)	75 (65-83)	74 (64-84)	0.0001
Continent of admission, n (%)				
Europe	34456 (85.2)	12427 (61.9)	20029 (98.2)	<0.0001
Asia	3292 (8.1)	3140 (15.6)	152 (0.7)	<0.0001
South America	1408 (3.5)	1308 (6.5)	100 (0.5)	<0.0001
North America	2614 (6.4)	2505 (12.5)	109 (0.5)	<0.0001
Africa	164 (0.4)	159 (0.6)	5 (0.0)	<0.0001
Oceania	506 (1.3)	505 (2.5)	1 (0.0)	<0.0001
Regional income stratification, n (%)				
High-income country	35956 (88.9)	15810 (78.8)	20146 (98.7)	<0.0001
Upper-middle-income country	1976 (4.8)	1821 (9.1)	155 (0.8)	<0.0001
Lower-middle-income country	2496 (6.2)	2401 (11.9)	96 (0.5)	<0.0001
Clinical outcomes	*n=38126*	*n=18831*	*n=19295*	
Hospital LOS, median (IQR)	10 (5-19)	12 (6-23)	8 (4-15)	<0.0001
28-day fatality ratio, n (%)	13329 (34.9)	5797 (30.7)	7532 (39.0)	<0.0001
90-day fatality ratio, n (%)	14394 (37.7)	6358 (33.7)	8036 (41.6)	<0.0001

IQR, interquartile range; LOS, length of stay; AIDS, acquired immunodeficiency syndrome, HIV, human immunodeficiency virus.

Table 2. Treatments stratified by patients admitted to the Intensive Care Unit (ICU).

		Patients admitted to the ICU		
Treatment	**All** n=40440	**Yes** n=20044	**No** n=20396	*p value*
Invasive mechanical ventilation	12462 (30.8)	11957 (59.6)	505 (2.5)	<0.0001
Non-invasive mechanical ventilation	15522 (38.4)	9127 (45.5)	6395 (31.4)	<0.0001
High-flow nasal canula	25433 (62.9)	8891 (44.4)	16542 (81.1)	<0.0001
Inotropes or vasopressors	16542 (40.7)	8375 (41.8)	175 (0.9)	<0.0001
Antibiotic	35316 (87.3)	17800 (88.8)	17516 (85.9)	<0.0001
Prone positioning	7825 (19.3)	7390 (36.9)	435 (2.1)	<0.0001
Neuraminidase inhibitors	231 (0.6)	118 (0.6)	113 (0.6)	0.69
Neuromuscular blocking agents	3647 (9.0)	3597 (17.9)	50 (0.2)	<0.0001
Dialysis/hemofiltration	3191 (7.9)	2953 (14.7)	238 (1.2)	<0.0001
Corticosteroids	11435 (28.3)	7627 (38.1)	3808 (18.7)	<0.0001
Antivirals	8025 (19.8)	5925 (29.6)	2100 (10.3)	<0.0001
Tracheostomy inserted	2461 (6.1)	2422 (12.1)	39 (0.2)	<0.0001
ECMO	706 (1.7)	706 (3.5)	0 (0.0)	<0.0001
ACE Inhibitors	4399 (10.9)	1991 (9.9)	2408 (11.8)	<0.0001
Antifungal	3200 (7.9)	2384 (11.9)	816 (4.0)	<0.0001
Angiotensin II Receptor Blockers	2865 (7.1)	1674 (8.4)	1191 (5.8)	<0.0001
Therapeutic anticoagulant	532 (1.3)	510 (2.5)	22 (0.1)	<0.0001
Lopinavir/ritonavir	651 (1.6)	397 (2.0)	254 (1.2)	<0.0001
Non-steroidal anti-inflammatory	2317 (5.7)	1191 (5.9)	1126 (5.5)	0.07
Inhaled nitric oxide	505 (1.2)	491 (2.4)	14 (0.1)	<0.0001
Chloroquine/hydroxychloroquine	946 (2.3)	718 (3.6)	228 (1.1)	<0.0001
Convalescent plasma	398 (1.0)	248 (1.2)	150 (0.7)	<0.0001
Macrolides	83 (0.2)	66 (0.3)	17 (0.1)	<0.0001
Dexamethasone	4174 (10.3)	1992 (9.9)	2182 (10.7)	0.01
Interferon beta	131 (0.3)	118 (0.6)	13 (0.1)	<0.0001
Oral steroids	311 (0.8)	275 (1.4)	36 (0.2)	<0.0001
Remdesivir	2009 (5.0)	1092 (5.4)	917 (4.5)	<0.0001
IL6 inhibitor	122 (0.3)	90 (0.4)	32 (0.2)	<0.0001
Tocilizumab	51 (0.1)	42 (0.2)	9 (0.0)	<0.0001

ECMO, Extracorporeal membrane oxygenation; **ACE,** Angiotensin Converting Enzyme; **IL,** interleukin.

Table 3. Patients with severe COVID-19 that developed complications stratified by patients admitted to the Intensive Care Unit (ICU).

		ICU admitted		
Complications	**All** n=40440	**Yes** n=20044	**No** n=20396	***p** value*
Neurologic, n (%)				
Seizures	393 (1.0)	240 (1.2)	153 (0.8)	<0.0001
Stroke	489 (1.2)	281 (1.4)	208 (1.0)	<0.0001
Meningitis or Encephalitis	113 (0.3)	93 (0.5)	20 (0.1)	<0.0001
Other neurological complication	490 (1.2)	228 (1.1)	262 (1.3)	0.19
Cardiovascular, n (%)				
Congestive Heart Failure	1183 (2.9)	432 (2.2)	751 (3.7)	<0.0001
Endocarditis, Myocarditis, Pericarditis	223 (0.6)	191 (1.0)	32 (0.2)	<0.0001
Cardiac Arrhythmia	2992 (7.4)	1995 (10.0)	997 (4.9)	<0.0001
Cardiac Arrest	1457 (3.6)	1012 (5.0)	445 (2.2)	<0.0001
Cardiac Ischemia	556 (1.4)	303 (1.5)	253 (1.2)	0.021
Cardiomyopathy	195 (0.5)	138 (0.7)	57 (0.3)	<0.0001
Myocardial Infarction	34 (0.1)	31 (0.2)	3 (0.0)	<0.0001
Pulmonary, n (%)				
Bacterial Pneumonia	4695 (11.6)	2591 (12.9)	2104 (10.3)	<0.0001
Acute Respiratory Distress Syndrome	7928 (19.6)	5747 (28.7)	2181 (10.7)	<0.0001
Pneumothorax	555 (1.4)	447 (2.2)	108 (0.5)	<0.0001
Pleural Effusion	2198 (5.4)	1093 (5.5)	1105 (5.4)	0.89
Pulmonary Embolism	272 (0.7)	237 (1.2)	35 (0.2)	<0.0001
Cryptogenic Organizing Pneumonia	122 (0.3)	95 (0.5)	27 (0.1)	<0.0001
Gastrointestinal, n (%)				
Pancreatitis	138 (0.3)	103 (0.5)	35 (0.2)	<0.0001
Liver Dysfunction	2385 (5.9)	1703 (8.5)	682 (3.3)	<0.0001
Gastrointestinal Haemorrhage	393 (1.0)	221 (1.1)	172 (0.8)	0.008
Renal, n (%)				
Acute kidney Injury	6566 (16.2)	4030 (20.1)	2536 (12.4)	<0.0001
Metabolic, n (%)				
Hyperglycaemia	3232 (8.0)	2265 (11.3)	967 (4.7)	<0.0001
Hypoglycaemia	757 (1.9)	355 (1.8)	402 (2.0)	0.14
Hematologic, n (%)				
Anaemia	5057 (12.5)	3203 (16.0)	1854 (9.1)	<0.0001
Disseminated Intravascular Coagulation	1296 (3.2)	844 (4.2)	452 (2.2)	<0.0001
Bleeding	84 (0.2)	80 (0.4)	4 (0.0)	<0.0001
Others, n (%)				
Other complication	6321 (15.6)	2883 (14.4)	3438 (16.9)	<0.0001
Bacteraemia	1848 (4.6)	1366 (6.8)	482 (2.4)	<0.0001
Rhabdomyolysis or Myositis	246 (0.6)	185 (0.9)	61 (0.3)	<0.0001

Table 4. Generalised Additive Model (GAM) fitted to assess the association of being admitted to the intensive care unit (ICU) with 28-day fatality ratio.

		95% CI		
Variable	**OR**	**Lower**	**Upper**	***p value***
ICU admission	0.70	0.65	0.75	<0.0001
High flow nasal cannula	1.05	1.00	1.11	0.052
Non-invasive respiratory support	1.37	1.31	1.44	<0.0001
Invasive mechanical ventilation	1.97	1.81	2.14	<0.0001
Vasopressors or inotropes	1.56	1.44	1.70	<0.0001
Number of comorbidities	1.07	1.06	1.09	<0.0001
Temperature on hospital admission	0.92	0.90	0.94	<0.0001
Heart rate on hospital admission	1.01	1.00	1.01	<0.0001
Respiratory rate on hospital admission	1.03	1.02	1.03	<0.0001
Systolic blood pressure on hospital admission	1.00	1.00	1.01	<0.0001
Diastolic blood pressure on hospital admission	0.99	0.99	0.99	<0.0001
Acute Respiratory Distress Syndrome	1.47	1.39	1.56	<0.0001
Male	1.25	1.19	1.31	<0.0001
Month of hospital admission	0.98	0.96	0.99	<0.0001
New cases per million	1.00	1.00	1.00	<0.0001
Age (years)	Estimated marginal means	Lower	Upper	
20	7.1%	5.8%	8.7%	
40	9.1%	8.3%	9.9%	
60	19.8%	19.0%	20.6%	
80	51.8%	50.7%	52.9%	

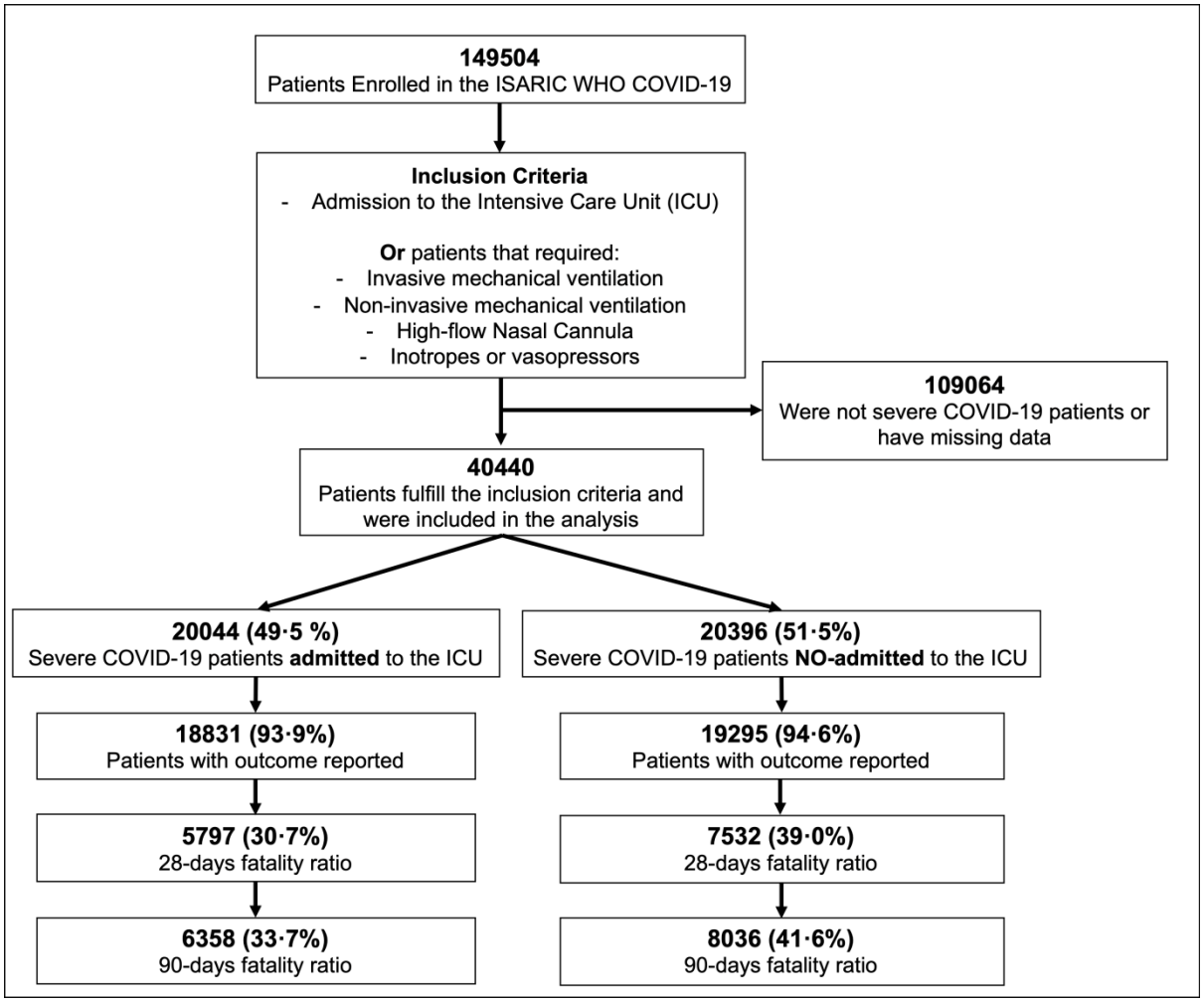
FIGURE LEGENDS

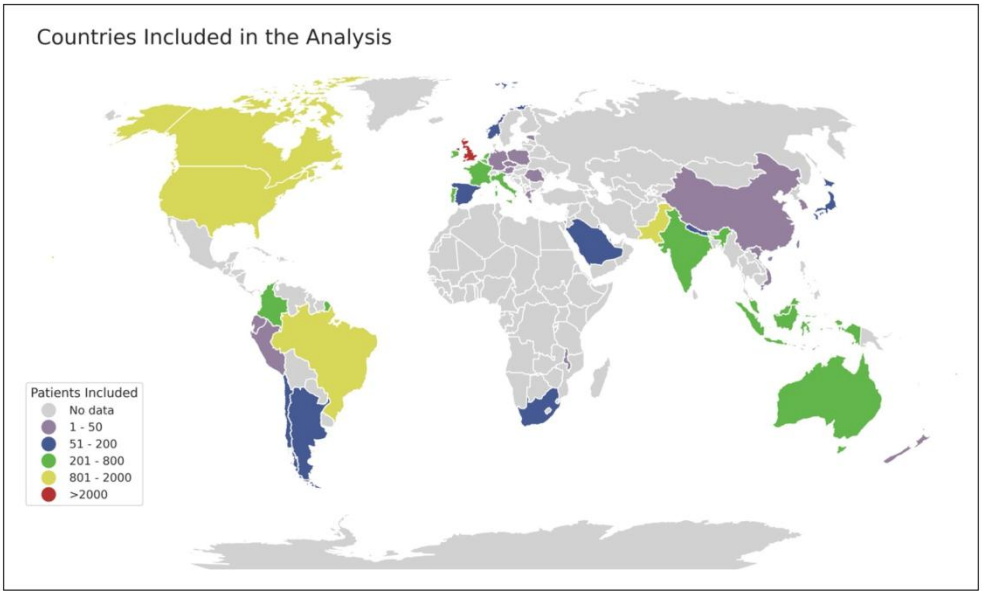
Figure 1. Study flow chart.

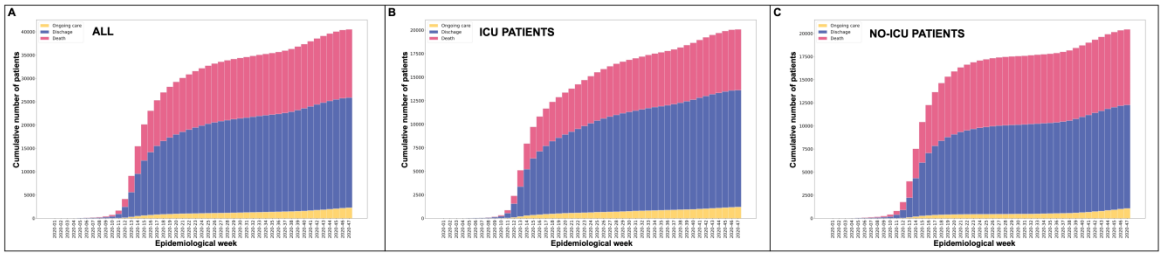
Figure 2. Patients with severe COVID-19 were enrolled in six continents. Map with a colour scale showing the number of patients included in each country. In grey, countries with no patients included in this analysis.

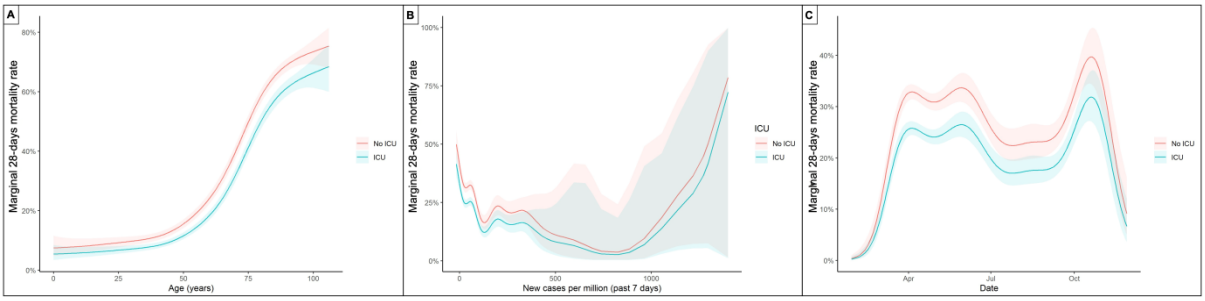
Figure 3. Patients admitted to the ICU have lower cumulative dead over time. In the figure is presented the cumulative number of cases included in the study (**A**), stratified by patients admitted to the Intensive Care Unit (ICU) (**B**) and patients with no admission to the ICU (**C**). In yellow are presented the proportion of patients that are still hospitalized at the moment of data extraction; in blue are presented the proportion of patients discharged alive; and, in red, the proportion of patients reported dead.

Figure 4. Estimation of the non-linear effect on 28-day fatality ratio using a Generalised Additive Model (GAM) in patients with severe COVID-19 stratified by Intensive Care Unit (ICU) admission. Age is shown to be an essential factor for higher fatality ratio in patients with severe COVID-19; however, patients admitted to the ICU have a lower fatality ratio independently of the age (**A**). Even after adjusting by the number of new cases per million at the moment of hospital admission (**B**) and the interaction over time (**C**), the marginal 28-day fatality ratio was lower in patients admitted to the ICU.


149504
Patients Enrolled in the ISARIC WHO COVID-19
Inclusion Criteria
- Admission to the Intensive Care Unit (ICU)
Or patients that required:
- Invasive mechanical ventilation
- Non-invasive mechanical ventilation
- High-flow Nasal Cannula
- Inotropes or vasopressors
109064
Were not severe COVID-19 patients or have missing data
40440
Patients fulfill the inclusion criteria and were included in the analysis
20044 (49·5 %)
Severe COVID-19 patients admitted to the ICU
20396 (51·5%)
Severe COVID-19 patients NO-admitted to the ICU
18831 (93·9%)
Patients with outcome reported
19295 (94·6%)
Patients with outcome reported
5797 (30·7%)
28-days fatality ratio
7532 (39·0%)
28-days fatality ratio
6358 (33·7%)
90-days fatality ratio
8036 (41·6%)
90-days fatality ratio


Countries Included in the Analysis
Patients Included
No data
1 - 50
51 - 200
201 - 800
801 - 2000
>2000


A
ALL
Ongoing care
Discharge
Death
Cumulative number of patients
Epidemiological week
B
ICU PATIENTS
Ongoing care
Discharge
Death
Cumulative number of patients
Epidemiological week
C
NO-ICU PATIENTS
Ongoing care
Discharge
Death
Cumulative number of patients
Epidemiological week


A
Marginal 28-days mortality rate
80%
60%
40%
20%
0%
0
25
50
75
100
Age (years)
No ICU
ICU
B
Marginal 28-days mortality rate
100%
75%
50%
25%
0%
0
500
1000
New cases per million (past 7 days)
ICU
No ICU
ICU
C
Marginal 28-days mortality rate
40%
30%
20%
10%
0%
Apr
Jul
Oct
Date
No ICU
ICU

Supplementary appendix

TITLE: Clinical Characteristics, Risk Factors and Outcomes in Patients with Severe COVID-19 Registered in the ISARIC WHO Clinical Characterisation Protocol: A Prospective, Multinational, Multicentre, Observational Study.

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Abbreviated running title: Severe COVID-19 Cohort.

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Ewen M.; Harrison, Janet; Hayat, Muhammad; Hays, Leanne; Heerman, Jan; Heggelund, Lars; Hendry, Ross; Hennessy, Martina; Henriquez-Trujillo, Aquiles; Hentzien, Maxime; Herekar, Fivzia; Hernandez-Montfort, Jaime; Hershey, Andrew; Hesstvedt, Liv; Hidayah, Astarini; Higgins, Eibhilin; Higgins, Dawn; Hinton, Samuel; Hipólito-Reis, Ana; Hiraiwa, Hiroaki; Ho, Antonia Ying Wai; Hoctin, Alexandre; Hoffmann, Isabelle; Hoiting, Oscar; Holt, Rebecca; Holter, Jan Cato; Horby, Peter; Horcajada, Juan Pablo; Hoshino, Koji; Houas, Ikram; Hough, Catherine L.; Hsu, Jimmy Ming-Yang; Hulot, Jean-Sébastien; Ijaz, Samreen; Illes, Hajnal-Gabriela; Imbert, Patrick; Inácio, Hugo; Isgett, Sarah; Ishani, Palliya Guruge Pramodya Ishani; Isidoro, Tiago; Isnard, Margaux; Itai, Junji; Ivulich, Daniel; Jaafar, Danielle; Jaafoura, Salma; Jackson, Clare; Jacquet, Pierre; Jamieson, Nina; Jaureguiberry, Stéphane; Jawad, Issrah; Jayakumar, Devachandran; Jego, Florence; Jenum, Synne; Jimbo-Sotomayor, Ruth; Jorge García, Ruth Noemí; Joseph, Cédric; Joseph, Mark; Joshi, Swosti; Jourdain, Mercé; Jouvet, Philippe; Jung, Hanna; Juzar, Dafsah; Kafif, Ouifiya; Kaguelidou, Florentia; Kali, Sabina; Kalomoiri, Smaragdi; Kambiya, Paul; Kandamby, Darshana Hewa; Kandel, Chris; Kant, Ravi; Kartsonaki, Christiana; Kasugai, Daisuke; Kataria, Anant; Katz, Kevin; Kaur Johal, Simreen; Kay, Christy; Keating, Sean; Kelly, Andrea; Kelly, Sadie; Kennedy, Ryan; Kennon, Kalynn; Kerroumi, Younes; Kestelyn, Evelyne; Khalid, Imrana; Khalil, Antoine; Khan, Coralie; Khan, Irfan; Khanal, Sushil; Kho, Michelle E; Khoo, Saye; Khoso, Nasir; Kida, Yuri; Kiiza, Peter; Kildal, Anders Benjamin; Kim, Jae Burm; Kimmoun, Antoine; Kindgen-Milles, Detlef; Kitamura, Nobuya; Klenerman, Paul; Kloumann Bekken, Gry; Knight, Stephen; Kodippily, Chamira; Kohns Vasconcelos, Malte; Koirala, Sabin; Komatsu, Mamoru; Kosgei, Caroline; Kpangon, Arsène; Krawczyk, Karolina; Kumar, Ashok; Kumar, Deepali; Kumar, Mukesh; Kumar Vecham, Pavan; Kurtzman, Ethan; Kusumastuti, Neurinda Permata; Kutsogiannis, Demetrios; Kyriakoulis, Konstantinos; Lachatre, Marie; Laffey, John G; Laine, Fabrice; Lambert, Marc; Lamontagne, François; Langelot-Richard, Marie; Langlois, Vincent; Lantang, Eka Yudha; Lanza, Marina; Laouénan, Cédric; Laribi, Samira; Lariviere, Delphine; Launay, Odile; Law, Andrew; Lawrence, Cassie; Le, Minh; Le Bris, Cyril; Le Falher, Georges; Le Fevre, Lucie; Le Hingrat, Quentin; Le Maréchal, Marion; Le Mestre, Soizic; Le Nagard, Hervé; Le Turnier, Paul; Lee, Su Hwan; Lee, James; Lee, Todd C.; Leeming, Gary; Lefebvre, Bénédicte; Lefevre, Benjamin; LeGac, Sylvie; Lelievre, Jean-Daniel; Lellouche, François; Lemaignen, Adrien; Lemee, Véronique; Lemeur, Anthony; Lemmink, Gretchen; León, Rafael; Leone, Michela; Lepiller, Quentin; Lescure, François-Xavier; Lesens, Olivier; Lesouhaitier, Mathieu; Levy, Bruno; Levy, Yves; Levy-Marchal, Claire; L'Her, Erwan; Li Bassi, Gianluigi; Liang, Janet; Liaquat, Ali; Liegeon, Geoffrey; Lim, Wei Shen; Lima, Chantre; Lina, Bruno; Lind, Andreas; Lingas, Guillaume; Link, Linda; Lion-Daolio, Sylvie; Lissauer, Samantha; Liu, Keibun; Livrozet, Marine; Lolong, Navy; Lopes, Diogo; Lopez-Colon, Dalia; Loschner, Anthony L.; Loufti, Bouchra; Louis, Guillame; Lourenco, Silvia; Lucet, Jean Christophe; Luna, Carlos M.; Lungu, Olguta; Luong, Liem; Luton, Dominique; Lwin, Nilar; Lyons, Ruth; Maasikas, Olavi; Mabiala, Oryane; Macheda, Gabriel; Macias Sanchez, Juan; Madhok, Jai; Madiha, Hashmi; Mahy, Sophie; Maia, Raquel; Maier, Lars Siegfried; Maillet, Mylène; Maitre, Thomas; Malfertheiner, Maximilian; Malik, Nadia; Malvy, Denis; Manda, Victoria; Mandei, Jose M.; Mandelbrot, Laurent; Mankikian, Julie; Manning, Edmund; Manuel, Aldric; Maria Sant`Ana Malaque, Ceila; Marino, Daniel; Marino, Flávio; Mariz, Carolline de Araújo; Markowicz, Samuel; Marques, Ana; Marquis, Catherine; Marsh, Brian; Marsh, Laura;

Marshall, John; Martelli, Celina Turchi; Martin, Emily; Martin-Blondel, Guillaume; Martinelli, Alessandra; Martin-Loeches, Ignacio; Martins, Ana; Martins, João; Martins, Nuno; Martins Rego, Caroline; Martucci, Gennaro; Marwali, Eva Miranda; Maslove, David; Mason, Sabina; Mat Nor, Basri; Mathieu, Daniel; Mattei, Mathieu; Matulevics, Romans; May, Jennifer; Maynar, Javier; Mazzoni, Thierry; Mc Evoy, Natalie; McCarthy, Aine; McCarthy, Anne; McCloskey, Colin; McConnochie, Rachael; McConnochie, Rachael; McDermott, Sherry; McDonald, Sarah; McElwee, Samuel; McGeer, Allison; McKay, Chris; McKeown, Johnny; McLean, Kenneth A.; McNicholas, Bairbre; Meaney, Edel; Mear-Passard, Cécile; Mechlin, Maggie; Mele, Ferruccio; Melo, Luis; Mendes, Joao Joao; Menkiti, Ogechukwu; Menon, Kusum; Mentré, France; Mentzer, Alexander J.; Mercier, Emmanuelle; Mercier, Noémie; Mergeay-Fabre, Mayka; Mergler, Blake; Merson, Laura; Mesquita, António; Meybeck, Agnès; Meyer, Dan; Meynert, Alison M.; Meysonnier, Vanina; Meziane, Amina; Mezidi, Mehdi; Michelet, Isabelle; Mihelis, Efstathia; Mihnovitš, Vladislav; Miranda-Maldonado, Hugo; Moin, Asma; Molina, David; Molinos, Elena; Mone, Mary; Monteiro, Agostinho; Montes, Claudia; Montrucchio, Giorgia; Moore, Sarah; Moore, Shona C.; Morales Cely, Lina; Moro, Lucia; Morton, Ben; Motherway, Catherine; Motos, Ana; Mouquet, Hugo; Mouton Perrot, Clara; Moyet, Julien; Mullaert, Jimmy; Müller, Fredrik; Müller, Karl Erik; Muneeb, Syed; Murris, Marlène; Murthy, Srinivas; Myrodia, Dimitra Melia; Nagpal, Dave; Nagrebetsky, Alex; Narasimhan, Mangala; Nasim Khan, Rashid; Neant, Nadège; Neb, Holger; Neto, Raul; Neumann, Emily; Ng, Wing Yiu; Ng, Pauline Yeung; Nguyen, Duc; Ni Choileain, Orna; Nichol, Alistair; Nonas, Stephanie; Noret, Marion; Norman, Lisa; Notari, Alessandra; Noursadeghi, Mahdad; Nseir, Saad; Nunez, Jose I; Nurnaningsih, Nurnaningsih; Occhipinti, Giovanna; O'Donnell, Max; Ogston, Tawnya; Ogura, Takayuki; Oh, Tak-Hyuk; O'Hearn, Katie; Ohshimo, Shinichiro; Oinam, Budhacharan Singh; Oliveira, João; Oliveira, Larissa; Olliaro, Piero L.; O'Neil, Conar; Ong, David S.Y.; Oosthuyzen, Wilna; Opavsky, Anne; Openshaw, Peter; Orakzai, Saijad; Orozco-Chamorro, Claudia Milena; Ortoleva, Jamel; Osatnik, Javier; Ouamara, Nadia; Ouissa, Rachida; Owyang, Clark; Oziol, Eric; Pabasara, H M Upulee; Pagadoy, Maïder; Pages, Justine; Palacios, Mario; Palacios, Amanda; Palmarini, Massimo; Panarello, Giovanna; Panda, Prasan Kumar; Paneru, Hem; Panigada, Mauro; Papadopoulos, Aurélie; Parker, Melissa; Parra, Briseida; Pasquier, Jérémie; Patauner, Fabian; Patel, Junaid; Patrão, Luís; Patricio, Patricia; Patrier, Juliette; Patterson, Lisa; Paul, Christelle; Paul, Mical; Paulos, Jorge; Paxton, William A.; Payen, Jean-François; Peek, Giles; Peelman, Florent; Peiffer-Smadja, Nathan; Peigne, Vincent; Pejkovska, Mare; Peltan, Ithan D.; Pereira, Rui; Perez, Daniel; Periel, Luis; Perpoint, Thomas; Pesenti, Antonio; Pestre, Vincent; Petroušová, Lenka; Petrov-Sanchez, Ventzislava; Pettersen, Frank Olav; Peytavin, Gilles; Pharand, Scott; Piagnerelli, Michael; Picard, Walter; Picone, Olivier; Pierobon, Carola; Pimentel, Carlos; Piroth, Lionel; Pius, Riinu; Piva, Simone; Plantier, Laurent; Plotkin, Daniel; Poissy, Julien; Pokeerbux, Ryadh; Poli, Sergio; Pollakis, Georgios; Ponscarme, Diane; Post, Andra-Maris; Postma, Douwe F.; Povoa, Pedro; Póvoas, Diana; Powis, Jeff; Prapa, Sofia; Preau, Sébastien; Prebensen, Christian; Preiser, Jean-Charles; Prinssen, Anton; Pritchard, Mark; Priyadarshani, Gamage Dona Dilanthi; Proença, Lúcia; Puéchal, Oriane; Pulicken, Matthew; Purcell, Gregory; Quesada, Luisa; Quinones-Cardona, Vilmaris; Quist-Paulsen, Else; Quraishi, Mohammed; Rabaud, Christian; Rafael, Aldo; Rafiq, Marie; Rahutullah, Arsalan; Rainieri, Fernando; Ralib, Azrina; Ramakrishnan, Nagarajan; Ramos, Grazielle Viana; Rana, Asim; Rashan, Aasiyah;

Rashan, Thalha; Rasmin, Menaldi; Rätsep, Indrek; Real, Andre; Rebaudet, Stanislas; Reeve, Brenda; Rehan, Ali; Rehman, Attaur; Reid, Liadain; Reikvam, Dag Henrik; Reis, Renato; Remppis, Jonathan; Remy, Martine; Ren, Hongru; Renk, Hanna; Resende, Liliana; Revest, Matthieu; Rewa, Oleksa; Reyes, Luis F.; Reyes, Tiago; Ribeiro, Maria Ines; Richardson, David; Richardson, Denise; Richier, Laurent; Riera, Jordi; Rios, Ana Lúcia; Rishu, Asgar; Rizer, Nicholas; Roberto, André; Roberts, Stephanie; Robertson, David L.; Robineau, Olivier; Roche-Campo, Ferran; Rodari, Paola; Rodeia, Simão; Roger, Pierre-Marie; Rojek, Amanda; Romaru, Juliette; Roncon-Albuquerque Jr, Roberto; Rosa-Calatrava, Manuel; Rose, Michael; Rosenberger, Dorothea; Rossanese, Andrea; Rossetti, Matteo; Rossignol, Bénédicte; Rossignol, Patrick; Rössler, Bernhard; Rousset, Stella; Roy, Carine; Roze, Benoît; Rusmawatiningtyas, Desy; Russell, Clark D.; Ryckaert, Steffi; Rygh Holten, Aleksander; Saba, Isabela; Sadaf, Sairah; Sadat, Musharaf; Sahraei, Valla; Saint-Gilles, Maximilien; Salahuddin, Nawal; Salazar, Leonardo; Sales, Gabriele; Sallaberry, Stéphane; Salmon Gandonniere, Charlotte; Salvator, Hélène; Sanchez, Olivier; Sanchez-Miralles, Angel; Sancho-Shimizu, Vanessa; Sandhu, Gyan; Sandrine, Pierre-François; Sandulescu, Oana; Santos, Marlene; Sarfo-Mensah, Shirley; Sarmiento, Iam Claire E.; Sarton, Benjamine; Satyapriya, Sree; Saviciute, Egle; Schaffer, Justin; Schermer, Tjard; Scherpereel, Arnaud; Schneider, Marion; Schroll, Stephan; Schwameis, Michael; Scott, Janet T.; Scott-Brown, James; Sedillot, Nicholas; Seitz, Tamara; Semaille, Caroline; Semple, Malcolm G.; Senneville, Eric; Sepulveda, Claudia; Sequeira, Filipa; Sequeira, Tânia; Serpa Neto, Ary; Shadowitz, Ellen; Shamsah, Mohammad; Sharma, Pratima; Shaw, Catherine A.; Shaw, Victoria; Sheharyar, Ashraf; Shi, Haixia; Shiekh, Mohiuddin; Shime, Nobuaki; Shimizu, Hiroaki; Shimizu, Keiki; Shimizu, Naoki; Shrapnel, Sally; Shum, Hoi Ping; Si Mohammed, Nassima; Sibiude, Jeanne; Siddiqui, Atif; Sigfrid, Louise; Sillaots, Piret; Silva, Catarina; Silva, Maria Joao; Silva, Rogério; Sin, Wai Ching; Skogen, Vegard; Smith, Sue; Smood, Benjamin; Smyth, Michelle; Snacken, Morgane; So, Dominic; Solis, Monserrat; Solomon, Joshua; Solomon, Tom; Somers, Emily; Sommet, Agnès; Song, Myung Jin; Song, Rima; Song, Tae; Sonntagbauer, Michael; Soum, Edouard; Sousa, Ana Chora; Sousa, Marta; Sousa Uva, Maria; Souza-Dantas, Vicente; Sperry, Alexandra; Sri Darshana, B. P. Sanka Ruwan; Sriskandan, Shiranee; Stabler, Sarah; Staudinger, Thomas; Stecher, Stephanie-Susanne; Stienstra, Ymkje; Stiksrud, Birgitte; Streinu-Cercel, Anca; Streinu-Cercel, Adrian; Strudwick, Samantha; Stuart, Ami; Stuart, David; Suen, Jacky Y.; Suen, Gabriel; Sultana, Asfia; Summers, Charlotte; Surovcová, Magdalena; Syrigos, Konstantinos; Sztajnbok, Jaques; Szuldrzynski, Konstanty; Tabrizi, Shirin; Taccone, Fabio; Tagherset, Lysa; Taleb, Sara; Talsma, Jelmer; Tan, Le Van; Tanaka, Hiroyuki; Tanaka, Taku; Taniguchi, Hayato; Tanveer, Hussain; Tardivon, Coralie; Tattevin, Pierre; Taufik, M Azhari; Tedder, Richard S.; Teixeira, João; Tejada, Sofia; Tellier, Marie-Capucine; Teotonio, Vanessa; Téoulé, François; Terpstra, Pleun; Terrier, Olivier; Terzi, Nicolas; Tessier-Grenier, Hubert; Thibault, Vincent; Thill, Benoît; Thompson, MD, Shaun; Thomson, Emma C.; Thomson, David; Thuy, Duong Bich; Thwaites, Ryan S.; Timsit, Jean-François; Tirupakuzhi Vijayaraghavan, Bharath Kumar; Tissot, Noémie; Toki, Maria; Tolppa, Timo; Tonby, Kristian; Torres, Antoni; Torres-Zevallos, Hernando; Trapani, Tony; Treoux, Théo; Trieu, Huynh Trung; Tromeur, Cécile; Trontzas, Ioannis; Troost, Jonathan; Trouillon, Tiffany; Truong, Jeanne; Tual, Christelle; Tubiana, Sarah; Tuite, Helen; Turmel, Jean-Marie; Turtle, Lance C.W.; Twardowski, Pawel; Uchiyama, Makoto; Udayanga, PG Ishara; Udy, Andrew; Ullrich, Roman; Uribe, Alberto; Usman,

Asad; Val-Flores, Luís; Valran, Amélie; Van De Velde, Stijn; van den Berge, Marcel; Van der Feltz, Machteld; Van Der Vekens, Nicky; Van der Voort, Peter; Van Der Werf, Sylvie; van Gulik, Laura; Van Hattem, Jarne; van Lelyveld, Steven; van Netten, Carolien; van Twillert, G; Vanel, Noémie; Vanoverschelde, oHenk; Vauchy, Charline; Veislinger, Aurélie; Ventura, Sara; Verbon, Annelies; Vidal, José Ernesto; Vieira, César; Villanueva, Joy Ann; Villar, Judit; Villeneuve, Pierre-Marc; Villoldo, Andrea; Vinh Chau, Nguyen Van; Visseaux, Benoit; Visser, Hannah; Vitiello, Chiara; Vuotto, Fanny; Wang, Chih-Hsien; Wei, Jia; Weil, Katharina; Wesselius, Sanne; Wham, Murray; Whelan, Bryan; White, Nicole; Wicky, Paul Henri; Wiedemann, Aurélie; Wille, Keith; Williams, Virginie; Wils, Evert-Jan; Wolf, Timo; Xynogalas, Ioannis; Yacoub, Sophie; Yamazaki, Masaki; Yazdanpanah, Yazdan; Yelnik, Cécile; Yerkovich, Stephanie; Yokoyama, Toshiki; Yonis, Hodane; Yuliarto, Saptadi; Zaaqoq, Akram; Zabbe, Marion; Zacharowski, Kai; Zahran, Maram; Zambon, Maria; Zambrano, Miguel; Zanella, Alberto; Zoufaly, Alexander; Zucman, David.

2. Strobe Checklist

	Item No.	Recommendation	Section or Page in the manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Background
Objectives	3	State specific objectives, including any prespecified hypotheses	Background, last paragraph
Methods			
Study design	4	Present key elements of study design early in the paper	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	Methods, statistical analysis
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods
Bias	9	Describe any efforts to address potential sources of bias	Methods (statistical analysis) and limitation section in the discussion
Study size	10	Explain how the study size was arrived at	No sample size was calculated
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods
		(*b*) Describe any methods used to examine subgroups and interactions	Methods
		(*c*) Explain how missing data were addressed	Methods
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	Methods
		(*e*) Describe any sensitivity analyses	Methods and supplementary appendix
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results, first paragraph
		(b) Give reasons for non-participation at each stage	Results first paragraph
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results, second paragraph
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Methods
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Results
Main	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	Results

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results, subgroup section
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitation section at the end of the discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion and Limitation section
Generalisability	21	Discuss the generalisability (external validity) of the study results	Limitation section
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	At the end of the methods
results		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	Results
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable

3. Supplementary tables

Supplementary Table 1. Generalised Additive Model (GAM) fitted to assess the association of being admitted to the intensive care unit (ICU) with 90-day mortality.

		95% CI		
Variable	**OR**	**Lower**	**Upper**	***p value***
ICU admission	0·69	0·64	0·74	<0·0001
High flow nasal cannula	1·08	1·02	1·14	0·005
Non-invasive respiratory support	1·38	1·31	1·45	<0·0001
Invasive mechanical ventilation	2·06	1·89	2·24	<0·0001
Vasopressors or inotropes	1·73	1·60	1·88	<0·0001
Comorbidities	1·08	1·07	1·10	<0·0001
Temperature on hospital admission	0·90	0·88	0·92	<0·0001
Heart rate on hospital admission	1·01	1·00	1·01	<0·0001
Respiratory rate on hospital admission	1·03	1·02	1·03	<0·0001
Systolic blood pressure on hospital admission	0·99	0·98	0·99	<0.0001
Diastolic blood pressure on hospital admission	0·99	0·98	0·99	<0·0001
Acute Respiratory Distress Syndrome	1·51	1·42	1·60	<0·0001
Male	1·26	1·20	1·32	<0·0001
Month of hospital admission	0·96	0·95	0·97	<0·0001
New cases per million	0·99	0·99	0·99	<0·0001
Age	Estimated marginal means	Lower	Upper	
20	7·4%	6·0%	9·1%	
40	9·7%	8·9%	10·7%	
60	21·7%	20·8%	22·6%	
80	55·5%	54·4%	56·6%	

Supplementary Table 2. Sensitivity analysis excluding patients enrolled in the United Kingdom. Generalised Additive Model (GAM) fitted to assess the association of being admitted to the intensive care unit (ICU) with 28-day mortality.

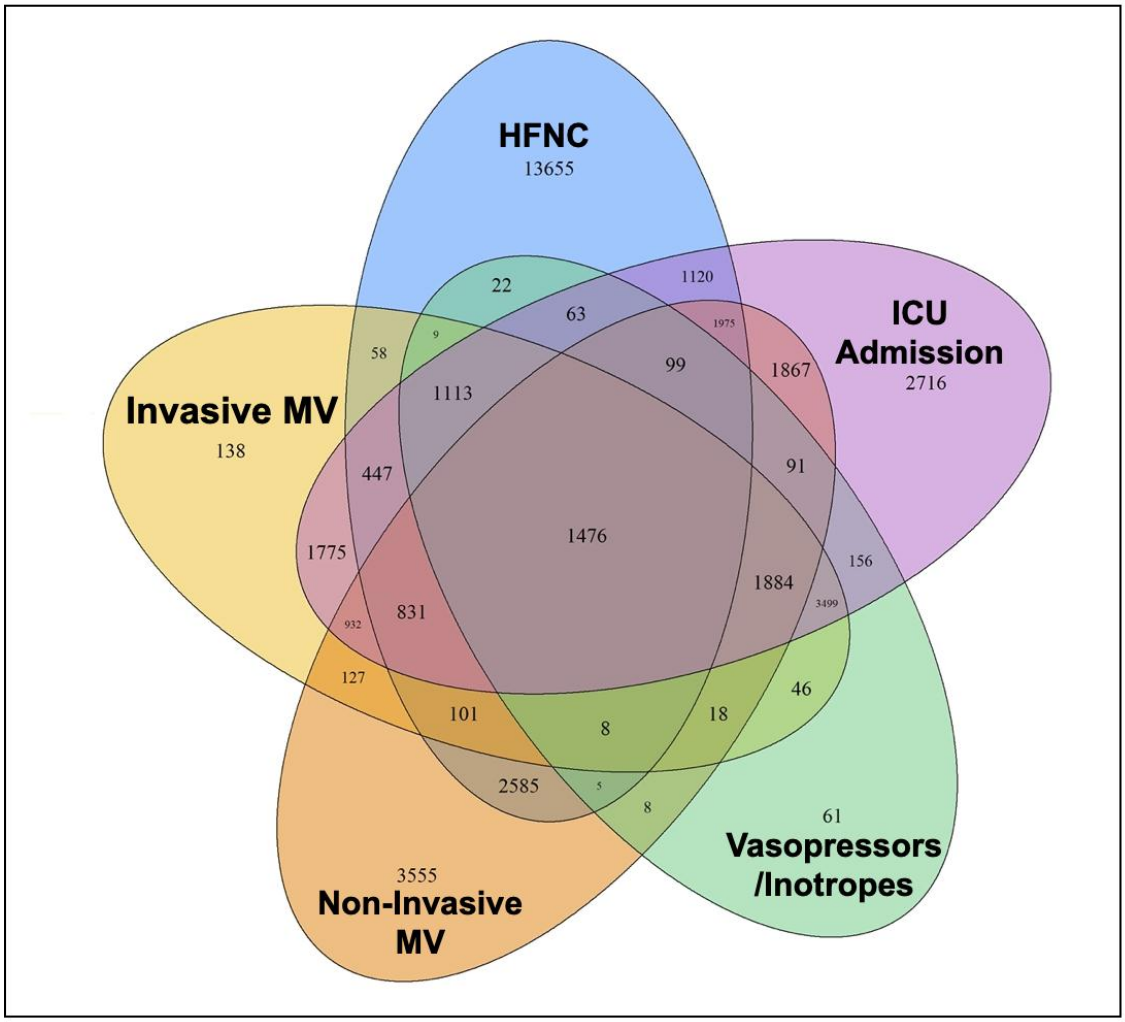
		95% CI		
Variable	**OR**	**Lower**	**Upper**	***p value***
ICU admission	0·69	0·65	0·75	<0·0001
High flow nasal cannula	1·05	0·9	1·11	0.052
Non-invasive respiratory support	1·37	1·31	1·44	<0·0001
Invasive mechanical ventilation	1·97	1·81	2·14	<0·0001
Vasopressors or inotropes	1·56	1·44	1·70	<0·0001
Comorbidities	1·07	1·06	1·09	<0·0001
Temperature on hospital admission	0·92	0·89	0·93	<0·0001
Heart rate on hospital admission	1·01	1·00	1·01	<0·0001
Respiratory rate on hospital admission	1·03	1·02	1·03	<0·0001
Systolic blood pressure on hospital admission	1·00	1·00	1·01	<0.0001
Diastolic blood pressure on hospital admission	0·99	0·98	0·99	<0·0001
Acute Respiratory Distress Syndrome	1·47	1·39	1·56	<0·0001
Male	1·25	1·19	1·31	<0·0001
Month of hospital admission	0·98	0·96	0·99	<0·0001
New cases per million	0·99	0·99	0·99	<0·0001
Age	Estimated marginal means	Lower	Upper	
20	10·1%	7·9%	12·9%	
40	12·8%	11·2%	14·6%	
60	20·4%	18·6%	22·3%	
80	42·7%	39·8%	45·7%	

Supplementary Table 3. Sensitivity analysis for ethnicity. Generalised Additive Model (GAM) fitted to assess the association of being admitted to the intensive care unit (ICU) with 28-day mortality.

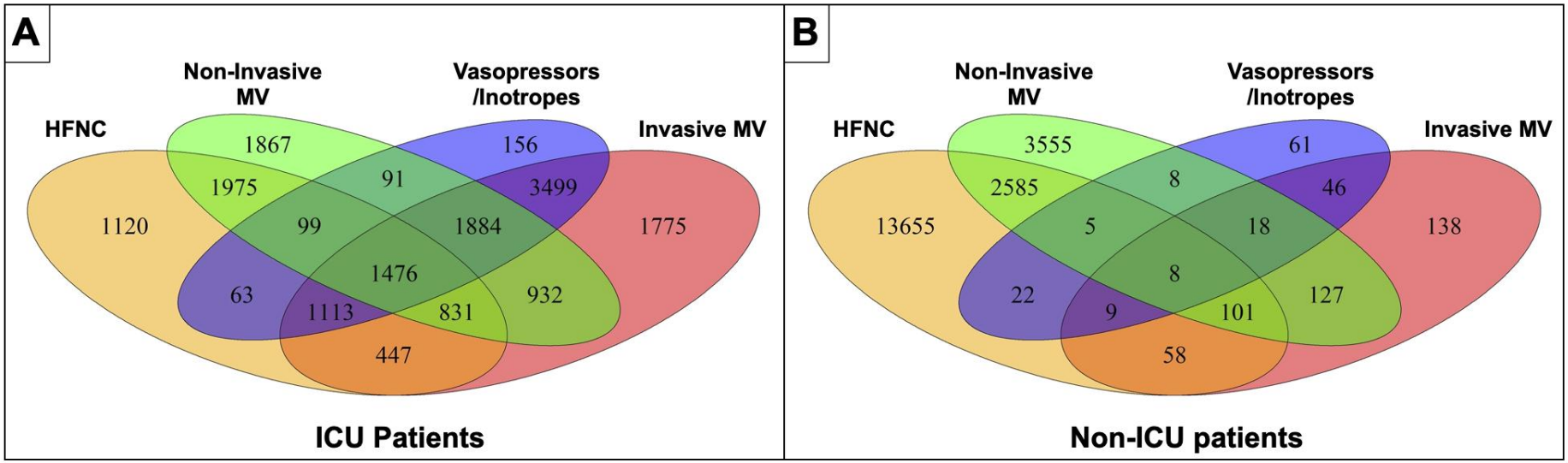
		95% CI		
Variable	**OR**	**Lower**	**Upper**	***p value***
ICU admission	0·60	0·56	0·65	<0·0001
High flow nasal cannula	1·02	0·97	1·08	0.052
Non-invasive respiratory support	1·24	1·18	1·30	<0·0001
Invasive mechanical ventilation	1·91	1·75	2·07	<0·0001
Vasopressors or inotropes	1·57	1·45	1·71	<0·0001
Comorbidities	1·08	1·07	1·10	<0·0001
Temperature on hospital admission	0·89	0·87	0·91	<0·0001
Heart rate on hospital admission	1·01	1·00	1·01	<0·0001
Respiratory rate on hospital admission	1·03	1·02	1·03	<0·0001
Systolic blood pressure on hospital admission	0·99	0·99	1·10	0·17
Diastolic blood pressure on hospital admission	0·99	0·98	0·99	<0·0001
Acute Respiratory Distress Syndrome	1·49	1·40	1·58	<0·0001
Male	1·20	1·14	1·25	<0·0001
Month of hospital admission	0·97	0·96	0·99	<0·0001
New cases per million	0·99	0·99	0·99	<0·0001
Age (>65 years old)	4·13	3·92	4·36	<0·0001
Asian	1·61	0·91	2·97	0·10
Black	1·26	0·71	2·34	0·43
White	1·53	0·87	2·81	0·14
Latino	0·84	0·46	1·63	0·60
Unknown	1·05	0·60	1·93	0·86

4. Supplementary figures

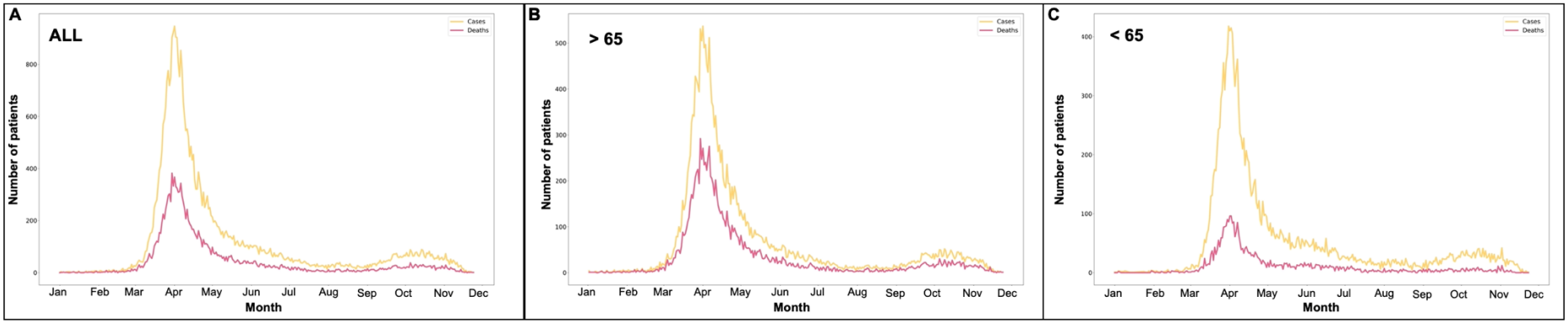
Supplementary figure 1. Venn diagram presenting how treatments (i.e., High-flow nasal cannula, Invasive mechanical ventilation, non-invasive mechanical ventilation, vasopressors/inotropes, and admission to the intensive care) interact among patients included in the cohort.



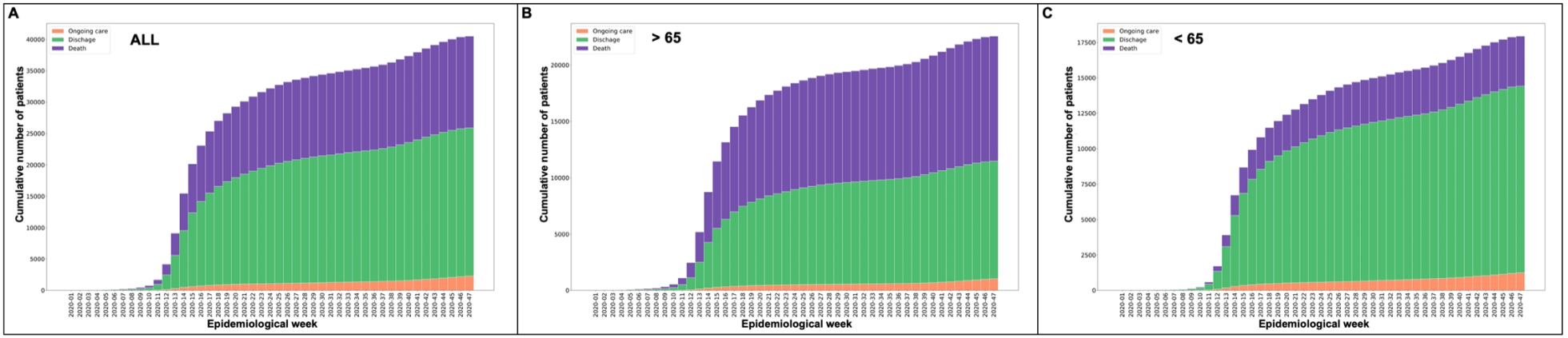
Supplementary figure 2. Venn diagram presenting how treatments (i.e., High-flow nasal cannula, Invasive mechanical ventilation, non-invasive mechanical ventilation, and vasopressors/inotropes) interact among patients included in the cohort, stratified by admission to the intensive care unit.



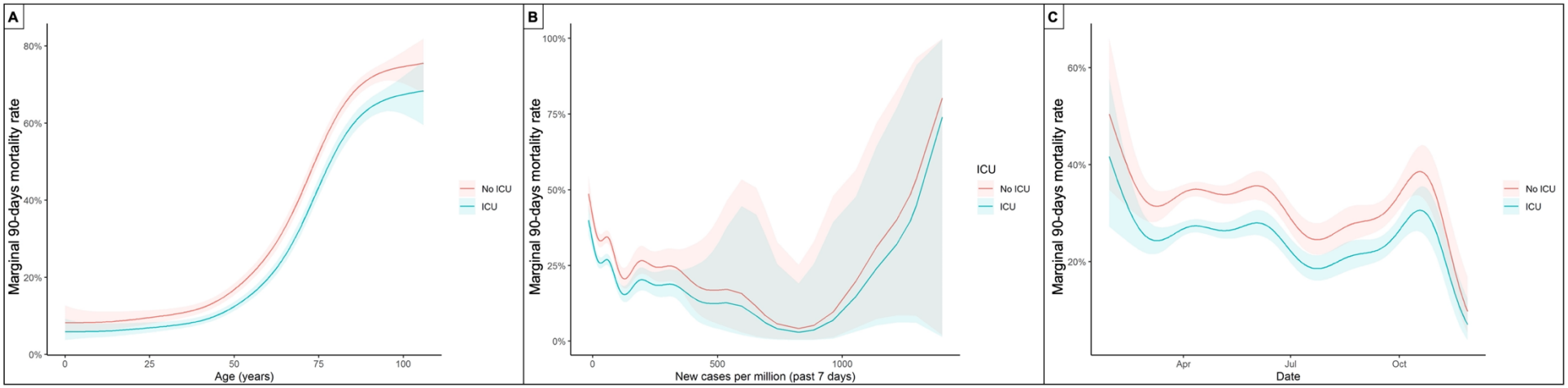
Supplementary figure 3. Histogram representing the number of new cases (in yellow) and the number of deaths (in red), in all patients (A), in patients older than 65 years old (B), and patients younger than 65 years old (C), during the study period.



Supplementary figure 4. Cumulative histogram presenting the number of patients discharged alive (green), patients who died (purple), and patients that remained hospitalised at the time of the data extraction. Panel, A represents all the patients included in the study, panel B patients older than 65, and panel C the patients younger than 65.



Supplementary figure 5. Estimation of the non-linear effect on 90-day mortality using a Generalised Additive Model (GAM) in patients with severe COVID-19 stratified by Intensive Care Unit (ICU) admission. Age is shown to be an essential factor for higher mortality in patients with severe COVID-19; however, patients admitted to the ICU have a lower mortality rate independently of the age (**A**). Even after adjusting by the number of new cases per million at the moment of hospital admission (B) and the interaction over time (C), the marginal 90-day mortality rate was lower in patients admitted to the ICU.



CRF Completion Guide

DESIGN OF THIS CASE REPORT FORM (CRF)

This CRF is set up in modules to be used for recording data on the ISARIC_nCov Core Database or for independent studies.

Module 1 and Module 2 complete on the first day of admission or on first day of COVID-19 assessment.
Module 2 also complete on first day of admission to ICU or high dependency unit. In addition, complete daily for as many days as resources allow up to a maximum of 14 days. Continue to follow-up patients who transfer between wards.
Module 3 (Outcome) complete at discharge or death

GENERAL GUIDANCE

- The CRF is designed to collect data obtained through examination, interview and review of hospital notes. Data may be collected prospectively or retrospectively if the patient is enrolled after the admission date.
- Participant Identification Numbers consist of a 5 digit site code and a 4 digit participant number. You can obtain a site code and registering on the data management system by contacting ncov@isaric.org. Participant numbers should be assigned sequentially for each site beginning with 0001. In the case of a single site recruiting participants on different wards, or where it is otherwise difficult to assign sequential numbers, it is acceptable to assign numbers in blocks or incorporating alpha characters. E.g. Ward X will assign numbers from 0001 or A001 onwards and Ward Y will assign numbers from 5001 or B001 onwards. Enter the Participant Identification Number at the top of every page.
- Printed paper CRFs may be used for later transfer of the data onto the electronic database.
- In the case of a participant transferring between sites, it is preferred to maintain the same Participant Identification Number (PIN) across the sites. When this is not possible, the first site should record 'Transfer to other facility' as an OUTCOME and the second site should start a new form with a new PIN and indicate 'YES-transferred' in the RE-ADMISSION section. If the PIN from the previous site is eventually obtained this can be entered under 'If YES 'Participant Identification Number:'
- For participants who are re-admitted with COVID-19 to the same site, **start a new form with a different Participant Identification Number (PIN)** and enter the previous PIN in response to the question 'Previous participant ID'.
- Complete every line of every section, except where the instructions say to skip a section based on a response.
- Selections with circles (O) are single selection answers (choose one answer only). Selections with square boxes (☐) are multiple selection answers (choose as many answers as are applicable).
- Mark 'Not done' for any results of laboratory values that are not available, not applicable or unknown.
- Avoid recording data outside of the dedicated areas. Sections are available for recording additional information.
- If using paper CRFs, we recommend writing clearly in ink, using BLOCK-CAPITAL LETTERS.
- Place an (X) when you choose the corresponding answer. To make corrections, strike through (-------) the data you wish to delete and write the correct data above it. Please initial and date all corrections.
- Please keep all of the sheets for a single participant together e.g. with a staple or participant-unique folder.
- Please transfer all paper CRF data to the electronic database. All paper CRFs needs to be stored locally, do not send any forms to us. Data are accepted only via secure electronic database.
- Please enter data on the electronic data capture system at https://ncov.medsci.ox.ac.uk/. If your site would like to collect data independently, we are happy to support the establishment of locally hosted databases.
- Please contact us at ncov@isaric.org if you need help with databases, if you have comments and to let us know that you are using the forms.

CRF Completion Guide

FURTHER GUIDANCE AND DEFINITIONS

Comorbidities

Comorbidities present before the onset of COVID-19 and are still present. Do not include those that developed following the onset of COVID-19 symptoms. More detailed guidance is provided.

Hospital admission

For patients who were admitted to hospital with COVID-19 or symptoms consistent with possible COVID-19 infection, please enter details for the date of hospital admission. For patients with a clear alternative diagnosis leading to admission who subsequently acquired COVID-19, original admission date should be provided, but all subsequent references to admission should be taken as referring to day COVID-19 was first clinically suspected (or within the first 24 hours after first day of suspected or confirmed COVID-19 infection).

Where a patient was admitted via multiple hospital departments, count admission from the time they came to the first department during the visit that led to their admission (e.g. arrival at the Emergency Department).

Oxygen therapy

Include any form of supplemental oxygen received using any methods.

Invasive ventilation

Please include any mechanical ventilation delivered following intubation or via a tracheostomy. Do not include patients who are breathing independently via a tracheostomy.

Non-invasive ventilation

Please include any positive-pressure treatment given via a tight-fitted mask. This can be continuous positive pressure (CPAP) or bi-level positive pressure (BIPAP).

Renal replacement therapy or dialysis

Please include any form of continuous renal replacement therapy or intermittent haemodialysis.

Worst result

References to ‘worst result’ refer to those furthest from the normal physiological range or laboratory normal range.

Results that were rejected by the clinical team (e.g. pulse oximetry on poorly perfused extremities, haemolysed blood samples, contaminated microbiology results) should not be reported.

The following measures should be considered as a single observation and entered together:

Blood gas results: Please report the measures from the blood gas with the lowest pH (most acidotic).

Blood pressure: Please report the systolic and diastolic blood pressure from the observation with the lowest mean arterial pressure (if mean arterial pressure has not been calculated, report the measurement with lowest systolic blood pressure).

Respiratory rate: If both abnormal low and high rate observed, record the abnormally high rate.

MODULE 1: PRESENTATION/ADMISSION CASE REPORT FORM

CLINICAL INCLUSION CRITERIA

Suspected or confirmed novel coronavirus (COVID-19) infection:

Select yes if patient has either clinically suspected or laboratory-confirmed SARS-CoV-2 /COVID-19 infection.

DEMOGRAPHICS

Enrolment date: Date of enrolment into the study or for in-patients is the date that COVID-19 was first assessed as suspected or confirmed by a clinician.

Ethnic group:

Please enter all that apply of the following choices which best describe the patient's ethnicity or major ethnic group at birth. Please exclude nationality as nations often include many different ethnic groups (For example, Singaporean is the nationality but the ethnic grouping within Singapore could be East Asian, South Asian etc.) Cross (X) all that apply. If 'Other' write the full name of the ethnic group of the patient. Please do not enter a letter or number corresponding to a local/national ethnicity coding system.

If the patient's ethnicity is not known, please place a cross (X) in the 'Unknown' box.

Post-partum: Defined as within six weeks of delivery.

If the baby is positive for COVID-19 please complete a separate form for the baby as well.

ONSET & ADMISSION

Onset date of first/earliest symptom: Please provide the date of patient reported onset of the first symptom that you clinically believe was related to this episode of COVID-19 infection.

Most recent presentation/admission date at this facility:

Where a patient was admitted via multiple hospital departments, count admission from the time they came to the first department during the visit that led to their admission (e.g. arrival at the Emergency Department). For patients with a clear alternative diagnosis leading to admission who subsequently acquired COVID-19 report the date of admission as the day they were admitted to the healthcare facility.

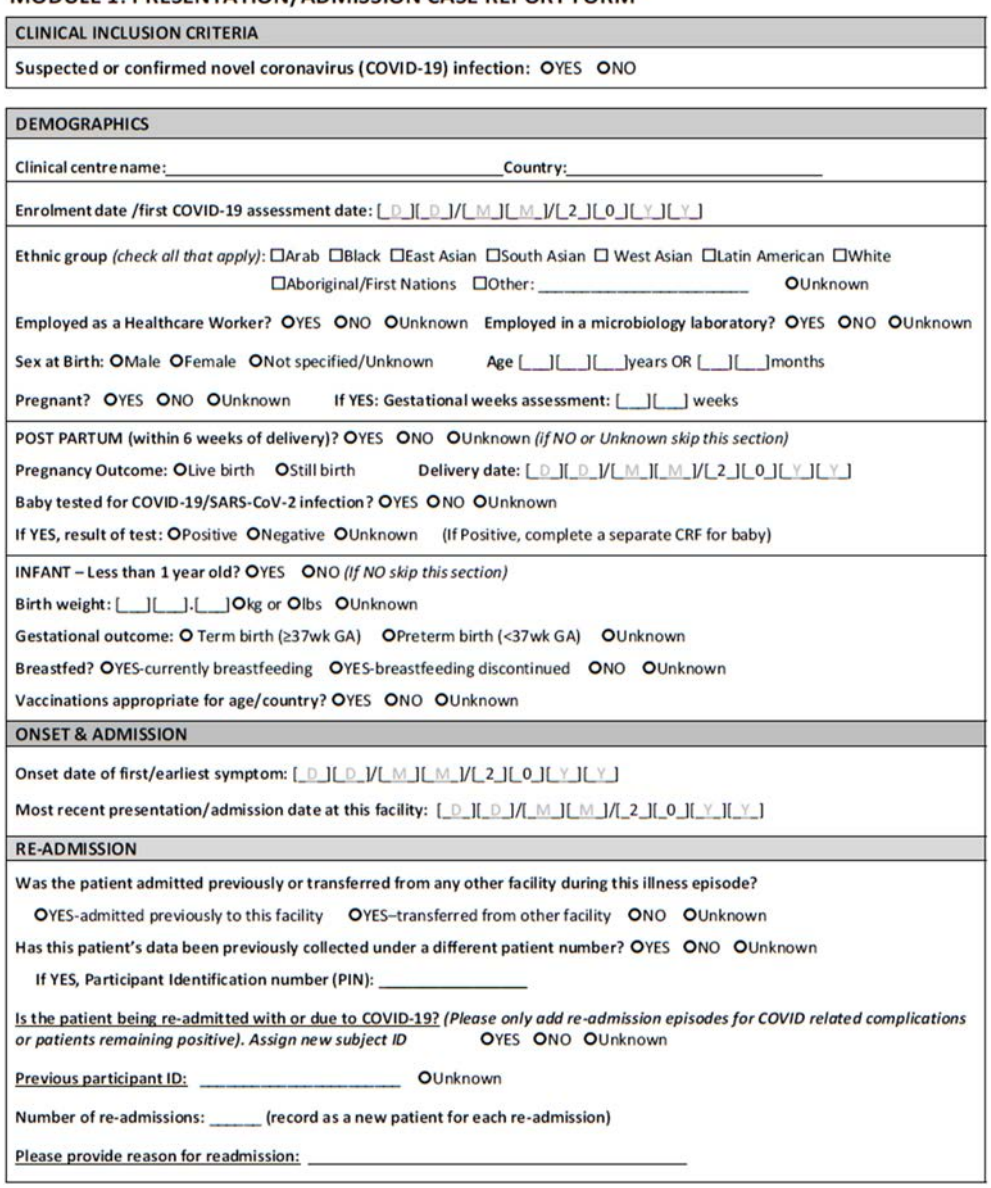
RE-ADMISSION

Was the patient admitted previously or transferred from any other facility during this illness episode?

For participants who return for re-admission to the same site, start a new form with the same Participant Identification Number. Please check "YES-admitted previously to this facility". Enter each re-admission as a separate entry in the electronic database.

For participants who transfer between two sites that are both collecting data on this form, it is preferred to have the data entered by a single site as a single admission, under the same Participant Identification Number. When this is not possible, the first site should record "Transfer to other facility" as an OUTCOME, and the second site should start a new form with a new patient number and indicate "YES-transferred from other facility" in RE- ADMISSION.

For participants who return for re-admission to the same site, **start a new form with a different Participant Identification Number**. Please check "YES-admitted previously to this facility" in the RE-ADMISSION section. Enter as a separate entry in the electronic database.



MODULE 1: PRESENTATION/ADMISSION CASE REPORT FORM

CLINICAL INCLUSION CRITERIA

Suspected or confirmed novel coronavirus (COVID-19) infection: OYES ONO

DEMOGRAPHICS

Clinical centre name:_____Country:_____

Enrolment date /first COVID-19 assessment date: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

Ethnic group *(check all that apply)*: ☐Arab ☐Black ☐East Asian ☐South Asian ☐ West Asian ☐Latin American ☐White ☐Aboriginal/First Nations ☐Other: _____ OUnknown

Employed as a Healthcare Worker? OYES ONO OUnknown Employed in a microbiology laboratory? OYES ONO OUnknown

Sex at Birth: OMale OFemale ONot specified/Unknown Age [___][___][___]years OR [___][___]months

Pregnant? OYES ONO OUnknown If YES: Gestational weeks assessment: [___][___] weeks

POST PARTUM (within 6 weeks of delivery)? OYES ONO OUnknown *(if NO or Unknown skip this section)*

Pregnancy Outcome: OLive birth OStill birth Delivery date: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

Baby tested for COVID-19/SARS-CoV-2 infection? OYES ONO OUnknown

If YES, result of test: OPositive ONegative OUnknown (If Positive, complete a separate CRF for baby)

INFANT – Less than 1 year old? OYES ONO *(If NO skip this section)*

Birth weight: [___][___].[___]Okg or Olbs OUnknown

Gestational outcome: O Term birth (≥37wk GA) OPreterm birth (<37wk GA) OUnknown

Breastfed? OYES-currently breastfeeding OYES-breastfeeding discontinued ONO OUnknown

Vaccinations appropriate for age/country? OYES ONO OUnknown

ONSET & ADMISSION

Onset date of first/earliest symptom: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

Most recent presentation/admission date at this facility: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

RE-ADMISSION

Was the patient admitted previously or transferred from any other facility during this illness episode?

OYES-admitted previously to this facility OYES–transferred from other facility ONO OUnknown

Has this patient's data been previously collected under a different patient number? OYES ONO OUnknown

If YES, Participant Identification number (PIN): _____

Is the patient being re-admitted with or due to COVID-19? *(Please only add re-admission episodes for COVID related complications or patients remaining positive). Assign new subject ID* OYES ONO OUnknown

Previous participant ID: _____ OUnknown

Number of re-admissions: _____ (record as a new patient for each re-admission)

Please provide reason for readmission: _____

SIGNS AND SYMPTOMS AT HOSPITAL ADMISSION

Please provide details of clinical observations made as close to presentation/admission, or within 24 hours of admission. For observations not made immediately at admission, please record the first available data (patient reported and/or from medical records) within 24 hours of admission. For patients with a clear alternative diagnosis leading to admission who subsequently acquired COVID-19, complete these observations for the 24 hours after onset of symptoms of suspected or confirmed COVID-19 infection.

Temperature

Please enter the peripheral body temperature (rectal if < 3 months) in the space provided and indicate the unit of measurement, either degrees Celsius (°C) or Fahrenheit (°F).

Heart rate (HR)

Enter the heart rate measured in beats per minute. This may be measured manually or by electronic monitoring.

Respiratory rate (RR)

Enter the respiratory rate in breaths per minute. Manual rather than electronic measurement is preferred where possible (this is achieved by counting the number of breaths for one minute, counting how many times the chest rises within this time period). Record the highest respiratory rate documented on admission.

Systolic BP

Please enter the systolic blood pressure measured in millimetres of mercury (mmHg), in the relevant sections. For example, if the blood pressure is 120/85 mmHg, enter 120 in the section marked 'systolic BP'. Use any recognised method for measuring blood pressure.

Diastolic BP

Please enter the diastolic blood pressure measured in millimetres of mercury (mmHg), in the relevant sections. For example, if the blood pressure is 120/85 mmHg, enter 85 in the section marked 'diastolic BP'. Use any recognised method for measuring blood pressure.

Oxygen saturation

For all patients, irrespective of ventilation or supplemental oxygen requirement, please enter the percentage oxygen saturation (the percentage of haemoglobin binding sites in the bloodstream occupied by oxygen) at the time of admission. This may be measured by pulse oximetry or by arterial blood gas analysis.

Sternal capillary refill time > 2 seconds?

Sternal capillary refill time is measured by pressing on the sternum for five seconds with a finger or thumb until the underlying skin turns white and then noting the time in seconds needed for the colour to return once the pressure is released.

MODULE 1: PRESENTATION/ADMISSION CASE REPORT FORM

SIGNS AND SYMPTOMS AT HOSPITAL ADMISSION *(first available data at presentation/admission – within 24 hours)*

Temperature: [____][____][____].[____]O°C *or* O°F

HR: [____][____][____]beats/minute RR: [____][____]breaths/minute

Systolic BP: [___][___][___]mmHg Diastolic BP: [____][____][____]mmHg

Oxygen saturation: [___][___][___]% On: O Room air O Oxygen therapy O Unknown

Sternal capillary refill time >2sec. O YES O NO O Unknown Height: [___][___][___]cm Weight: [___][___][___]kg

SIGNS AND SYMPTOMS ON ADMISSION *(Unk = Unknown)*

History of fever	O YES O NO O Unk	Fatigue / Malaise	O YES O NO O Unk
Cough O YES - non-productive O YES - productive O YES - with haemoptysis O NO O Unk		Anorexia	O YES O NO O Unk
		Altered consciousness/confusion	O YES O NO O Unk
Sore throat	O YES O NO O Unk	Muscle aches (myalgia)	O YES O NO O Unk
Runny nose (rhinorrhoea)	O YES O NO O Unk	Joint pain (arthralgia)	O YES O NO O Unk
Wheezing	O YES O NO O Unk	Inability to walk	O YES O NO O Unk
Shortness of breath	O YES O NO O Unk	Abdominal pain	O YES O NO O Unk
Lower chest wall indrawing	O YES O NO O Unk	Diarrhoea	O YES O NO O Unk
Chest pain	O YES O NO O Unk	Vomiting / Nausea	O YES O NO O Unk
Conjunctivitis	O YES O NO O Unk	Skin rash	O YES O NO O Unk
Lymphadenopathy	O YES O NO O Unk	Bleeding (Haemorrhage)	O YES O NO O Unk
Headache	O YES O NO O Unk	If YES, specify site(s):_____	
Loss of smell (Anosmia)	O YES O NO O Unk	Other symptom(s)	O YES O NO O Unk
Loss of taste (Ageusia)	O YES O NO O Unk	If YES, specify:_____	
Seizures	O YES O NO O Unk		

VACCINATIONS

Covid-19 vaccination O YES O NO O Unk Estimated date of most recent dose:[_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

If YES, number of doses received: _____

If YES, specify type of the most recent vaccine: _____

If more than one dose has been given, specify all types of vaccine previously received:

_____

Influenza vaccination within the last 6 months: O YES O NO O Unknown

PRE-ADMISSION MEDICATION *(taken within 14 days prior to admission/presentation at healthcare facility)*

Steroids	O YES O NO O Unk If YES, O Oral O Inhaled O Unk
Other immunosuppressant agents (not oral steroids)	O YES O NO O Unk
Antibiotics	O YES O NO O Unk If YES, agent(s):_____
Antivirals	O YES O NO O Unk If YES, agent(s):_____
Other targeted COVID-19 Medications	O YES O NO O Unk If YES, agent(s):_____

SIGNS AND SYMPTOMS ON ADMISSION

Please provide details of clinical observations made as close to presentation/admission, or within 24 hours of admission. For observations not made immediately at admission, please record the first available data (patient reported and/or from medical records) within 24 hours of admission. For patients with a clear alternative diagnosis leading to admission who subsequently acquired COVID-19, complete these observations for the 24 hours after onset of symptoms of suspected or confirmed COVID-19 infection.

VACCINATIONS

If the exact date of the most recent dose of COVID-19 vaccine isn't available, please provide an estimate of the day the vaccine was given. Partial dates (e.g. Jan-2021) cannot be entered in the database.

PRE-ADMISSION MEDICATION *(taken within 14 days of admission/presentation at healthcare facility)*

Steroids: Examples include prednisolone, betamethasone, dexamethasone, hydrocortisone, methylprednisolone, deflazacort and fludrocortisone (oral), budesonide, fluticasone (inhaled).

Other immunosuppressant agents (not oral steroids): Examples include tofacitinib, cyclosporine, tacrolimus, sirolimus, everolimus, azathioprine, leflunomide, mycophenolate and biologics such as abatacept, adalimumab, anakinra, certolizumab, etanercept, adalimumab, infliximab and rituximab

Antibiotics: 'Antibiotic' refers to any agent(s) that selectively target bacteria. Please list generic names. Topical preparations should not be recorded.

Antivirals: Examples include ribavirin, lopinavir, ritonavir, remdesivir, oseltamivir, zanamivir, acyclovir, ganciclovir, and interferons. Please list generic names. Topical preparations should not be recorded.

Other targeted COVID-19 Medications: Includes for example: chloroquine, hydroxychloroquine, Interferon antibodies, convalescent plasma or any other COVID-19 therapeutics not included in the categories listed above. Please list generic names.

General Note: For free text entry of medications, please ensure correct spelling. For reference you may use: www.drugs.com

MODULE 1: PRESENTATION/ADMISSION CASE REPORT FORM

SIGNS AND SYMPTOMS AT HOSPITAL ADMISSION *(first available data at presentation/admission – within 24 hours)*

Temperature: [____][____][____].[____]O°C *or* O°F

HR: [____][____][____]beats/minute RR: [____][____]breaths/minute

Systolic BP: [___][___][___]mmHg Diastolic BP: [____][____][____]mmHg

Oxygen saturation: [___][___][___]% On: O Room air O Oxygen therapy O Unknown

Sternal capillary refill time >2sec. O YES O NO O Unknown Height: [___][___][___]cm Weight: [___][___][___]kg

SIGNS AND SYMPTOMS ON ADMISSION *(Unk = Unknown)*

History of fever	O YES O NO O Unk	Fatigue / Malaise	O YES O NO O Unk
Cough O YES - non-productive O YES - productive O YES - with haemoptysis O NO O Unk		Anorexia	O YES O NO O Unk
		Altered consciousness/confusion	O YES O NO O Unk
Sore throat	O YES O NO O Unk	Muscle aches (myalgia)	O YES O NO O Unk
Runny nose (rhinorrhoea)	O YES O NO O Unk	Joint pain (arthralgia)	O YES O NO O Unk
Wheezing	O YES O NO O Unk	Inability to walk	O YES O NO O Unk
Shortness of breath	O YES O NO O Unk	Abdominal pain	O YES O NO O Unk
Lower chest wall indrawing	O YES O NO O Unk	Diarrhoea	O YES O NO O Unk
Chest pain	O YES O NO O Unk	Vomiting / Nausea	O YES O NO O Unk
Conjunctivitis	O YES O NO O Unk	Skin rash	O YES O NO O Unk
Lymphadenopathy	O YES O NO O Unk	Bleeding (Haemorrhage)	O YES O NO O Unk
Headache	O YES O NO O Unk	If YES, specify site(s):_____	
Loss of smell (Anosmia)	O YES O NO O Unk	Other symptom(s)	O YES O NO O Unk
Loss of taste (Ageusia)	O YES O NO O Unk	If YES, specify:_____	
Seizures	O YES O NO O Unk		

VACCINATIONS

Covid-19 vaccination O YES O NO O Unk Estimated date of most recent dose:[_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

If YES, number of doses received: _____

If YES, specify type of the most recent vaccine: _____

If more than one dose has been given, specify all types of vaccine previously received:

_____

Influenza vaccination within the last 6 months: O YES O NO O Unknown

PRE-ADMISSION MEDICATION *(taken within 14 days prior to admission/presentation at healthcare facility)*

Steroids	O YES O NO O Unk If YES, O Oral O Inhaled O Unk
Other immunosuppressant agents (not oral steroids)	O YES O NO O Unk
Antibiotics	O YES O NO O Unk If YES, agent(s):_____
Antivirals	O YES O NO O Unk If YES, agent(s):_____
Other targeted COVID-19 Medications	O YES O NO O Unk If YES, agent(s):_____

CO-MORBIDITIES AND RISK FACTORS

Please record if any of these comorbidities existed prior to admission.

In general, do not include past comorbidities that are no longer ongoing. Additional details are given below. Where example conditions are given, these are not intended to be exhaustive and other conditions of equivalent severity should be included.

Chronic cardiac disease (not hypertension)

Please include any of coronary artery disease, heart failure, congenital heart disease, cardiomyopathy, rheumatic heart disease.

Hypertension

Elevated arterial blood pressure diagnosed clinically, >140mmHg systolic or >90mmHg diastolic.

Chronic pulmonary disease (not asthma)

Please include any of chronic obstructive pulmonary disease (chronic bronchitis, chronic obstructive pulmonary disease (COPD), emphysema), cystic fibrosis, bronchiectasis, interstitial lung disease, pre-existing requirement for long term oxygen therapy. Do not include asthma.

Asthma (physician diagnosed)

Clinician-diagnosed asthma

Chronic Kidney Disease

Please include any of clinician-diagnosed chronic kidney disease, chronic estimated glomerular filtration rate < 60 mL/min/1.73m^2, history of kidney transplantation

Obesity (as defined by clinical staff)

This refers to patients for whom an attending clinician has assessed them to be obese - ideally but not necessarily with an objective measurement of obesity, such as calculation of the body mass index (BMI of 30 or more) or measurement of abdominal girth.

Moderate or severe liver disease

This is defined as cirrhosis with portal hypertension, with or without bleeding or a history of variceal bleeding.

Mild liver disease

This is defined as cirrhosis without portal hypertension or chronic hepatitis

Asplenia

Please include any of splenectomy, non-functional spleen, and congenital asplenia**.**

Chronic neurological disorder

Please include any of cerebral palsy, multiple sclerosis, motor neurone disease, muscular dystrophy, myasthenia gravis, Parkinson's disease, stroke, severe learning difficulty

Malignant neoplasm

Current solid organ or haematological malignancy. Please do not include malignancies that have been declared 'cured' ≥5 years ago with no evidence of ongoing disease. Do not include non-melanoma skin cancers. Do not include benign growths or dysplasia.

MODULE 1: PRESENTATION/ADMISSION CASE REPORT FORM

CO-MORBIDITIES AND RISK FACTORS *(existing prior to admission and ongoing)*			
Chronic cardiac disease *(not hypertension)*	O YES O NO O Unk	Chronic hematologic disease	O YES O NO O Unk
Hypertension	O YES O NO O Unk	AIDS / HIV O YES-on ART O YES-not on ART O NO O Unk If YES, most recent CD4 count: O < 200 O 200-< 500 O ≥ 500 cells/uL O Unk	
Chronic pulmonary disease *(not asthma)*	O YES O NO O Unk	Diabetes Mellitus O YES-Type 1 O YES -Type 2 O YES -Gestational O NO O Unk If YES, HbA1C results (within last 6 months) :_____ Units: O mmol/mol O mmol/L O %	
Asthma *(physician diagnosed)*	O YES O NO O Unk	Rheumatologic disorder	O YES O NO O Unk
Chronic kidney disease	O YES O NO O Unk	Dementia	O YES O NO O Unk
Obesity *(as defined by clinical staff)*	O YES O NO O Unk	Tuberculosis	O YES O NO O Unk
Moderate or severe liver disease	O YES O NO O Unk	Malnutrition	O YES O NO O Unk
Mild liver disease	O YES O NO O Unk	Smoking O YES O Never smoked O Former smoker O Unk	
Asplenia	O YES O NO O Unk	Other relevant risk factor(s) O YES O NO O Unk	
Chronic neurological disorder	O YES O NO O Unk	If YES, specify:	
Malignant neoplasm	O YES O NO O Unk		

MODULE 2: CASE REPORT FORM ON ADMISSION, CRITICAL CARE, RESEARCH SAMPLING

Complete on the day of admission or first COVID-19 investigation, and on the first day of ICU admission (if different from day of admission). In addition, complete for days when biochemical results are available.

SIGNS AND SYMPTOMS ***(Record the worst value between 00:00 to 24:00 on day of assessment)(worst=furthest from normal range)***

DATE OF ASSESSMENT *(DD/MM/YYYY)*: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

Highest temperature: [___][___][___].[___] O °C *or* O °F **HR:** [___][___][___]beats/minute **RR:** [___][___][___]breaths/minute

Systolic BP: [___][___][___]mmHg **Diastolic BP:** [___][___][___]mmHg

Oxygen saturation SaO_2 [___][___][___]%

Any supplemental oxygen: O YES O NO O Unknown If yes,

FiO_2 *(0.21-1.0)* [___].[___][___] or [___][___] % or [___][___]L/min (Highest L/min)

PaO_2 *(at time nearest to the FiO_2 recorded at top of page)* [___][___][___] O kPa *or* O mmHg O Not done

PaO_2 sample type: O Arterial O Capillary O Venous O Unknown

From same blood gas record as PaO_2:

PCO_2 _____ O kPa *or* O mmHg | **pH** _____ | **HCO_3-** _____ mEq/L | **Base excess** _____ mmol/L

Sternal capillary refill time >2seconds O YES O NO O Unknown

AVPU: Alert [___] Verbal[___] Pain [___] Unresponsive [___] **Glasgow Coma Score (GCS / 15)** [___][___]

Richmond Agitation-Sedation Scale (RASS) [___]

Mean Arterial Blood Pressure [___][___][___]mmHg O Unknown

Urine flow rate [___][___][___][___][___]mL/24 hours O Check if estimated O Unknown

CO-MORBIDITIES, continued

Chronic hematologic disease

Any long-term disorder of the red or white blood cells, platelets or coagulation system requiring regular or intermittent treatment. Do not include leukaemia, lymphoma or myeloma, which should be entered under malignancy. Do not include iron-deficiency anaemia which is explained by diet or chronic blood loss.

AIDS/HIV

History of laboratory-confirmed HIV infection. Indicate whether or not the patient is on ART (antiretroviral therapy). Please provide the most recent CD4 count, if available.

Diabetes Mellitus

Type 1 or Type 2 diabetes mellitus requiring oral or subcutaneous treatment. Please indicate whether Type 1 or Type 2..If HbA1c results are available from the last 6 months only, please provide the most recent value.

Rheumatologic disorder

This is defined as an inflammatory and degenerative diseases of connective tissue structures. It includes chronic arthropathies and arthritis, connective tissue disorders and vasculitides.

Dementia

This is defined as clinical diagnosis of dementia

Tuberculosis

Patients currently receiving treatment for tuberculosis. Do not include latent tuberculosis.

Malnutrition

Any clinically identified deficiency in intake, either of total energy or of specific nutrients that led to a dietetic intervention or referral prior to the onset of COVID-19 symptoms. Do not include people who needed supplementary nutrition solely due to reduced intake during their current illness episode.

Smoking

Smoking at least one cigarette, cigar, pipe or equivalent per day before the onset of the current illness. Do not include smoke-free tobacco products such as chewed tobacco or electronic nicotine delivery devices.

Other relevant risk factor List any significant risk factors or comorbidities that existed prior to admission, are ongoing, that are not already listed.

MODULE 1: PRESENTATION/ADMISSION CASE REPORT FORM

CO-MORBIDITIES AND RISK FACTORS *(existing prior to admission and ongoing)*			
Chronic cardiac disease *(not hypertension)*	O YES O NO O Unk	Chronic hematologic disease	O YES O NO O Unk
Hypertension	O YES O NO O Unk	AIDS / HIV O YES-on ART O YES-not on ART O NO O Unk If YES, most recent CD4 count: O < 200 O 200-< 500 O ≥ 500 cells/uL O Unk	
Chronic pulmonary disease *(not asthma)*	O YES O NO O Unk	Diabetes Mellitus O YES-Type 1 O YES -Type 2 O YES -Gestational O NO O Unk If YES, HbA1C results (within last 6 months) :_____ Units: O mmol/mol O mmol/L O %	
Asthma *(physician diagnosed)*	O YES O NO O Unk	Rheumatologic disorder	O YES O NO O Unk
Chronic kidney disease	O YES O NO O Unk	Dementia	O YES O NO O Unk
Obesity *(as defined by clinical staff)*	O YES O NO O Unk	Tuberculosis	O YES O NO O Unk
Moderate or severe liver disease	O YES O NO O Unk	Malnutrition	O YES O NO O Unk
Mild liver disease	O YES O NO O Unk	Smoking O YES O Never smoked O Former smoker O Unk	
Asplenia	O YES O NO O Unk	Other relevant risk factor(s) O YES O NO O Unk	
Chronic neurological disorder	O YES O NO O Unk	If YES, specify:	
Malignant neoplasm	O YES O NO O Unk		

MODULE 2: CASE REPORT FORM ON ADMISSION, CRITICAL CARE, RESEARCH SAMPLING

Complete on the day of admission or first COVID-19 investigation, and on the first day of ICU admission (if different from day of admission). In addition, complete for days when biochemical results are available.

SIGNS AND SYMPTOMS ***(Record the worst value between 00:00 to 24:00 on day of assessment)(worst=furthest from normal range)***

DATE OF ASSESSMENT *(DD/MM/YYYY)*: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

Highest temperature: [___][___].[___] O °C *or* O °F **HR:** [___][___][___]beats/minute **RR:** [___][___][___]breaths/minute

Systolic BP: [___][___][___]mmHg **Diastolic BP:** [___][___][___]mmHg

Oxygen saturation SaO_2 [___][___][___]%

Any supplemental oxygen: O YES O NO O Unknown If yes,

FiO_2 *(0.21-1.0)* [___].[___][___] or [___][___] % or [___][___]L/min (Highest L/min)

PaO_2 *(at time nearest to the FiO_2 recorded at top of page)* [___][___][___]O kPa *or* O mmHg O Not done

PaO_2 sample type: O Arterial O Capillary O Venous O Unknown

From same blood gas record as PaO_2:

PCO_2 _____ O kPa *or* O mmHg | **pH** _____ | **HCO_3-** _____ mEq/L | **Base excess** _____ mmol/L

Sternal capillary refill time >2seconds O YES O NO O Unknown

AVPU: Alert [___] Verbal[___] Pain [___] Unresponsive [___] **Glasgow Coma Score (GCS / 15)** [___][___]

Richmond Agitation-Sedation Scale (RASS) [___]

Mean Arterial Blood Pressure [___][___][___]mmHg O Unknown

Urine flow rate [___][___][___][___][___]mL/24 hours O Check if estimated O Unknown

MODULE 2 CASE REPORT FORM ON ADMISSION, CRITICAL CARE, RESEARCH SAMPLING

SIGNS AND SYMPTOMS

Highest Temperature

Please enter the highest peripheral body temperature (rectal if < 3 months) recorded during the course of the day in the space provided and indicate the unit of measurement, either degrees Celsius (°C) or Fahrenheit (°F).

Heart rate (HR)

Enter the heart rate measured in beats per minute. This may be measured manually or by electronic monitoring.

Respiratory rate (RR)

Enter the respiratory rate in breaths per minute. Manual rather than electronic measurement is preferred where possible (this is achieved by counting the number of breaths for one minute, counting how many times the chest rises within this time period). If both abnormal low and high rate observed, record the abnormally high rate.

Systolic BP

Please report the systolic and diastolic blood pressure from the observation with the lowest mean arterial pressure (if mean arterial pressure has not been calculated, report the measurement with lowest systolic blood pressure).

Please enter the systolic blood pressure measured in millimetres of mercury (mmHg), in the relevant sections. For example, if the blood pressure is 120/85 mmHg, enter 120 in the section marked 'systolic BP'. Use any recognised method for measuring blood pressure.

Diastolic BP

Please enter the diastolic blood pressure measured in millimetres of mercury (mmHg), in the relevant sections. For example, if the blood pressure is 120/85 mmHg, enter 85 in the section marked 'diastolic BP'. Use any recognised method for measuring blood pressure.

Oxygen saturation SaO_2

For all patients, irrespective of ventilation or supplemental oxygen requirement, please enter the percentage oxygen saturation. This may be measured by pulse oximetry or by arterial blood gas analysis.

Any supplemental oxygen: FiO_2 (0.21-1.0)

This is a key indicator to complete for all patients. If the patient received any form of supplemental oxygen through a mask or nasal cannula that delivers a known concentration of oxygen or is being ventilated, please provide the fraction of inspired oxygen (FiO_2) delivered. For patients receiving oxygen through any means, such as a face mask or nasal cannula, that does not deliver a known oxygen concentration provide the maximum flow rate received on day of completion in L/min.

MODULE 1: PRESENTATION/ADMISSION CASE REPORT FORM

CO-MORBIDITIES AND RISK FACTORS *(existing prior to admission and ongoing)*			
Chronic cardiac disease *(not hypertension)*	OYES ONO OUnk	Chronic hematologic disease	OYES ONO OUnk
Hypertension	OYES ONO OUnk	AIDS / HIV OYES-on ART OYES-not on ART ONO OUnk If YES, most recent CD4 count: O< 200 O200-< 500 O≥ 500 cells/uL OUnk	
Chronic pulmonary disease *(not asthma)*	OYES ONO OUnk	Diabetes Mellitus OYES-Type 1 OYES -Type 2 OYES -Gestational ONO OUnk If YES, HbA1C results (within last 6 months) :_____ Units: Ommol/mol Ommol/L O%	
Asthma *(physician diagnosed)*	OYES ONO OUnk	Rheumatologic disorder	OYES ONO OUnk
Chronic kidney disease	OYES ONO OUnk	Dementia	OYES ONO OUnk
Obesity *(as defined by clinical staff)*	OYES ONO OUnk	Tuberculosis	OYES ONO OUnk
Moderate or severe liver disease	OYES ONO OUnk	Malnutrition	OYES ONO OUnk
Mild liver disease	OYES ONO OUnk	Smoking OYES ONever smoked OFormer smoker OUnk	
Asplenia	OYES ONO OUnk	Other relevant risk factor(s) OYES ONO OUnk	
Chronic neurological disorder	OYES ONO OUnk	If YES, specify:	
Malignant neoplasm	OYES ONO OUnk		

MODULE 2: CASE REPORT FORM ON ADMISSION, CRITICAL CARE, RESEARCH SAMPLING

Complete on the day of admission or first COVID-19 investigation, and on the first day of ICU admission (if different from day of admission). In addition, complete for days when biochemical results are available.

SIGNS AND SYMPTOMS *(Record the worst value between 00:00 to 24:00 on day of assessment)(worst=furthest from normal range)*

DATE OF ASSESSMENT *(DD/MM/YYYY)*: [_D_][_D_]/[_M_][_M_]/[__2_][__0_][_Y_][_Y_]

Highest temperature: [___][___][___].[___] O°C *or* O°F HR: [___][___][___]beats/minute RR: [___][___][___]breaths/minute

Systolic BP: [___][___][___]mmHg Diastolic BP: [___][___][___]mmHg

Oxygen saturation SaO_2 [___][___][___]%

Any supplemental oxygen: OYES ONO OUnknown If yes,

FiO_2 *(0.21-1.0)* [___].[___][___] or [___][___] % or [___][___]L/min (Highest L/min)

PaO_2 *(at time nearest to the FiO_2 recorded at top of page)* [___][___][___]OkPa *or* OmmHg ONot done

PaO_2 sample type: OArterial OCapillary OVenous OUnknown

From same blood gas record as PaO_2:

PCO_2 _____OkPa *or* OmmHg | pH _____ | HCO_3- _____mEq/L | Base excess _____ mmol/L

Sternal capillary refill time >2seconds OYES ONO OUnknown

AVPU: Alert [___] Verbal[___] Pain [___] Unresponsive [___] Glasgow Coma Score (GCS / 15) [___][___]

Richmond Agitation-Sedation Scale (RASS) [___]

Mean Arterial Blood Pressure [___][___][___]mmHg OUnknown

Urine flow rate [___][___][___][___][___]mL/24 hours O Check if estimated OUnknown

SIGNS AND SYMPTOMS, continued

PaO_2 (*at time nearest to the FiO_2 recorded at top of page)*

PaO_2 (partial pressure of oxygen in blood) as determined by arterial/ capillary blood gas analysis. This PaO_2 must correspond with the oxygen therapy documented in the FiO_2 field. Please fill in the lowest value in either mmHg or kPa depending on the output of your blood gas analyser. If the PaO_2 is not known, place NA in the data field.

From the same blood gas record as PaO_2:

$PaCO_2$ is the partial pressure of carbon dioxide measured in the sample. pH is the measure of the activity of the (solvated) hydrogen ion (H+) measured in the sample. HCO_3- refers to the bicarbonate measured in the blood gas sample. Base excess refers to standardised base excess (SBE). If standardised base excess is not reported, enter the base excess value presented, this can be either a positive or negative value.

Sternal capillary refill time > 2 seconds?

Sternal capillary refill time is measured by pressing on the sternum for five seconds with a finger or thumb until the underlying skin turns white and then noting the time in seconds needed for the colour to return once the pressure is released.

AVPU

Alert – responding to voice – responding to pain – unresponsive: please state the least responsive condition of the patient during the calendar day (not counting normal sleep). On day of admission record the value as close to admission as possible before treatments have been administered. For daily records, if the patient is being sedated on the day of assessment record the value before the sedation.

Glasgow Coma Score (GCS / 15)

Please state the lowest GCS recorded. For intubated patients and patients with a non-fenestrated tracheostomy, give 1 point for the voice component and calculate the total as usual. Suffixes such as t for tracheostomy cannot be entered on to the database. If the patient is sedated on the day of assessment these parameters should correspond to the values observed before sedation. For daily recording, if the patient is fully sedated for the duration of the day of assessment (from 00:00 to 24:00) record non testable. Glasgow Coma Score: https://www.glasgowcomascale.org/downloads/GCS-Assessment-Aid-English.pdf?v=3

Richmond Agitation-Sedation Scale (RASS)

RASS – If done, enter the lowest calculated value (between -5 and 4) on the date of assessment.

MODULE 1: PRESENTATION/ADMISSION CASE REPORT FORM

CO-MORBIDITIES AND RISK FACTORS *(existing prior to admission and ongoing)*			
Chronic cardiac disease *(not hypertension)*	O YES O NO O Unk	Chronic hematologic disease	O YES O NO O Unk
Hypertension	O YES O NO O Unk	AIDS / HIV O YES-on ART O YES-not on ART O NO O Unk If YES, most recent CD4 count: O < 200 O 200-< 500 O ≥ 500 cells/uL O Unk	
Chronic pulmonary disease *(not asthma)*	O YES O NO O Unk	Diabetes Mellitus O YES-Type 1 O YES -Type 2 O YES -Gestational O NO O Unk If YES, HbA1C results (within last 6 months) :_____ Units: O mmol/mol O mmol/L O %	
Asthma *(physician diagnosed)*	O YES O NO O Unk	Rheumatologic disorder	O YES O NO O Unk
Chronic kidney disease	O YES O NO O Unk	Dementia	O YES O NO O Unk
Obesity *(as defined by clinical staff)*	O YES O NO O Unk	Tuberculosis	O YES O NO O Unk
Moderate or severe liver disease	O YES O NO O Unk	Malnutrition	O YES O NO O Unk
Mild liver disease	O YES O NO O Unk	Smoking O YES O Never smoked O Former smoker O Unk	
Asplenia	O YES O NO O Unk	Other relevant risk factor(s) O YES O NO O Unk	
Chronic neurological disorder	O YES O NO O Unk	If YES, specify:	
Malignant neoplasm	O YES O NO O Unk		

MODULE 2: CASE REPORT FORM ON ADMISSION, CRITICAL CARE, RESEARCH SAMPLING

Complete on the day of admission or first COVID-19 investigation, and on the first day of ICU admission (if different from day of admission). In addition, complete for days when biochemical results are available.

SIGNS AND SYMPTOMS ***(Record the worst value between 00:00 to 24:00 on day of assessment)(worst=furthest from normal range)***

DATE OF ASSESSMENT *(DD/MM/YYYY)*: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

Highest temperature: [___][___].[___] O °C *or* O °F **HR:** [___][___][___]beats/minute **RR:** [___][___][___]breaths/minute

Systolic BP: [___][___][___]mmHg **Diastolic BP:** [___][___][___]mmHg

Oxygen saturation SaO_2 [___][___][___]%

Any supplemental oxygen: O YES O NO O Unknown If yes,

FiO_2 ***(0.21-1.0)*** [___].[___][___] or [___][___] % or [___][___]L/min (Highest L/min)

PaO_2 *(at time nearest to the FiO_2 recorded at top of page)* [___][___][___] O kPa *or* O mmHg O Not done

PaO_2 sample type: O Arterial O Capillary O Venous O Unknown

From same blood gas record as PaO_2:

PCO_2 _____ O kPa *or* O mmHg | **pH** _____ | **HCO_3-** _____ mEq/L | **Base excess** _____ mmol/L

Sternal capillary refill time >2seconds O YES O NO O Unknown

AVPU: Alert [___] Verbal[___] Pain [___] Unresponsive [___] **Glasgow Coma Score (GCS / 15)** [___][___]

Richmond Agitation-Sedation Scale (RASS) [___]

Mean Arterial Blood Pressure [___][___][___]mmHg O Unknown

Urine flow rate [___][___][___][___][___]mL/24 hours O Check if estimated O Unknown

Current admission to ICU/ITU/IMC/HDU?

If the patient has been admitted to an intensive care, intensive therapy, intermediate care or high dependency unit please tick 'yes'. If the patient is on a general care ward then select 'no' or 'Unknown'.

See Outcome Case Report Form (below) for guidelines on recording treatment data

LABORATORY RESULTS

Please record all laboratory results available on day of admission, or the day that COVID-19 was first clinically suspected in patients already admitted to hospital, and on day of admission to ICU/HDU.
For daily records: record the date of assessment as the day the blood sample/s were taken.. If the unit of measurement is not shown on the paper form it will likely appear in the dropdown list in the eCRF. If you cannot find the correct unit on the eCRF please use a unit converter, such as: http://unitslab.com/ or equivalent or email ncov@isaric.org to let us know.
'Worst value' refers to values furthest from the normal physiological range or laboratory normal range. Results that were rejected by the clinical team (e.g. haemolysed blood samples, contaminated microbiology results) should not be reported.

Haemoglobin (Hb or Hgb) refers to haemoglobin concentration measurement in blood.

WBC count is the total white blood cell count in blood.

Haematocrit (Ht or HCT), also known as packed cell volume (PCV) or erythrocyte volume fraction (EVF), is the volume percentage (%) of red blood cells in blood.

APTT is the activated partial thromboplastin time. Record the highest value.

APTR is the activated partial thromboplastin ratio. Record the highest value.

PT is the prothrombin time. Record the highest value.

INR is the international normalised ratio. Record the highest value.

ALT/SGPT: ALT is alanine transaminase (also called serum glutamic pyruvate transaminase, SGPT). Record the highest value.

Total Bilirubin refers to total bilirubin measured in the blood. Record the highest value.

AST/SGOT is aspartate transaminase (also called serum glutamic oxaloacetic transaminase, SGOT). Record the highest value.

Glucose refers to blood glucose test. Random glucose measurement is preferred to a fasted measurement.

Blood urea nitrogen is also known as 'urea', measured in a blood sample. Record the highest value.

Lactate refers to blood lactate. Record the highest value.

Creatinine refers to serum creatinine. Record the highest value.

Procalcitonin or PCT refers to blood procalcitonin. Record the highest value.

CRP is C-reactive protein and refers to the blood (serum or plasma) CRP level. Record the highest value.

MODULE 2: CASE REPORT FORM ON ADMISSION, CRITICAL CARE, RESEARCH SAMPLING

Complete on the day of admission or first COVID-19 investigation, and on the first day of ICU admission (if different from day of admission). In addition, depending on available resources, complete every day for a maximum of 14 days, or for days when biochemical results are available.

Is the patient currently receiving, or has received *(between 00:00 to 24:00 on day of assessment)*

Current admission to ICU/ITU/IMC/HDU? OYES ONO OUnknown

High-flow nasal cannula oxygen therapy? OYES ONO OUnknown

Non-invasive ventilation *(Any)*? OYES ONO OUnknown If YES: OBIPAP OCPAP OOther OUnknown

Invasive ventilation? OYES ONO OUnknown

Prone positioning? OYES ONO OUnknown If yes, Oduring invasive ventilation Owhilst self-ventilating OUnknown

Inhaled Nitric Oxide? OYES ONO OUnknown

Tracheostomy inserted? OYES ONO OUnknown

Extra corporeal life support (ECLS/ ECMO)? OYES ONO OUnknown If YES: OVV OAV OCentral OUnknown

Renal replacement therapy (RRT) or dialysis? OYES ONO OUnknown

Any vasopressor/inotropic support? OYES ONO OUnknown *(if NO, select NO for the next 3 questions)*

Dopamine <5µg/kg/min OR Dobutamine OR milrinone OR levosimendan: OYES ONO

Dopamine 5-15µg/kg/min OR Epinephrine/Norepinephrine < 0.1µg/kg/min OR vasopressin OR phenylephrine: OYES ONO

Dopamine >15µg/k/min OR Epinephrine/Norepinephrine > 0.1µg/kg/min: OYES ONO

Neuromuscular blocking agents? OYES ONO OUnknown

Other intervention(s) or procedure(s)? OYES ONO OUnknown If YES, Specify: _____

LABORATORY RESULTS (on admission, on any admission to ICU, then daily) – complete every line

DATE OF ASSESSMENT *(DD/MM/YYYY)*: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

LABORATORY RESULTS (**record units if different from those listed)*
Record the worst value between 00:00 to 24:00 on day of assessment (if Not Available write 'N/A')

Parameter	Value*	Not done	Parameter	Value*	Not done
Haemoglobin (g/L)		O	Urea (BUN) (mmol/L)		O
WBC count (x10^9/L)		O	Lactate (mmol/L)		O
Lymphocyte count (10^9/L)		O	Creatinine (µmol/L)		O
Neutrophil count (10^9/L)		O	Sodium (mmol/L)		O
Haematocrit (%)		O	Potassium (mmol/L)		O
Platelets (x10^9/L)		O	Procalcitonin (ng/mL)		O
APTT (seconds))		O	CRP (mg/L)		O
APTR		O	LDH (U/L)		O
PT (seconds)		O	Creatine kinase (U/L)		O
INR		O	Troponin I (ng/mL)		O
ALT/SGPT (U/L)		O	D-dimer (mg/L)		O
Total bilirubin (µmol/L)		O	Ferritin (ng/mL)		O
AST/SGOT (U/L)		O	IL-6 (pg/mL)		O
Glucose (mmol/L)		O	Fibrinogen (mg/dl)		O

LDH is lactate dehydrogenase. Record the highest value.

Creatine kinase (CK, or creatine phosphokinase, CPK) refers to total creatine kinase measured in the blood. Record the highest value.

Troponin I Record the highest value

D-dimer Record the highest value

Ferritin Record the highest value

IL-6 is Interleukin 6. Record the highest value

MODULE 2: CASE REPORT FORM ON ADMISSION, CRITICAL CARE, RESEARCH SAMPLING

Complete on the day of admission or first COVID-19 investigation, and on the first day of ICU admission (if different from day of admission). In addition, depending on available resources, complete every day for a maximum of 14 days, or for days when biochemical results are available.

Is the patient currently receiving, or has received *(between 00:00 to 24:00 on day of assessment)*

Current admission to ICU/ITU/IMC/HDU? OYES ONO OUnknown

High-flow nasal cannula oxygen therapy? OYES ONO OUnknown

Non-invasive ventilation *(Any)*? OYES ONO OUnknown If YES: OBIPAP OCPAP OOther OUnknown

Invasive ventilation? OYES ONO OUnknown

Prone positioning? OYES ONO OUnknown If yes, Oduring invasive ventilation Owhilst self-ventilating OUnknown

Inhaled Nitric Oxide? OYES ONO OUnknown

Tracheostomy inserted? OYES ONO OUnknown

Extra corporeal life support (ECLS/ ECMO)? OYES ONO OUnknown If YES: OVV OAV OCentral OUnknown

Renal replacement therapy (RRT) or dialysis? OYES ONO OUnknown

Any vasopressor/inotropic support? OYES ONO OUnknown *(if NO, select NO for the next 3 questions)*

Dopamine <5µg/kg/min OR Dobutamine OR milrinone OR levosimendan: OYES ONO

Dopamine 5-15µg/kg/min OR Epinephrine/Norepinephrine < 0.1µg/kg/min OR vasopressin OR phenylephrine: OYES ONO

Dopamine >15µg/k/min OR Epinephrine/Norepinephrine > 0.1µg/kg/min: OYES ONO

Neuromuscular blocking agents? OYES ONO OUnknown

Other intervention(s) or procedure(s)? OYES ONO OUnknown If YES, Specify: _____

_____

LABORATORY RESULTS (on admission, on any admission to ICU, then daily) – complete every line

DATE OF ASSESSMENT *(DD/MM/YYYY)*: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

LABORATORY RESULTS (**record units if different from those listed)*
Record the worst value between 00:00 to 24:00 on day of assessment (if Not Available write 'N/A')

Parameter	Value*	Not done	Parameter	Value*	Not done
Haemoglobin (g/L)		O	Urea (BUN) (mmol/L)		O
WBC count (x10^9/L)		O	Lactate (mmol/L)		O
Lymphocyte count (10^9/L)		O	Creatinine (µmol/L)		O
Neutrophil count (10^9/L)		O	Sodium (mmol/L)		O
Haematocrit (%)		O	Potassium (mmol/L)		O
Platelets (x10^9/L)		O	Procalcitonin (ng/mL)		O
APTT (seconds))		O	CRP (mg/L)		O
APTR		O	LDH (U/L)		O
PT (seconds)		O	Creatine kinase (U/L)		O
INR		O	Troponin I (ng/mL)		O
ALT/SGPT (U/L)		O	D-dimer (mg/L)		O
Total bilirubin (µmol/L)		O	Ferritin (ng/mL)		O
AST/SGOT (U/L)		O	IL-6 (pg/mL)		O
Glucose (mmol/L)		O	Fibrinogen (mg/dl)		O

MODULE 3: OUTCOME CASE REPORT FORM

TREATMENT

For all questions of duration, please count the number of calendar days that the patient received the treatment. For treatments that were stopped and restarted, count those days on which the treatment was given but don't count any calendar days on which it was not given at all.

Oxygen therapy

Complete this field for all patients. If the patient received any form of supplementary oxygen, via nose cannula, mask or non-invasive or invasive ventilation tick 'yes' and indicate the total days they received any form of oxygen (O_2) therapy.

If any supplemental oxygen (at any concentration) was given by any means of delivery **at any point** during the patient's hospital stay, place a cross in the box marked 'yes'. This includes any supplementary oxygen (O_2) delivered via non-invasive facemasks/nasal cannula/mask or via invasive mechanical ventilation. Please also indicate the maximum O_2 flow volume. If it is not possible to access record of the absolute highest O_2 volume delivered during the admission indicate the highest known.

Non-invasive ventilation (Any)

If the patient received non-invasive ventilation (NIV), defined as the provision of ventilatory support through the patient's upper airway using a mask or similar device, at any time during their hospital stay, place tick 'yes' and enter the total duration in days if known.

Invasive ventilation (Any)

Invasive ventilation means that patient has undergone tracheal intubation, for the purpose of invasive mechanical ventilation. Invasive ventilation is a method to mechanically assist or replace spontaneous breathing in patients by use of a powered device that forces oxygenated air into the lungs. The mode of intubation may be orotracheal, nasotracheal, or via a cricothyrotomy or tracheotomy.

Prone Positioning

Prone ventilation refers to ventilation with the patient lying in the prone position. If the patient received prone ventilation at any time during their hospital stay, please tick 'yes' and indicate the total duration in days.

Renal replacement therapy (RRT) or dialysis

Renal replacement therapy includes haemodialysis, peritoneal dialysis (PD), intermittent haemodialysis (IHD), on-line intermittent haemofiltration (IHF), on-line haemodiafiltration (IHDF), continuous haemofiltration (CHF) and continuous haemodiafiltration (CHDF), continuous venovenous haemofiltration (CVVH), continuous venovenous haemodialysis (CVVHD), continuous venovenous haemodiafiltration (CVVHDF), slow continuous ultrafiltration (SCUF), continuous arteriovenous haemofiltration (CAVHD), sustained low-efficiency dialysis (SLED) and continuous renal replacement therapy (CRRT)

Inotropes/vasopressors?

A vasopressor is a pharmaceutical agent that causes vasoconstriction. Agents include norepinephrine, epinephrine, vasopressin, terlipressin and phenylephrine. An inotrope is a pharmaceutical agent that alters the force of myocardial contractility. Commonly used 'positive' inotropes include dobutamine, dopamine, milrinone and adrenaline (epinephrine). If the patient received a vasopressor or inotrope for at least one hour during their hospital stay, place tick 'yes' and the total duration in days if known.

MODULE 3: OUTCOME CASE REPORT FORM

TREATMENT: At ANY time during hospitalisation, did the patient receive/undergo:

Any Oxygen therapy? O YES O NO O Unknown If YES, total duration: _____ days O Unknown

Maximum O_2 flow volume: O <2 L/min O 2-5 L/min O 6-10 L/min O 11-15 L/min O >15 L/min

Non-invasive ventilation? *(Any)* O YES O NO O Unknown If YES, total duration: _____ days O Unknown

Invasive ventilation? *(Any)* O YES O NO O Unknown If YES, total duration: _____ days O Unknown

High flow nasal oxygen O YES O NO O Unknown If YES, total duration: _____ days O Unknown

Prone Positioning? O YES O NO O Unknown

Inhaled Nitric Oxide? O YES O NO O Unknown

Tracheostomy inserted? O YES O NO O Unknown

Extracorporeal support (ECMO)? O YES O NO O Unknown If YES, total duration: _____ days O Unknown

Renal replacement therapy (RRT) or dialysis? O YES O NO O Unknown

Inotropes/vasopressors? O YES O NO O Unknown

ICU or High Dependency Unit admission? O YES O NO O Unknown If YES, total duration: _____ days O Unknown

If YES, date of ICU admission: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] O Unknown

date of ICU discharge: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] O Unknown

COMPLICATIONS: At any time during hospitalisation did the patient experience: *(Unk = Unknown)*

Viral pneumonia/pneumonitis	O YES O NO O Unk	Meningitis / Encephalitis	O YES O NO O Unk
Bacterial pneumonia	O YES O NO O Unk	Bacteremia	O YES O NO O Unk
Acute Respiratory Distress Syndrome	O YES O NO O Unk	Coagulation disorder / DIC	O YES O NO O Unk
Pneumothorax	O YES O NO O Unk	Pulmonary Embolism	O YES O NO O Unk
Pleural effusion	O YES O NO O Unk	Deep Vein Thrombosis	O YES O NO O Unk
Cryptogenic organizing pneumonia (COP)	O YES O NO O Unk	Other thromboembolism (not PE or DVT)	O YES O NO O Unk
Bronchiolitis	O YES O NO O Unk	Anemia	O YES O NO O Unk
Cardiac arrest	O YES O NO O Unk	Rhabdomyolysis / Myositis	O YES O NO O Unk
Myocardial infarction	O YES O NO O Unk	Acute renal injury/ Acute renal failure	O YES O NO O Unk
Cardiac ischaemia	O YES O NO O Unk	Gastrointestinal haemorrhage	O YES O NO O Unk
Cardiac arrhythmia	O YES O NO O Unk	Pancreatitis	O YES O NO O Unk
Myocarditis / Pericarditis	O YES O NO O Unk	Liver dysfunction	O YES O NO O Unk
Endocarditis	O YES O NO O Unk	Hyperglycemia	O YES O NO O Unk
Cardiomyopathy	O YES O NO O Unk	Hypoglycemia	O YES O NO O Unk
Congestive heart failure	O YES O NO O Unk	Other	O YES O NO O Unk
Seizure	O YES O NO O Unk	If YES, specify:_____	
Stroke / Cerebrovascular accident	O YES O NO O Unk		

COMPLICATIONS

Please select all that were clinically identified at any time during the hospital admission.
Do not include known comorbidities (e.g. previous atrial fibrillation should not be included but new onset during this admission should). Record physician diagnosed complications.

Viral pneumonitis/pneumonia
Clinically or radiologically diagnosed viral pneumonitis/pneumonia.

Bacterial pneumonia
Clinically or radiologically diagnosed bacterial pneumonia (including community, hospital and ventilator acquired) managed with antimicrobials. Bacteriological confirmation not required.

Acute Respiratory Distress Syndrome (ARDS)
Defined according to Berlin criteria as:

- Occurring within 1 week of a known clinical insult or worsening respiratory symptoms
- Bilateral radiological opacities not fully explained by effusions, lobar/lung collapse, or nodules
- Respiratory failure not fully explained by cardiac failure or fluid overload

Pneumothorax
Is defined as the abnormal presence of air in the pleural cavity (between the lungs and the chest wall), causing collapse of the lung. It may be diagnosed clinically, usually with radiological confirmation.

Pleural effusion
Is defined as increased amounts of fluid within the pleural cavity. It may be diagnosed clinically, with or without radiological or interventional confirmation.

Cryptogenic organizing pneumonia (COP)
Idiopathic diffuse interstitial lung disease, diagnosed radiologically (multiple consolidative or ground glass opacities) or histologically (granulation tissue and chronic inflammatory infiltrate in alveoli). Formerly known as bronchiolitis obliterans organizing pneumonia (BOOP)

Bronchiolitis
This is a clinical diagnosis.

Cardiac arrest
Sudden cessation of cardiac activity with no normal breathing and no signs of circulation.

Myocardial infarction
Myocardial ischaemia (MI) leading to injury/necrosis, diagnosed by clinical findings, altered electrocardiography and elevated cardiac enzymes.

Cardiac ischaemia
Is defined as diminished blood and oxygen supply to the heart muscle, also known as myocardial ischemia, It is confirmed by an electrocardiogram (showing ischaemic changes, e.g. ST depression or elevation) and/or cardiac enzyme elevation.

Cardiac arrhythmia
If a cardiac arrhythmia is identified and there is no previous record of it, select 'yes'.

MODULE 3: OUTCOME CASE REPORT FORM

TREATMENT: At ANY time during hospitalisation, did the patient receive/undergo:

Any Oxygen therapy? O YES O NO O Unknown If YES, total duration: _____ days O Unknown

Maximum O_2 flow volume: O <2 L/min O 2-5 L/min O 6-10 L/min O 11-15 L/min O >15 L/min

Non-invasive ventilation? *(Any)* O YES O NO O Unknown If YES, total duration: _____ days O Unknown

Invasive ventilation? *(Any)* O YES O NO O Unknown If YES, total duration: _____ days O Unknown

High flow nasal oxygen O YES O NO O Unknown If YES, total duration: _____ days O Unknown

Prone Positioning? O YES O NO O Unknown

Inhaled Nitric Oxide? O YES O NO O Unknown

Tracheostomy inserted? O YES O NO O Unknown

Extracorporeal support (ECMO)? O YES O NO O Unknown If YES, total duration: _____ days O Unknown

Renal replacement therapy (RRT) or dialysis? O YES O NO O Unknown

Inotropes/vasopressors? O YES O NO O Unknown

ICU or High Dependency Unit admission? O YES O NO O Unknown If YES, total duration: _____ days O Unknown

If YES, date of ICU admission: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] O Unknown

date of ICU discharge: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] O Unknown

COMPLICATIONS: At any time during hospitalisation did the patient experience: *(Unk = Unknown)*

Viral pneumonia/pneumonitis	O YES O NO O Unk	Meningitis / Encephalitis	O YES O NO O Unk
Bacterial pneumonia	O YES O NO O Unk	Bacteremia	O YES O NO O Unk
Acute Respiratory Distress Syndrome	O YES O NO O Unk	Coagulation disorder / DIC	O YES O NO O Unk
Pneumothorax	O YES O NO O Unk	Pulmonary Embolism	O YES O NO O Unk
Pleural effusion	O YES O NO O Unk	Deep Vein Thrombosis	O YES O NO O Unk
Cryptogenic organizing pneumonia (COP)	O YES O NO O Unk	Other thromboembolism (not PE or DVT)	O YES O NO O Unk
Bronchiolitis	O YES O NO O Unk	Anemia	O YES O NO O Unk
Cardiac arrest	O YES O NO O Unk	Rhabdomyolysis / Myositis	O YES O NO O Unk
Myocardial infarction	O YES O NO O Unk	Acute renal injury/ Acute renal failure	O YES O NO O Unk
Cardiac ischaemia	O YES O NO O Unk	Gastrointestinal haemorrhage	O YES O NO O Unk
Cardiac arrhythmia	O YES O NO O Unk	Pancreatitis	O YES O NO O Unk
Myocarditis / Pericarditis	O YES O NO O Unk	Liver dysfunction	O YES O NO O Unk
Endocarditis	O YES O NO O Unk	Hyperglycemia	O YES O NO O Unk
Cardiomyopathy	O YES O NO O Unk	Hypoglycemia	O YES O NO O Unk
Congestive heart failure	O YES O NO O Unk	Other	O YES O NO O Unk
Seizure	O YES O NO O Unk	If YES, specify:_____	
Stroke / Cerebrovascular accident	O YES O NO O Unk		

COMPLICATIONS, continued

Myocarditis / Pericarditis

Myocarditis / pericarditis refers to an inflammation of the heart or pericardium (outer lining of the heart). Diagnosis can be clinical, biochemical (cardiac enzymes) or radiological

Endocarditis

Endocarditis is an inflammation of the endocardium (inner lining of the heart). Diagnosis is according to modified Duke criteria, using evidence from microbiological results, echocardiogram and clinical signs.

Cardiomyopathy

Structural and functional disorders of myocardium commonly diagnosed by echocardiography. Can be primary (genetic) or secondary (e.g. following myocardial infarction).

. Physician diagnosis,

Congestive heart failure

Is defined as failure of the heart to pump a sufficient amount of blood to meet the needs of the body tissues, resulting in tissue congestion and oedema.

Seizure

Select 'yes' for any seizure regardless of cause (e.g. febrile or due to epilepsy)

Stroke / Cerebrovascular accident

Stroke may be a clinical diagnosis, with or without supportive radiological findings.

Meningitis / Encephalitis

Inflammation of the meninges or the brain parenchyma. Select yes if diagnosed clinically, radiologically or microbiologically.

Bacteremia

Growth of bacteria on a blood culture. Select 'no' if the only bacteria grown were believed to be skin contaminants (e.g. coagulase negative Staphylococci or diphtheroids).

Coagulation disorder / DIC

Abnormal coagulation identified by abnormal prothrombin time or activated partial thromboplastin time. Disseminated intravascular coagulation (DIC; consumption coagulopathy; defibrination syndrome) is defined by thrombocytopenia, prolonged prothrombin time, low fibrinogen, elevated D-dimer and thrombotic microangiopathy.

Pulmonary embolism

Obstruction of pulmonary artery by thrombus, air or fat. Physician diagnosis based on clinical signs, computed tomographic pulmonary angiography and/or ventilation/perfusion scanning.

Deep Vein Thrombosis

Blood clots in deep veins of leg, pelvis or arm. Physician diagnosis based on clinical signs, and/or duplex ultrasonography, d-dimer blood test, contrast venography or magnetic resonance imaging (MRI),

Other thromboembolism (not Pulmonary Embolism or Deep Vein Thrombosis)

Please record any other type of physician diagnosed thromboembolism

MODULE 3: OUTCOME CASE REPORT FORM

TREATMENT: At ANY time during hospitalisation, did the patient receive/undergo:

Any Oxygen therapy? O YES O NO O Unknown If YES, total duration: _____ days O Unknown

Maximum O_2 flow volume: O <2 L/min O 2-5 L/min O 6-10 L/min O 11-15 L/min O >15 L/min

Non-invasive ventilation? *(Any)* O YES O NO O Unknown If YES, total duration: _____ days O Unknown

Invasive ventilation? *(Any)* O YES O NO O Unknown If YES, total duration: _____ days O Unknown

High flow nasal oxygen O YES O NO O Unknown If YES, total duration: _____ days O Unknown

Prone Positioning? O YES O NO O Unknown

Inhaled Nitric Oxide? O YES O NO O Unknown

Tracheostomy inserted? O YES O NO O Unknown

Extracorporeal support (ECMO)? O YES O NO O Unknown If YES, total duration: _____ days O Unknown

Renal replacement therapy (RRT) or dialysis? O YES O NO O Unknown

Inotropes/vasopressors? O YES O NO O Unknown

ICU or High Dependency Unit admission? O YES O NO O Unknown If YES, total duration: _____ days O Unknown

If YES, date of ICU admission: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] O Unknown

date of ICU discharge: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] O Unknown

COMPLICATIONS: At any time during hospitalisation did the patient experience: *(Unk = Unknown)*

Viral pneumonia/pneumonitis	O YES O NO O Unk	Meningitis / Encephalitis	O YES O NO O Unk
Bacterial pneumonia	O YES O NO O Unk	Bacteremia	O YES O NO O Unk
Acute Respiratory Distress Syndrome	O YES O NO O Unk	Coagulation disorder / DIC	O YES O NO O Unk
Pneumothorax	O YES O NO O Unk	Pulmonary Embolism	O YES O NO O Unk
Pleural effusion	O YES O NO O Unk	Deep Vein Thrombosis	O YES O NO O Unk
Cryptogenic organizing pneumonia (COP)	O YES O NO O Unk	Other thromboembolism (not PE or DVT)	O YES O NO O Unk
Bronchiolitis	O YES O NO O Unk	Anemia	O YES O NO O Unk
Cardiac arrest	O YES O NO O Unk	Rhabdomyolysis / Myositis	O YES O NO O Unk
Myocardial infarction	O YES O NO O Unk	Acute renal injury/ Acute renal failure	O YES O NO O Unk
Cardiac ischaemia	O YES O NO O Unk	Gastrointestinal haemorrhage	O YES O NO O Unk
Cardiac arrhythmia	O YES O NO O Unk	Pancreatitis	O YES O NO O Unk
Myocarditis / Pericarditis	O YES O NO O Unk	Liver dysfunction	O YES O NO O Unk
Endocarditis	O YES O NO O Unk	Hyperglycemia	O YES O NO O Unk
Cardiomyopathy	O YES O NO O Unk	Hypoglycemia	O YES O NO O Unk
Congestive heart failure	O YES O NO O Unk	Other	O YES O NO O Unk
Seizure	O YES O NO O Unk	If YES, specify:_____	
Stroke / Cerebrovascular accident	O YES O NO O Unk		

Anemia

Select 'yes' if haemoglobin levels were lower than age- and sex-specific thresholds listed below

	Haemoglobin threshold	
Age or gender group	**(g/L)**	**(mmol/l)**
Age 6 months to 5 years	110	6.8
Age 5–12 years	115	7.1
Age 12–15 years	120	7.4
Age > 15 years, non-pregnant women	120	7.4
Pregnant women	110	6.8
Age >15 years, men	130	8.1

Rhabdomyolysis / Myositis

Rhabdomyolysis is a syndrome characterised by muscle necrosis and the release of myoglobin into the blood. Muscle biopsy, electromyography, radiological imaging and the presence of myoglobinuria are not required for the diagnosis.

Myositis may be a clinical diagnosis with supporting evidence from laboratory tests e.g. elevated serum creatine kinase; histological confirmation is not required to make the diagnosis. Myositis can occur without progression to rhabdomyolysis.

Acute renal injury/Acute renal failure

Acute renal injury is defined as any of:

- Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days
- Urine volume <0.5 mL/kg/hour for 6 hours

Gastrointestinal haemorrhage

Refers to bleeding originating from any part of the gastrointestinal tract (from the oropharynx to the rectum).

Pancreatitis

Inflammation of the pancreas, diagnosed from clinical, biochemical, radiological or histological evidence.

MODULE 3: OUTCOME CASE REPORT FORM

TREATMENT: At ANY time during hospitalisation, did the patient receive/undergo:

Any Oxygen therapy? OYES ONO OUnknown If YES, total duration: _____days OUnknown

Maximum O_2 flow volume: O <2 L/min O2-5 L/min O6-10 L/min O11-15 L/min O>15 L/min

Non-invasive ventilation? *(Any)* OYES ONO OUnknown If YES, total duration: _____days OUnknown

Invasive ventilation? *(Any)* OYES ONO OUnknown If YES, total duration: _____days OUnknown

High flow nasal oxygen OYES ONO OUnknown If YES, total duration: _____days OUnknown

Prone Positioning? OYES ONO OUnknown

Inhaled Nitric Oxide? OYES ONO OUnknown

Tracheostomy inserted? OYES ONO OUnknown

Extracorporeal support (ECMO)? OYES ONO OUnknown If YES, total duration: _____days OUnknown

Renal replacement therapy (RRT) or dialysis? OYES ONO OUnknown

Inotropes/vasopressors? OYES ONO OUnknown

ICU or High Dependency Unit admission? OYES ONO OUnknown If YES, total duration: _____days OUnknown

If YES, date of ICU admission: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] OUnknown

date of ICU discharge: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] OUnknown

COMPLICATIONS: At any time during hospitalisation did the patient experience: *(Unk = Unknown)*

Viral pneumonia/pneumonitis	OYES ONO OUnk	Meningitis / Encephalitis	OYES ONO OUnk
Bacterial pneumonia	OYES ONO OUnk	Bacteremia	OYES ONO OUnk
Acute Respiratory Distress Syndrome	OYES ONO OUnk	Coagulation disorder / DIC	OYES ONO OUnk
Pneumothorax	OYES ONO OUnk	Pulmonary Embolism	OYES ONO OUnk
Pleural effusion	OYES ONO OUnk	Deep Vein Thrombosis	OYES ONO OUnk
Cryptogenic organizing pneumonia (COP)	OYES ONO OUnk	Other thromboembolism (not PE or DVT)	OYES ONO OUnk
Bronchiolitis	OYES ONO OUnk	Anemia	OYES ONO OUnk
Cardiac arrest	OYES ONO OUnk	Rhabdomyolysis / Myositis	OYES ONO OUnk
Myocardial infarction	OYES ONO OUnk	Acute renal injury/ Acute renal failure	OYES ONO OUnk
Cardiac ischaemia	OYES ONO OUnk	Gastrointestinal haemorrhage	OYES ONO OUnk
Cardiac arrhythmia	OYES ONO OUnk	Pancreatitis	OYES ONO OUnk
Myocarditis / Pericarditis	OYES ONO OUnk	Liver dysfunction	OYES ONO OUnk
Endocarditis	OYES ONO OUnk	Hyperglycemia	OYES ONO OUnk
Cardiomyopathy	OYES ONO OUnk	Hypoglycemia	OYES ONO OUnk
Congestive heart failure	OYES ONO OUnk	Other	OYES ONO OUnk
Seizure	OYES ONO OUnk	If YES, specify:_____	
Stroke / Cerebrovascular accident	OYES ONO OUnk		

COMPLICATIONS, continued

Liver dysfunction

A finding that indicates abnormal liver function, may refer to any of the following:

- Clinical jaundice
- Hyperbilirubinaemia (blood bilirubin level twice the upper limit of the normal range)
- An increase in alanine transaminase or aspartate transaminase that is twice the upper limit of the normal range

Hyperglycaemia

For adults, is defined as an abnormally high level of glucose in the blood, blood glucose level that is consistently above 126mg/dL or 7 mmol/L. For children, is defined as a blood glucose level consistently above 8.3 mmol/L.

Hypoglycaemia

For adults, is defined as an abnormally low level of glucose in the blood, a blood glucose level that is consistently below 70mg/dL or 4 mmol/L. For children, is defined as a blood glucose level below 3 mmol/L.

Other

Please specify other complications in the space provided.

MODULE 3: OUTCOME CASE REPORT FORM

TREATMENT: At ANY time during hospitalisation, did the patient receive/undergo:

Any Oxygen therapy? O YES O NO O Unknown If YES, total duration: _____ days O Unknown

Maximum O_2 flow volume: O <2 L/min O 2-5 L/min O 6-10 L/min O 11-15 L/min O >15 L/min

Non-invasive ventilation? *(Any)* O YES O NO O Unknown If YES, total duration: _____ days O Unknown

Invasive ventilation? *(Any)* O YES O NO O Unknown If YES, total duration: _____ days O Unknown

High flow nasal oxygen O YES O NO O Unknown If YES, total duration: _____ days O Unknown

Prone Positioning? O YES O NO O Unknown

Inhaled Nitric Oxide? O YES O NO O Unknown

Tracheostomy inserted? O YES O NO O Unknown

Extracorporeal support (ECMO)? O YES O NO O Unknown If YES, total duration: _____ days O Unknown

Renal replacement therapy (RRT) or dialysis? O YES O NO O Unknown

Inotropes/vasopressors? O YES O NO O Unknown

ICU or High Dependency Unit admission? O YES O NO O Unknown If YES, total duration: _____ days O Unknown

If YES, date of ICU admission: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] O Unknown

date of ICU discharge: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] O Unknown

COMPLICATIONS: At any time during hospitalisation did the patient experience: *(Unk = Unknown)*

Viral pneumonia/pneumonitis	O YES O NO O Unk	Meningitis / Encephalitis	O YES O NO O Unk
Bacterial pneumonia	O YES O NO O Unk	Bacteremia	O YES O NO O Unk
Acute Respiratory Distress Syndrome	O YES O NO O Unk	Coagulation disorder / DIC	O YES O NO O Unk
Pneumothorax	O YES O NO O Unk	Pulmonary Embolism	O YES O NO O Unk
Pleural effusion	O YES O NO O Unk	Deep Vein Thrombosis	O YES O NO O Unk
Cryptogenic organizing pneumonia (COP)	O YES O NO O Unk	Other thromboembolism (not PE or DVT)	O YES O NO O Unk
Bronchiolitis	O YES O NO O Unk	Anemia	O YES O NO O Unk
Cardiac arrest	O YES O NO O Unk	Rhabdomyolysis / Myositis	O YES O NO O Unk
Myocardial infarction	O YES O NO O Unk	Acute renal injury/ Acute renal failure	O YES O NO O Unk
Cardiac ischaemia	O YES O NO O Unk	Gastrointestinal haemorrhage	O YES O NO O Unk
Cardiac arrhythmia	O YES O NO O Unk	Pancreatitis	O YES O NO O Unk
Myocarditis / Pericarditis	O YES O NO O Unk	Liver dysfunction	O YES O NO O Unk
Endocarditis	O YES O NO O Unk	Hyperglycemia	O YES O NO O Unk
Cardiomyopathy	O YES O NO O Unk	Hypoglycemia	O YES O NO O Unk
Congestive heart failure	O YES O NO O Unk	Other	O YES O NO O Unk
Seizure	O YES O NO O Unk	If YES, specify:_____	
Stroke / Cerebrovascular accident	O YES O NO O Unk		

DIAGNOSTICS

Radiology

Chest X-Ray/ CT performed?
Record if X-ray and/or CT were performed, even if no infiltrates were present.

Pathogen Testing Details

Details of pathogen testing per biospecimen type
If the patient had samples taken for pathogen detection testing during their hospital stay, please complete a row for every type of sample collected (e.g. nasal/NP swab, sputum, etc.).

Where both positive and negative results for a particular sample type exist (from samples taken at different time points during the patient's hospital stay) please record the earliest positive result.

If results are indeterminate' or considered by the clinical team to represent contamination/colonisation, record on the form as Negative

If only multiple negative results exist for a particular sample type (from samples taken at different time points during the patient's hospital stay), please document the earliest negative result.

MODULE 3: OUTCOME CASE REPORT FORM

DIAGNOSTICS

Section 1: RESPIRATORY VIRUS PCR TESTING

SARS-CoV-2 (COVID-19): OPositive ONegative ONot done OUnknown

Was other pathogen testing done during this illness episode? OYES *(complete section)* ONO OUnknown

Influenza : OPositive ONegative ONot done OUnknown

If Positive: OA-not typed OA/H3N2 OA/H1N1pdm09 OA/H7N9 OA/H5N1 OB OOther:___________ ..OUnk

Respiratory Syncytial Virus (RSV): OPositive ONegative ONot done OUnknown

Adenovirus: OPositive ONegative ONot done OUnknown

Section 2: BACTERIAL TESTING

Bacteria: OPositive ONegative ONot done If Positive, specify: ___________ OUnknown

Other pathogen/s detected: OYES ONO OUnknown If YES, specify all:___________ OUnknown

Section 3: RADIOLOGY

Clinical pneumonia diagnosed? OYES ONO OUnknown

Chest X-Ray performed? OYES ONO OUnknown If Yes: Were infiltrates present? OYES ONO OUnknown

CT performed? OYES ONO OUnknown If Yes: Were infiltrates present? OYES ONO OUnknown

Section 4: PATHOGEN TESTING DETAILS

Collection Date *(DD/MM/YYYY)*	Biospecimen Type	Laboratory test Method	Result	Pathogen Tested/Detected
_D_ _D_/_M_ _M_/20_Y_ _Y_	ONasal/NP swab OThroat swab OCombined nasal/NP+throat swab OSputum OBAL OETA OUrine OFeces/rectal swab OBlood OOther, *Specify:* ________	OPCR OCulture OOther, *Specify:* ________	OPositive ONegative OUnknown	________
_D_ _D_/_M_ _M_/20_Y_ _Y_	ONasal/NP swab OThroat swab OCombined nasal/NP+throat swab OSputum OBAL OETA OUrine OFeces/rectal swab OBlood OOther, *Specify:* ________	OPCR OCulture OOther, *Specify:* ________	OPositive ONegative OUnknown	________
_D_ _D_/_M_ _M_/20_Y_ _Y_	ONasal/NP swab OThroat swab OCombined nasal/NP+throat swab OSputum OBAL OETA OUrine OFeces/rectal swab OBlood OOther, *Specify:* ________	OPCR OCulture OOther, *Specify:* ________	OPositive ONegative OUnknown	________
_D_ _D_/_M_ _M_/20_Y_ _Y_	ONasal/NP swab OThroat swab OCombined nasal/NP+throat swab OSputum OBAL OETA OUrine OFaeces/rectal swab OBlood OOther, *Specify:* ________	OPCR OCulture OOther, *Specify:* ________	OPositive ONegative OUnknown	________

MEDICATION - While hospitalised or at discharge, were any of the following administered?

Antiviral or COVID-19 targeted agent

Record all antivirals or COVID-19 targeted agents administered from date of admission or during the hospitalisation. Record the total number of days the treatment was given.

Additional space is available under 'Other treatments…' at the end of this section if required

Antibiotic

'Antibiotic' refers to any agent(s) are substances naturally produced by microorganisms or their derivatives that selectively target microorganisms. These substances are used in the treatment of bacterial and other microbial infections. Topical preparations are not included.

Corticosteroid

'Corticosteroids' (commonly referred to as 'steroids') refers to all types of therapeutic corticosteroid, made in the adrenal cortex (the outer part of the adrenal gland). They are also made in the laboratory. Examples include: prednisolone, prednisone, methyl-prednisolone, dexamethasone, hydrocortisone, fluticasone, betamethasone (note that other examples exist). Topical preparations are not included, but inhaled preparations are included. The indication for administering corticosteroids does not need to be directly related to the treatment of COVID-19.

MODULE 3: OUTCOME CASE REPORT FORM

MEDICATION: While hospitalised or at discharge, were any of the following administered? *(Unk=Unknown)*

ANTIVIRAL OR COVID-19 TARGETED AGENT? OYES ONO OUnknown If YES, specify (all) :

☐ Ribavirin Date commenced[_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] OUnk Duration: _____ days OUnk

☐ Lopinavir/Ritonavir Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] OUnk Duration: _____ days OUnk

☐ Remdesivir (Veklury) Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] OUnk Duration: _____ days OUnk

☐ Interferon alpha Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] OUnk Duration: _____ days OUnk

☐ Interferon beta Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] OUnk Duration: _____ days OUnk

☐ Chloroquine/hydroxychloroquine:

Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] OUnk... Duration: _____days OUnk

☐ Interleukin-6 (IL-6) inhibitor IF YES which: ☐ Tocilizumab ☐ Sarilumab ☐ Other IL-6 inhibitor_____OUnk

Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] OUnk... Duration: _____days OUnk

☐ Convalescent plasma Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] OUnk Duration: _____days OUnk

☐ Anti-influenza anti-viral IF YES which: ☐Oseltamivir (Tamiflu®) ☐ Zanamivir OUnk

Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] OUnk... Duration: _____days OUnk

☐ Other_____ Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] OUnk Duration: _____days OUnk

---

ANTIBIOTIC? OYES ONO OUnknown If yes, specify all:

Agent 1:_____ Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] Duration: ____ days OUnk

Agent 2:_____ Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] Duration: ____ days OUnk

Agent 3:_____ Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] Duration: ____ days OUnk

---

CORTICOSTEROID? OYES ONO OUnknown

If YES: Dexamethasone? OYES ONO OUnknown

If YES, check all that apply:

☐ 6mg once per day (od)? OYES ONO OUnknown If YES, Route: ☐ Oral ☐ Intravenous OUnk

If YES, Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] Duration: _____ days OUnk

☐ other dose or frequency? OYES ONO OUnknown If YES, Route: ☐ Oral ☐ Intravenous OUnk

If YES, Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] Duration: _____ days OUnk

If YES: Other corticosteroid? OYES ONO OUnknown

If YES: Which steroid: ☐ Prednisolone ☐ Hydrocortisone ☐ Methylprednisolone ☐ Other

Route: ☐ Oral ☐ Intravenous OUnk

MEDICATION (continued)

Anticoagulants

These include heparin, enoxaparin, apixaban, dabigatran, rivaroxaban, edoxaban, warfarin. For heparin treatment, please specify if unfractionated or low molecular weight heparin was administered.

Antifungal Agent

'Antifungal agent' refers to any agent(s) prescribed specifically to treat systemic or topical infections caused by fungi. Examples include fluconazole, amphotericin, caspofungin, anidulafungin, posaconazole, itraconazole (note that other examples exist). Topical preparations should not be recorded.

Other treatment administered for COVID-19

Record any other medications, experimental or re-purposed, administered to modify the course of COVID-19 during the admission (including as part of a clinical trial). This could include convalescent plasma, immuno-modulatory agents and anti-viral agents not already recorded above.

MODULE 3: OUTCOME CASE REPORT FORM

MEDICATION (continued):

ANTICOAGULATION? O YES O NO O Unk

If YES: Agent: _____

Route: ☐ Subcutaneous ☐ Intravenous (IV) O Unk

Indication: ☐ therapeutic (treatment of DVT/PE) ☐ enhanced prophylaxis for COVID-19 ☐ routine inpatient prophylaxis ☐ Unk

---

ANTIFUNGAL AGENT? O YES O NO O Unk

OTHER treatments administered for COVID-19 including experimental or compassionate use? O YES O NO O Unk

If YES, specify agent and timing of administration:

Agent 1: _____

Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] O Unk Duration: _____ days O Unk

Agent 2: _____

Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] O Unk Duration: _____ days O Unk

Agent 3: _____

Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] O Unk Duration: _____ days O Unk

OUTCOME

Was patient diagnosed with Covid-19? O YES O NO O Unknown

If yes, was the diagnosis based on: O laboratory confirmation O clinical assessment

Outcome: O Discharged alive O Hospitalised O Transfer to other facility O Death O Palliative discharge O Unknown

Outcome date: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] O Unknown

If alive at outcome date:

Ability to self-care at discharge versus before illness: O Same as before illness O Worse O Better O Unknown

Post-discharge treatment: Oxygen therapy? O YES O NO O Unknown

Ongoing health care needs relating to this admission for COVID-19: O YES O NO O Unknown

Ongoing health care needs NOT related to COVID episode: O YES O NO O Unknown

Medically fit for discharge (COVID-19 resolved) but remains in hospital for other reason (e.g. awaiting suitable care in community, resident in long term health care or mental health facility): O YES O NO O Unknown

OUTCOME

Was patient diagnosed with Covid-19?

Please confirm method of diagnosis, confirming diagnosis by clinical assessment only if no positive laboratory result was obtained.

Discharged alive can mean discharge to their usual place of residence before their illness, to the home of a relative or friend, or to a social care facility, because their illness is no longer severe enough to warrant treatment in a medical facility.

Hospitalized means they are still in hospital but have recovered from COVID-19 infection and the form has been completed as the patient is in a part of the hospital for care of other conditions and where the form will not be completed at a later date.

Transfer to other facility means they have been transferred to another facility that provides medical care. This could be a specialist centre for more intensive treatment or a step-down for rehabilitation. It does not include facilities that solely provide social care (these patients should be listed as discharged alive).

Death means the patient died in the hospital.

Palliative discharge means the patient has been discharged with the expectation that they will not recover from this or other co-existing illness. This could be to a specialist hospice facility, or to their usual home address with anticipatory end of life medications.

Outcome date Please state the date for the outcome listed above.

If Discharged Alive: (answer these questions only if outcome is 'Discharged Alive'

Ability to self-care at discharge versus before illness: the patient is able to care for themselves at discharge (in terms of activities of daily living) at the same level as before they developed illness then tick 'same as before illness'. If their ability to self-care has decreased or increased, then tick the appropriate circle ('worse' or 'better').

Post-discharge treatment

Oxygen therapy includes, NIV or home ventilation (respiratory support/treatment).

MODULE 3: OUTCOME CASE REPORT FORM

MEDICATION (continued):

ANTICOAGULATION? OYES ONO OUnk

If YES: Agent: _____

Route: ☐ Subcutaneous ☐ Intravenous (IV) OUnk

Indication: ☐ therapeutic (treatment of DVT/PE) ☐ enhanced prophylaxis for COVID-19 ☐ routine inpatient prophylaxis ☐ Unk

---

ANTIFUNGAL AGENT? OYES ONO OUnk

OTHER treatments administered for COVID-19 including experimental or compassionate use? OYES ONO OUnk

If YES, specify agent and timing of administration:

Agent 1: _____

Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] OUnk Duration: _____ days OUnk

Agent 2: _____

Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] OUnk Duration: _____ days OUnk

Agent 3: _____

Date commenced [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] OUnk Duration: _____ days OUnk

OUTCOME

Was patient diagnosed with Covid-19? OYES ONO OUnknown

If yes, was the diagnosis based on: Olaboratory confirmation O clinical assessment

Outcome: ODischarged alive OHospitalised OTransfer to other facility ODeath OPalliative discharge OUnknown

Outcome date: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] OUnknown

If alive at outcome date:

Ability to self-care at discharge versus before illness: OSame as before illness OWorse OBetter OUnknown

Post-discharge treatment: Oxygen therapy? OYES ONO OUnknown

Ongoing health care needs relating to this admission for COVID-19: OYES ONO OUnknown

Ongoing health care needs NOT related to COVID episode: OYES ONO OUnknown

Medically fit for discharge (COVID-19 resolved) but remains in hospital for other reason (e.g. awaiting suitable care in community, resident in long term health care or mental health facility): OYES ONO OUnknown

CORE CRITICAL CARE MODULE

Complete this form for anyone receiving critical care regardless of type of ward, in addition to the CORE COVID-19 CRF.

Admission date: this is the date the patient was admitted to the critical care ward.

Interventional clinical study: this could be a trial of a therapeutic agent (e.g. anti-viral, immunomodulator, convalescent plasma) or supportive intervention (e.g. high flow oxygen).

Reason for admission: these are the diagnoses/complications that required critical care management as assessed by a physician select all that apply.

Clinical Frailty Scale: see last page

Severity scores:
Complete if assessed or score recorded in the medical notes.

PELOD score: see https://sfar.org/scores2/pelod2.php

PRISM III score: see https://www.cpccrn.org/calculators/prismiicalculator/

Fluid balance: net fluid balance over 24h assessment day or prior to assessment

Nutrition: select route of the main type of nutrition on day of assessment from parenteral, enteral (including nasogastric or gastrostomy/jejunostomy), or NPO (*nil per os* – no oral intake).

Physical mobility: score from options 0 to 10, record **best** score.

CRITICAL CARE MODULE PART B

ICU/HDU ADMISSION FORM

ICU ADMISSION DATE *(DD/MM/YYYY):* [_D_][_D_]/[_M_][_M_]/[__2_][__0_][_Y_][_Y_]

Enrolment in interventional clinical study? O YES O NO O Unknown **If YES,** name of study: _____ or

Treatment/s trialled: _____

_____ O Unknown

Reason for ICU admission (tick all that apply): ☐ Respiratory failure ☐ Septic shock ☐ Venous thromboembolism

☐ Cardiovascular complications ☐ Acute kidney injury ☐ Acute liver injury ☐ Neurological complications ☐ Secondary infection

☐ Pancreatic injury ☐ Disseminated intravascular coagulation ☐ Pregnancy related complications ☐ Rhabdomyolysis

☐ OTHER (please specify) _____ O Unknown

Clinical Frailty Score (CFS/9) [_____] O Unknown **Acute renal failure?** O YES O NO O Unknown

DAILY FORM (Complete daily for duration of ICU/ITU/IMC/HDU admission)
(between 00:00 to 24:00 on day of assessment) Record the 'worst' value on the day of assessment.

IF patient is <18 years: **PELOD Total Score** [_____] O Unknown **PRISM III score:** [_____] O Unknown

Fluid balance (in last 24 hours) (mL) _____ ☐ Unknown

Nutrition O Parenteral O Enteral O NPO O Unknown **Best physical mobility** [___]/10 *(see scoring below)* O Unknown

0 Passively moved by staff (incl. passive cycling only)
1 Any activity in bed, but not moving out of or over edge of bed (incl. cycling)
2 Passively moved to chair (no standing or sitting at edge of bed)
3 Actively sitting over side of bed with some trunk control (may be assisted)
4 Standing
5 Transferring from bed to chair
6 Marching on the spot (at bedside; > 2steps/foot)
7 Walking with assistance of 2 or more people (>5m)
8 Walking with assistance of 1 person (>5m)
9 Walking independently with gait aid (>5m)
10 Walking independently without gait aid (>5m)

Type of ventilation:

Record all types of ventilation received on day of assessment on or after admission to the critical care ward (ICU/HDU.

Abbreviations:

ETT: endotracheal tube

BIPAP: bi-level positive airway pressure

CPAP: continuous positive airway pressure

CRRT: continuous renal replacement therapy

IHD: intermittent haemodialysis

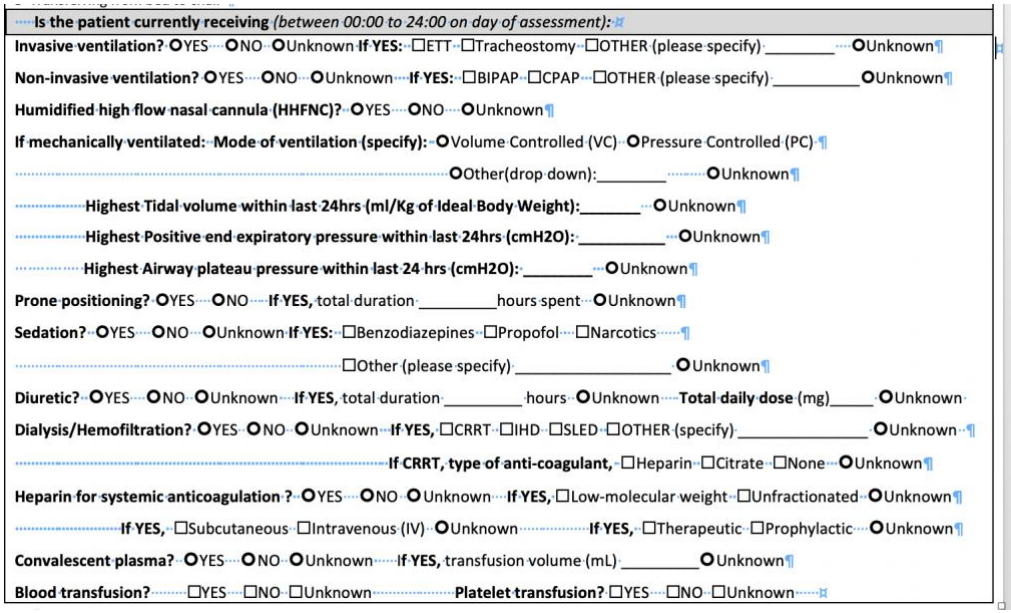
SLED: sustained low efficiency dialysis

For modes of ventilation (invasive, non-invasive, humidified high flow nasal cannula) please select all modes the patient received during the 24 hour assessment day.

Modes of mechanical ventilation:

- Synchronized Intermittent Mandatory Ventilation – Volume-Controlled (SIMV-V)
- Synchronized Intermittent Mandatory Ventilation – Pressure-Controlled (SIMV-P)
- Volume Controlled Ventilation
- Pressure Controlled Ventilation
- Pressure Regulated Volume Control (PRVC)
- Airway Pressure Release Ventilation (APRV)
- Pressure Support Ventilation (PSV)
- Volume Support Ventilation (VSV)
- High Frequency Oscillatory (HFO)
- Bilevel Positive Airway Pressure (BiPAP)
- Continuous Positive Airway Pressure (CPAP)
- Proportional Assist Ventilation (PAV)
- Neurally Adjusted Ventilatory Assist (NAVA)

Record highest tidal volume and airway pressures.



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*

ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections

ISARIC CCP Version 3.2

Version history

Version number 3.2 (2020)(amended by Clark D. Russell on behalf of international collaborators in the ISARIC CCP group)

Version number 3.1 (2020)(amended by J. Kenneth Baillie and international collaborators in the ISARIC CCP group)

Version number 3.01 (2016)(amended by Malcolm (Calum) G Semple and Gail Carson)

Version numbers 2.4.2 to 2.5.4 (2013)(amended by J. Kenneth Baillie and ISARIC working group 3)

Version number 1.0 (2012)(written by J. Kenneth Baillie on behalf of the ISARIC working group on observational research: Sylvie van der Werf, Peter J M Openshaw, Jake W Dunning, Laura Merson, Jeremy Farrar, Gail Carson, Gernot G U Rohde, Zhancheng Gao, Malcolm (Calum) G Semple, Dat Tran, Anthony Gordon, Piero L Olliaro, Saye H Khoo, Roberto Bruzzone, Peter Horby, J Perren Cobb, Kajsa-Stina Longuere, Paul Kellam, Alistair Nichol, Stephen Brett, Dean Everett, Timothy S Walsh, Tran-Tinh Hien, Hongjie Yu, Maria Zambon, Guillermo Ruiz-Palacios, Trudie Lang, Tamuna Akhvlediani, Frederick G Hayden, John Marshall, Steve Webb, Derek C Angus, Nahoko Shindo)

Table of Contents

1. Background and Objectives

1.1 Purpose of the Study

This is a standardized protocol for the rapid, coordinated clinical investigation of severe or potentially severe acute infections by pathogens of public health interest. Patients with acute illness suspected to be caused by emerging and unknown pathogens will be enrolled. This protocol has been designed to enable data and biological samples to be prospectively collected and shared rapidly through a globally-harmonised sampling schedule. Multiple independent studies can be easily aggregated, tabulated and analysed across many different settings globally. The protocol is the product of many years of discussion among international investigators from a wide range of scientific and medical disciplines (Lancet ID 14(1):8; https://doi.org/10.1016/S1473-3099(13)70327-X).

Recruitment under this protocol has been initiated in response to Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV) in 2012-2013, influenza A H7N9 in 2013, viral haemorrhagic fever (Ebola virus) in 2014, monkeypox & MERS-CoV in 2018, tick-borne encephalitis virus (TBEV) in 2019 and Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) in 2020.

1.2 Background Information

Infectious disease is the single biggest cause of death worldwide. New infectious agents, such as the SARS, MERS and other novel coronavirus, novel influenza viruses, viruses causing viral haemorrhagic fever (e.g. Ebola), and viruses that affect the central nervous system (CNS) such as TBEV & Nipah require investigation to understand pathogen biology and pathogenesis in the host. Even for known infections, resistance to antimicrobial therapies is widespread, and treatments to control potentially deleterious host responses are lacking.

In order to develop a mechanistic understanding of disease processes, such that risk factors for severe illness can be identified and treatments can be developed, it is necessary to understand pathogen characteristics associated with virulence, the replication dynamics and in-host evolution of the pathogen, the dynamics of the host response, the pharmacology of antimicrobial or host-directed therapies, the transmission dynamics, and factors underlying individual susceptibility.

The work proposed here may require sampling that will not immediately benefit the participants. It may also require analysis of the host genome, which may reveal other information about disease susceptibility or other aspects of health status.

1.3 Target Audience of this Document

This document is of primary interest to clinicians (including emergency and critical care providers) and others engaged in identification, triage and treatment of patients with severe acute or potentially severe infections due to the pathogens of interest. Any individuals or members of research units/networks are invited to use this document to facilitate their own studies and contribute data to the centralized database. We encourage any and all centres to contribute to this effort. The primary data remain with the individual sites but we hope by collecting similar data investigators will be willing to share their results and allow a much more complete analysis of the data.

1.4 Source of this Protocol

This document is a product of collaboration between the World Health Organization (WHO) and the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC), and builds on a global consensus on observational research in emerging infections of public health interest.

1.5 Primary Objectives

In potential participants meeting the entry criteria, our primary objectives for each individual pathogen are to:

- Describe the clinical features of the illness or syndrome and identify risk factors for severe disease.
- Describe, where appropriate, the response to treatment, including supportive care and novel therapeutics.
- Observe, where appropriate and feasible, pathogen replication, excretion and evolution, within the host, and identify determinants of severity and transmission using high-

throughput sequencing of pathogen genomes obtained from respiratory tract, blood, urine, stool, CSF and other samples.
- Characterise, where appropriate and feasible, the host responses to infection and therapy over time, including innate and acquired immune responses, circulating levels of immune signalling molecules and gene expression profiling in peripheral blood.
- Identify host genetic variants associated with disease progression or severity
- Understand transmissibility and the probabilities of different clinical outcomes following exposure and infection

1.6 Secondary Objectives

Secondary objectives are to collect evidence in order to:

- Facilitate effective triage and clinical management of patients with infections relevant to this protocol
- Determine infectivity and inform appropriate infection control measures of the various pathogens
- Develop clinical guidance documents and offer clinical recommendations to policy makers on the basis of evidence obtained

1.7 Structure of this document: stratified recruitment according to local resource.

The study will be conducted at multiple sites (to be determined by the spread of disease and availability of resources). It is appreciated that settings will vary in terms of clinical infrastructure, resources and capacity. Distinction is made to allow for resource-appropriate implementation of the protocol, and it is understood that data and/or specimen collection may be limited in certain settings. Observational analyses will be stratified according to available samples and data.

Outcome data for primary and secondary objectives will be derived from **(i)** data from *routine clinical and laboratory assessments* performed as part of standard inpatient medical management at the treating site, documented using proportionate case report forms (CRF; either paper or web-based electronic 'eCRF'), with or without **(ii)** *additional biological samples* obtained for research purposes (depending on which tier of the protocol the site is recruiting to).

Implementation of data and biological sample collection are classified into the following tiers:

- **TIER 0 (data collection only)**: Routine clinical and laboratory data will be collected but no biological samples will be obtained for research purposes. The minimum clinical data set will summarise the illness episode and outcome, with the option to collect additional detailed clinical data at frequent intervals, according to local resources/needs.
- **TIER 1 (1 biological sample set)**: Clinical samples will be collected on recruitment day (Day 1; ideally at initial presentation to a health care facility) but subsequent serial samples will not be obtained. Clinical information will be collected at recruitment and discharge.
- **TIER 2 (Serial biological sampling, schedules 2-11)**: Clinical samples and data will be collected on recruitment day (Day 1; ideally at initial presentation to a health care facility) followed by serial samples obtained at timepoints defined by the schedule (illustrated in Tables 2-5). The schedule ranges from 2 (recruitment and day 3) to 11 sample sets (recruitment, every second day for the next 14 days, then weekly [until maximum 100 days], then convalescent samples 3 & 6 months after recruitment). An interactive web app summarises the various schedules: https://isaric.net/ccp/
- **TIER 3 (Population pharmacokinetics** of antimicrobial/immunomodulatory drugs)

Each site will recruit at a given tier. This will be recorded in the site file, where the investigator will complete the "Tier Record Form". Any changes to the tier a given site is recruiting to will be documented by the Principal Investigator (PI). As an outbreak progresses, and more cases occur, it is anticipated that both the research priorities and the local resource availability will change. Within a given institution, cases recruited at different stages of an outbreak can be sampled at different intensities and may be recruited to different tiers of the study.

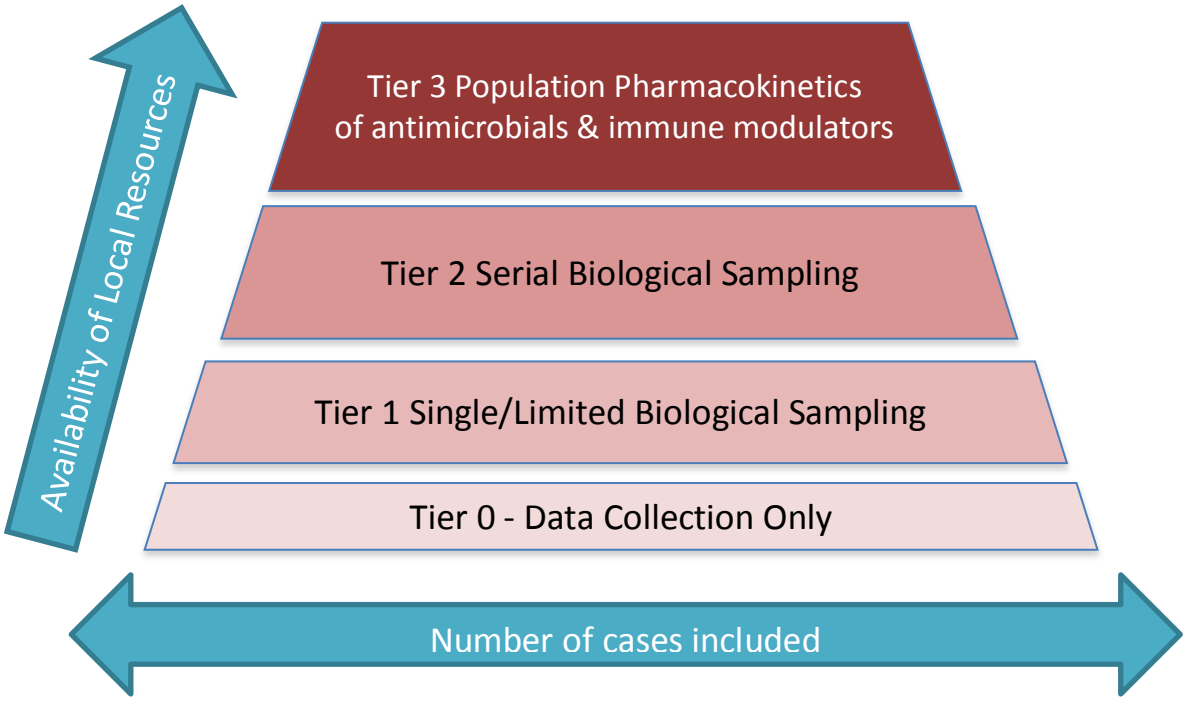


Figure 1. Tiered approach to recruitment in settings with different resources. This information is included to demonstrate the integration of this study with other studies following the same approach in other parts of the world.

1.8 Entry Criteria

This study will enrol eligible patients (children and adults) with confirmed or suspected infection with a pathogen relevant to the study objectives. Recruitment of patients with Day 1 (enrolment) data and biological samples is the priority. The local study team will dictate whether laboratory confirmation of infection is required prior to enrolment.

Daily follow-up and convalescent visits of patients should proceed according to local resources.

Inclusion criteria

Suspected or proven infection with an emerging pathogen.

Exclusion criteria:

Confirmed diagnosis of a pathogen unrelated to the objectives of this study (or other non-infectious diagnosis) and no indication or likelihood of co-infection with a relevant pathogen.

Refusal by participant, parent or appropriate representative.

2. Study Design

This protocol is for a prospective observational cohort study.

2.1 Sample Size

This is a descriptive study of a syndrome, which may be caused by a number of different known or poorly understood pathogens. Therefore, the sample size is not prospectively determined. Recruitment of participants will depend on the emergence and spread of the various pathogens and the resources available to the recruitment centres. The sample size will vary for each location but

should be as large as feasible and preferably without limit in order to capture as much clinical data as possible early in the outbreak.

This protocol will be opened at sites with capacity and capability to recruit to any tier of study intensity. The study has no set end date.

3. Methods

3.1 Identification of Potential Patients

In hospital, potential participants will be identified through hospital workers upon presentation at recruiting sites and through public health agencies. When resources limit the number of patients enrolled to less than the number of patients presenting, sites should establish procedures to minimize bias in the selection of participants.

3.2 Approach to Potential Participants

Tier Zero activity

This requires collection of limited clinical data from the routine health record in a form that does not identify the patient. This does not generally require consent.

Tiers One and Two

Patients will only be considered for enrolment if appropriate local infection control and prevention measures are in place and can be maintained.

When it has been decided that biological sampling can be performed safely and appropriate consent has been obtained, samples taken early may be most useful for identification or evaluation of risk factors for disease progression at a clinically-relevant decision point. Therefore it is desirable to begin sampling as early as possible during a patient's illness.

Where patients lack capacity to consent to participation, an appropriate representative/consultee/parent/guardian will be approached by staff trained in consent procedures that protect the rights of the patient, and adhere to the ethical principles within the Declaration of Helsinki. Staff will explain the details of the study to the participant or parent/guardian/consultee and allow them time to discuss and ask questions. The staff will review the informed consent form with the person giving consent and endeavour to ensure understanding of the contents, including study procedures, risks, benefits, the right to withdraw and alternatives to participation. The consenting party will be asked to sign and date an informed consent form. If the patient is a child, the person with parental responsibility and the child, if competent, should both provide consent/ assent.

In view of the importance of early samples, participants or their parent/guardian/consultee will be permitted to consent and begin to participate in the study immediately if they wish to do so. Those who prefer more time to consider participation will be approached again after an agreed time, normally one day, to discuss further.

An outbreak involving a pathogen of public health interest or pandemic is an emergency. Patients who are incapable of giving consent in emergency situations are an exception to the general rule of informed consent in clinical research. This is clearly acknowledged in the Declaration of Helsinki (2008). The process of consent will comply with the principles of Good Clinical Practice and with the laws regulating clinical research in the recruiting centre.

For studies that collect or collate only anonymised data that is normally collected, as part of routine care, consent may not be required.

Internal pilot study

An internal pilot study will only collate data that is being recorded or generated as part of routine clinical care (e.g. microbiology results). We will seek consent, be it deferred, proxy or assent, in order to test the processes within the overarching Clinical Characterisation Protocol, which include obtaining consent.

All patients will be treated according to clinical requirements regardless of their participation in the study.

3.3 Standard of Care

Provision of care will vary by site and by treating physician. It is not possible to define a single standard of care and therefore to define what samples will be taken as a part of medical management and when. Participants in Tiers 1 to 3 of this study may have samples taken in addition to those required for medical management. The results of tests performed on research samples are unlikely to benefit the health of the participants.

3.4 Data Collection and Sampling for Patients

Samples and data will be collected according to the protocol tier approach, available resources and the weight of the patient, to prevent excessive volume sampling from children, young people and small adults.

Samples required for clinical management will at all times have priority over samples taken for research tests. Aliquots or samples for research purposes should never compromise the quality or quantity of samples required for medical management. Wherever practical, taking research samples should be timed to coincide with clinical sampling. The research team will be responsible for sharing the sampling protocol with health care workers supporting patient management in order to minimise disruption to routine care and avoid unnecessary procedures.

Some samples should be processed and stored at -80°C (Table 1). We recognise that -80°C storage is not available at all sites. In this case please store at coldest available temperature and at least -20°C.

For patients with VHF such as Ebola virus, the biological sampling will at times be limited to extra volumes of blood taken at times to coincide when blood is being taken for clinical purposes and then only at the discretion of the clinical team.

3.5 Sample and Data Collection Schedules

Table 1: Proposed samples to be obtained

REQUIREMENTS	Samples	Processing/ storage	Purpose
CONSENT FORM		Site file	
SINGLE SAMPLE SET TAKEN AT RECRUITMENT ('R')	*Pathogen samples*: Urine (up to 10ml) Stool (up to 10ml) or rectal swab; respiratory samples [combined nose and throat swab, AND endotracheal aspirate if intubated, AND, where resources permit, nasopharyngeal aspirate (NPA) OR (if NPA impossible) flocked nose and throat swab]; samples from infected sites/sores. Also store any residual from samples taken for clinical care.	Do not process at site. Freeze at -80°C*	Pathogen studies to reveal changes in pathogen during infection and during spread between individuals, detect development of resistance.
	Blood sample in serum (clotted) tube (patients > 40kg only)	Centrifuge 1500g for 10mins. Serum (3 aliquots -80°C*)	Test for mediators and potential biomarkers
			Serology to detect development of antibodies
	Blood sample in EDTA tube	Centrifuge 1500g for 10mins at 4°C. Plasma (3 aliquots -80°C*)	Test for mediators, metabolites and potential biomarkers Test for drug levels.

			Extract RNA/DNA from causative pathogen and other circulating pathogens.
		Cell fraction (1 aliquot -80°C*)	Extract host DNA for genomic studies
			Extract RNA/DNA from causative pathogen and other circulating pathogens; leftover cellular fractions from research or clinical samples can be used for PBMC isolation if feasible.
	Blood sample in blood RNA tube (e.g Tempus™ or PAXgene®)	Freeze at -20°C; transfer to -80°C after 24h where possible	Microarray/RNAseq analysis of host immune cell transcriptome
	Cerebrospinal fluid sample (if suspected CNS disease) If after recruitment a lumbar puncture is clinically indicated, an additional sample of up to 5mls will be collected in a universal sterile tube, provided it is deemed appropriate by the supervising clinician. Any residual CSF from samples taken as part of routine clinical care will be collected and stored if available.	3 aliquots stored at -80°C*	Extract RNA/DNA from causative pathogens and other circulating pathogens for molecular testing, genomic studies and virus isolation
			Perform serological testing for pathogen-specific antibodies
			Test for mediators, metabolites and potential biomarkers
CASE REPORT FORM	Complete ISARIC CORE CRF module 1 and 2 or WHO NATURAL HISTORY PROTOCOL (depending on local resources) For VHFs collect any amount of clinical data e.g. <50 cases.	Site file (paper) REDCap (electronic) See section 3.7	Clinical data

SERIAL SAMPLES THROUGHOUT ACUTE ILLNESS (serial, 'S') AND CONVALESCENT ('C) SAMPLES WHERE POSSIBLE	*Pathogen samples*: Urine (up to 10ml) Stool (up to 10ml) or rectal swab; respiratory samples [combined nose and throat swab, AND endotracheal aspirate if intubated, AND, where resources permit, nasopharyngeal aspirate (NPA) OR (if NPA impossible) flocked nose and throat swab; samples from infected sites/sores. Also store any residual from samples taken for clinical care.	Do not process at site. Freeze at -80°C*	Pathogen studies to reveal changes in pathogen during infection and during spread between individuals, detect development of resistance.
	Blood sample in serum (clotted) tube (patients > 40kg only)	Centrifuge 1500g for 10mins. Serum (3 aliquots -80°C*)	Test for mediators and potential biomarkers
			Serology to detect

			development of antibodies
	Blood sample in EDTA	Centrifuge 1500g for 10mins at 4°C. Plasma (3 aliquots -80°C*) Cell fraction (1 aliquot -80°C*)	Test for mediators, metabolites, and potential biomarkers Test for drug levels.
			Serology to detect development of antibodies
			Extract RNA/DNA from causative pathogen and other circulating pathogens.
		Cell fraction (1 aliquot -80°C*)	Extract RNA/DNA from causative pathogen and other circulating pathogens; leftover cellular fractions from research or clinical samples can be used for PBMC isolation if feasible.
	Blood sample in blood RNA tube	Freeze at -20°C; transfer to -80 after 24h where possible	Microarray and CAGE analysis of host immune cell transcriptome
	Cerebrospinal fluid sample (if suspected CNS disease) If after recruitment a lumbar puncture is clinically indicated, an additional sample of up to 5mls will be collected in a universal sterile tube, provided it is deemed appropriate by the supervising clinician. Any residual CSF from samples taken as part of routine clinical care will be collected and stored if available.	3 aliquots stored at -80°C*	Extract RNA/DNA from causative pathogens and other circulating pathogens for molecular testing, genomic studies and virus isolation
			Perform serological testing for pathogen-specific antibodies
			Test for mediators, metabolites and potential biomarkers
SERIAL CLINICAL DATA	Complete ISARIC CORE CRF module 2 (serial) and module 3 (at discharge/death)	Site file (paper) REDCap (electronic) See section 3.7	Clinical data
ADDITIONAL SAMPLES FOR POPULATION PHARMACOKINETICS STUDIES	Blood sample in EDTA or fluoride oxalate tubes	Centrifuge 1500g for 10mins at 4°C. Plasma (2 aliquots -80°C*)	Test for drug levels. Store aliquot for other studies.

*freeze at -80°C where possible, or at least at -20°C. Further details of processing are provided in Table 9.

3.5.2 Tier 0

Collect data using CRF only. ***As you are collecting CRF data only and not biological samples, ethical approval or consent is generally not required.***

3.5.3 Tier 1

A single sample set is obtained at, or as soon as practical after, recruitment ('**recruitment sample set'**). Collect data using CRF.

3.5.4 Tier 2

A '**recruitment sample set'** is obtained followed by schedule-dependent '**serial sample sets'** and one '**convalescent sample set'** are obtained. Collect data using CRF. Example Tier 2 sampling schedules are shown below and all schedules are in Appendix 2.

Table 2: Tier 1 sampling schedule.

		Serial samples.															
	Recruitment	Week 1						Week 2								Further samples	Convalescent samples
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Weekly until max 100 days	3 months and 6 months after recruitment
>40kg	**R**																
20 to 40kg	**R**																
10 to 20kg	**R**																
4 to 10kg	**R**																
<4kg	**R**																
Sample priority*	**1**																

Table 3: Tier 2 sampling schedule 4.

		Serial samples.															
	Recruitment	Week 1						Week 2								Further samples	Convalescent samples
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Weekly until max 100 days	3 months and 6 months after recruitment
>40kg	**R**		**S**						**S**								**C**
20 to 40kg	**R**		**S**						**S**								**C**
10 to 20kg	**R**		**S**						**S**								**C**
4 to 10kg	**R**		**S**						**S**								**C**
<4kg	**R**		**S**						**S**								**C**
Sample priority*	**1**		**2**						**3**								**4**

Table 4: Tier 2 sampling schedule 6.

		Serial samples.															
	Recruitment	Week 1						Week 2								Further samples	Convalescent samples
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Weekly until max 100 days	3 months and 6 months after recruitment
>40kg	**R**		**S**		**S**				**S**							**S**	**C**
20 to 40kg	**R**		**S**		**S**				**S**							**S**	**C**
10 to 20kg	**R**		**S**		**S**				**S**							**S**	**C**
4 to 10kg	**R**		**S**		**S**				**S**							**S**	**C**
<4kg	**R**		**S**		**S**				**S**							**S**	**C**
Sample priority*	**1**		**2**		**5**				**3**							**6**	**4**

Table 5: Tier 2 sampling schedule 10.

		Serial samples.															
	Recruitment	Week 1						Week 2								Further samples	Convalescent samples
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Weekly until max 100 days	3 months and 6 months after recruitment
>40kg	**R**		**S**		**S**		**S**		**S**		**S**		**S**		**S**	**S**	**C**
20 to 40kg	**R**		**S**		**S**		**S**		**S**		**S**		**S**		**S**	**S**	**C**
10 to 20kg	**R**		**S**		**S**		**S**		**S**		**S**		**S**		**S**	**S**	**C**
4 to 10kg	**R**		**S**		**S**		**P**		**S**		**P**		**S**		**P**	**S**	**C**
<4kg	**R**		**S**		**S**		**P**		**S**		**P**		**S**		**P**	**S**	**C**
Sample priority*	**1**		**2**		**5**		**7**		**3**		**8**		**10**		**9**	**6**	**4**

Key (refer to Table 1)**:**
R: recruitment sample set
S: serial sample set
P: pathogen-only sample set
C: convalescent samples

***In the event that local resource limitations require sampling frequency to decrease, samples will be prioritised as shown (1=highest priority). Serial sampling will stop when acute illness resolves, or a patient is discharged from hospital: next samples taken will be the blood sample at 3 months and 6 months post recruitment.**

Table 6: Sample volumes by patient weight.

Weight	Samples at recruitment (R)	Serial samples (S)	Convalescent samples	Total Volumes of blood taken
>40kg	9ml (3x3ml) EDTA blood 3ml blood in serum(clotted) tube 3ml blood in blood RNA tube Research pathogen samples	3ml EDTA blood 3ml blood in serum(clotted) tube 3ml blood in blood RNA tube Up to 3 additional 1ml samples in EDTA or fluoride oxalate tubes spread throughout dosing schedule for pharmacokinetic/pharmacodynamic studies. Research pathogen samples	3ml EDTA blood 3ml blood in serum(clotted) tube 3ml blood in blood RNA tube Research pathogen samples	Maximum any day: 15ml (0.38ml/kg) Maximum any 4 weeks: 96ml (maximum 2.4ml/kg)
20 to 40kg	6ml (3x2ml) EDTA blood	1ml EDTA blood 2ml blood in blood RNA tube	1ml EDTA blood 3ml blood in	Maximum any day: 12ml (0.6ml/kg)

	3ml blood in serum(clotted) tube 3ml blood in blood RNA tube Research pathogen samples	Up to 3 additional 0.5ml samples in EDTA or fluoride oxalate tubes spread throughout dosing schedule for pharmacokinetic/pharmacodynamic studies. Research pathogen samples	serum(clotted) tube 2ml blood in blood RNA tube Research pathogen samples	Maximum any 4 weeks: 42ml (maximum 2.1ml/kg)
10 to 20kg	2ml (2x1ml) EDTA blood 2ml blood in serum(clotted) tube 2ml blood in blood RNA tube Research pathogen samples	1ml EDTA blood 1ml blood in blood RNA tube Up to 3 additional 0.2ml samples in EDTA or fluoride oxalate tubes spread throughout dosing schedule for pharmacokinetic/pharmacodynamic studies. Research pathogen samples	1ml EDTA blood 1ml blood in serum(clotted) tube 1ml blood in blood RNA tube Research pathogen samples	Maximum any day: 6ml (0.6ml/kg) Maximum any 4 weeks: 23.6ml (maximum 2.36ml/kg)
4 to 10kg	1ml EDTA blood 1ml blood in serum(clotted) tube ml blood in blood RNA tube Research pathogen samples	1ml EDTA blood Up to 3 additional 0.2ml samples in EDTA or fluoride oxalate tubes spread throughout dosing schedule for pharmacokinetic/pharmacodynamic studies. Research pathogen samples	1ml EDTA blood 1ml blood in serum(clotted) tube Research pathogen samples	Maximum any day: 2ml (0.5ml/kg) Maximum any 4 weeks: 9.4ml (maximum 2.35ml/kg)
< 4kg	0.5ml EDTA blood 0.1ml blood in serum(clotted) tube ml blood in blood RNA tube Research pathogen samples	0.2ml EDTA blood Up to 3 additional 0.1ml samples in EDTA or fluoride oxalate tubes spread throughout dosing schedule for pharmacokinetic/pharmacodynamic studies. Research pathogen samples	0.2ml EDTA blood 0.2ml blood in serum(clotted) tube Research pathogen samples	Maximum any day: 0.8ml (~0.27ml/kg) Maximum any 4 weeks: 2.4ml (maximum 2.4ml/kg)
Research pathogen samples (all patients)	**Pathogen samples taken solely for research purposes:** In all SARI or respiratory infection patients: combined nose and throat swab, otherwise a throat swab or nasopharyngeal swab alone In all intubated patients with SARI or respiratory infection: endotracheal aspirate also where resources permit in a respiratory case: 1. Nasopharyngeal aspirate (NPA) OR (if NPA impossible) flocked nose and throat swab 2. Urine (up to 10ml in sterile universal container, if available) 3. Rectal swab or stool (up to 10ml in sterile universal container or stool specimen container, if available) 4. samples/swabs from infected sites or sores.			No patient will give more than 0.6ml/kg (>1% blood volume) on any one day, or more than 2.4ml/kg (approx 3% blood volume) in any four week period (MCRN recommendations).
Clinician-requested CSF	**Separate aliquot of Cerebrospinal fluid (CSF) collected solely for research purposes:** When a lumbar puncture is clinically-indicated and performed in an infant or older patient, **an additional sample of up to 5mls of CSF** will be collected in a separate universal sterile tube, provided it is deemed appropriate by the supervising clinician. The volume of CSF taken from a child younger than an infant			See table 7 (below) for guidance on total safe volumes of CSF to take at lumbar puncture

	will be at the discretion of the attending clinician. Any residual CSF from samples taken as part of routine clinical care will be collected and stored	
Clinician-requested pathogen samples (all patients)	Where possible, we will obtain an aliquot of any residual and unwanted sample volume from specimens that have been sent by clinicians for pathogen detection, including those obtained before recruitment to the study: urine; stool; respiratory tract samples (NPA, ETA, BAL, sputum, ENT swabs); cerebrospinal fluid	

3.5.4.1 For CNS infections only – residual cerebrospinal fluid from clinical sampling

If after recruitment a lumbar puncture is clinically indicated, an additional sample of up to 5mls (Table 7) will be collected in a universal sterile tube, provided it is deemed appropriate by the supervising clinician. Any residual CSF from samples taken as part of routine clinical care will be collected and stored if available. This will allow:

- Extraction of RNA/DNA from causative pathogens and other circulating pathogens for molecular testing, genomic studies and virus isolation
- Serological testing for pathogen-specific antibodies
- Testing for mediators, metabolites and potential biomarkers

Table 7: Estimates of CSF production rate, total CSF volume and the safe recommended CSF volume taken at lumbar puncture for different age groups.
Taken from the British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system.

Age	Mean CSF production rate (mL/h)	Total CSF Volume (mL)	Safe CSF volume to take at LP (mL)
Adult (>18y)	22	150-170	Maximum: 15-17
Adolescent (11-18y)	18	120-170	Maximum: 12-17
Young child (1-10y)	12	100-150	Maximum: 10-15
Infant (>28d; <1y)	10	60-90	Maximum: 6-9
Term Neonate (≤28d)	1	20-40	Maximum: 2-4

3.5.5 Optional sub-studies

In addition to the tier and sampling schedule decided by the PI, optional sub-studies from Table 8 can be included.

Table 8: Optional sub-studies.

OPTIONAL SUB-STUDY	SAMPLE SET AND SAMPLE	PROCESSING/STORAGE	RATIONALE
(Each sub-study will only operate in a small minority of sites. Any site participating in a sub-study will alert staff to this fact in the TIER RECORD FORM at the front of the site file)			
PHARMACOKINETICS	ADD TO ALL SAMPLE SETS (R, S, and C) Blood sample in EDTA or fluoride oxalate tubes. Volumes >40kg: 3ml 20 to 40kg: 0.5ml 10 to 20kg: 0.2ml 4 to 10kg: 0.2ml < 4kg: 0.2ml	Separation and storage of plasma. (-80°C)	Test for drug levels. Store aliquot for other studies.
ENVIRONMENTAL TRANSMISSION	Air samples from within patient vicinity Swabs of environmental surfaces within patient vicinity		Establish routes of transmission
LARGE-VOLUME CONVALESCENT SAMPLING* (in a small number of selected patients in specific institutions)	Up to 240mls of blood in fully recovered patients	Separation and storage of plasma. Extraction of peripheral blood mononuclear cells.	Serology tests, development of products including international standards, cellular immunology, generation of monoclonal antibodies for research, diagnostic and therapeutic use
HUMORAL IMMUNE RESPONSE	Inclusion of oral (crevicular) fluid sampling with acute and convalescent sample sets	Determination of IgG and IgA.	Non-invasive determination of humoral immune response
SERIAL SEROLOGY*	Sample set obtained up to monthly for up to 3 years per weight schedule: 5-10mL clotted blood 2.5mL blood in RNA tube Oral crevicular fluid swab Throat swab in VTM Nose swab in VTM	See Table 9.	Quantify nature and duration of humoral immunity. T-cell and B-cell receptor sequencing.
SERIAL BAL DURING ECMO	120mL 0.9% saline BAL, performed on days 1, 3 and 9.	Centrifugation to obtain cell pellet and supernatant. Storage at -80°C.	Study host immune response, viral replication and co-infection

*separate consent forms are provided for these sub-studies which should be used *in addition to* the full consent form.

3.5.5.1 Serial bronchoalveolar lavage during extra-corporeal membrane oxygenation

In small numbers of patients with refractory respiratory failure due to SARI receiving extra-corporeal membrane oxygenation (ECMO) in a specialist centre, the opportunity exists to safely perform serial bronchoscopy for research purposes without the risk of impairing oxygenation (in contrast to bronchoscopy performed when oxygenation is dependent on mechanical ventilation). This is also safer for the operator since the patient can be paralysed and ventilation can be temporarily discontinued, reducing aerosol generation. Broncho-alveolar lavage specimens obtained in this context could be processed to allow analysis of viral load, bacterial or fungal co-infection, and host soluble immune mediators in the distal airway.

3.5.5.2 Large volume convalescent sampling

In a small number of patients (likely to be less than 10 patients for each emerging infection) there is a need for additional sampling after recovery from acute illness to enable generation of serological tests, setting of reference standards for serology, extraction and culture of peripheral blood mononuclear cells (PBMCs) for cellular immunology studies, and generation of monoclonal antibodies for research, diagnostic and therapeutic use. These studies are often extremely valuable in the global response to a new pathogen.

Immune cells, including monocytes, monocyte-derived macrophages, neutrophils and lymphocytes will be isolated from peripheral blood and studied immediately or following culture. Gene expression, protein synthesis and degradation, cytokine release and other functional studies will be measured in immune cells from cases and age- and sex- matched controls. Cells will be stored for future use and may be used in the generation of commercial products.

Patients who participated, with appropriate consent, in this study may be invited to provide additional samples under separate consent for this part of the study. All blood samples will be obtained by an experienced phlebotomist. Participants will be fully recovered, otherwise healthy individuals with no contraindications to blood donation, including:

- Infection with any blood borne diseases (e.g. HIV, Hepatitis B or Hepatitis C)
- Previous or current intravenous drug abuse
- Current anaemia
- Blood clotting disorders
- Current anticoagulant (blood thinning) drug therapy
- History of donations to the blood transfusion service (or any other donation) within the last 12 weeks.

Depending on the participant's weight, the following maximum volumes of blood will be obtained:

- >40kg: 240mls (6.0mls/kg)
- 20-40kg: 80mls (4.0mls/kg)

3.6 Enrolment Procedures for Patients

Patients who satisfy the inclusion/exclusion criteria and have given informed consent to participate directly, or have been consented by a parent/guardian or whose wishes have been declared by a consultee, or be it deferred, proxy or assent, will be enrolled to the study.

All patients will have clinical information collected either directly through examination including a review of medical, contact and travel history, or from available medical notes. Information will be recorded in the case report form.

At enrolment, sites with available resources will:

1. Separate and store an aliquot of all routine clinical samples taken at baseline/presentation including (as indicated) blood, cerebrospinal fluid (if CNS disease), infected sites/sores,

sputum, respiratory tract specimens, urine and stool or rectal swab. Any research pathogen samples which have not been taken for clinical care will be collected.

2. Take a blood sample (0.8 - 15ml dependent on weight).

The day of initial sample collection will be counted as Day 1. All study days will be counted from this point forward. Clinical information will also be collected on discharge.

During the one week of test activation for the internal pilot study, we will collect only anonymous data from patients that meet the selection criteria defined in Appendix 1.

See Appendix 3 for an example logistics guidance document for operationalising recruitment at study sites.

3.7 Case Report Form and Patient Numbers

Case Report Forms (CRFs) completed after site registration at https://redcap.medsci.ox.ac.uk/.

Patient numbers consist of a 3- or 5-digit site code and a 4-digit patient number. Local investigators should be assigned patient numbers 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. E.g. Outpatient ward will assign numbers from 0001 onwards. In-patient ward will assign numbers from 5001 onwards. The patient identification code is entered at the top of each and every sheet. For settings or circumstances in which resources are constrained, an abbreviated case report form is provided.

3.8 Follow-Up Procedures for Patients

Follow-up procedures (e.g. serial sampling) will be undertaken only when resources allow according to Tier 2 sampling outlined in Section 3.5. Follow-up procedures will only be undertaken if appropriate biological safety measures can be maintained. Sites unable to perform daily follow-up as described below may reduce the frequency of follow-up procedures or exclude follow-up if necessary.

Regular clinical assessment and sampling will follow local guidelines. All patients will have further clinical information recorded in the case report form to record events and treatment experienced during hospitalization and outcome. Some of the samples described below will coincide with clinical management. The number of these will depend on the applicable care guidelines, the treating physician and the health of the patient.

Procedures for serial sampling as shown in table 1

Collection of clinical information, blood sample (volume dependent on weight - see Table 6), urine, sputum (if possible), stool or rectal swab, infection site and respiratory samples.

Procedures for pathogen-only serial sampling as shown in table 1

Collection of clinical information, urine, sputum (if possible), stool or rectal swab, infection site and respiratory samples.

Once acute illness is resolved, or once patients are discharged from hospital, sampling will discontinue until the 3 month and 6-month visits. All patients will be asked to return for a convalescent visit and blood sample at 3 months and 6 months post recruitment.

Resolution of acute illness is defined as: Clearance of pathogen from appropriate samples, return of systemic inflammatory response to considered 'normal' values and one of: 1) recovery from organ failure(s)/need for organ support, 2) resolution of the presenting complaint(s), 3) return to life-style prior to illness.

3.8.1 Procedure for additional sampling for pharmacokinetic/ pharmacodynamics studies.

[Where a pharmacokinetic study is run concurrently with this protocol] Up to 3 additional samples may be obtained at intervals spread throughout the dosing schedule (ideally including one sample immediately before a dose) of the drug being studied. The spread of the samples can be determined on a case-by-case basis to fit in with clinical care; provided the precise times of administration and the precise time of blood sampling are recorded, samples taken at any time will be of use for analysis using population pharmacokinetic methods.

Samples will be taken in conjunction with those required for clinical care in order to minimize research-specific intervention. Samples taken outside of the scheduled days can be used for study testing and should be recorded with the accurate sampling date.

For respiratory samples for SARI patients, a combined nose and throat swab will be collected from all patients. If a patient is intubated an endotracheal aspirate will also be collected. Also, where resources permit, a Nasopharyngeal aspirate (NPA) OR (if NPA impossible) a flocked nose and throat swab sample will also be collected. A sputum sample will be collected when a productive cough is present, and the patient is able to produce one.

Infection site samples are samples of tissue or fluid or swabs taken from infected sites such as an inflamed oropharynx or inflamed conjunctiva.

Residual volumes of all other samples taken for clinical care will be stored.

3.9 Withdrawal of Patients

Patients enrolled to the study whose illness is subsequently confirmed to be the result of infection with a pathogen which is not relevant to the objectives of this study, and who have no indication or likelihood of co-infection with a relevant pathogen, will be withdrawn. No further follow-up will be conducted.

Patient autonomy to withdraw from the study at any time must be respected

4. Specimens and Laboratory Analysis

4.1 Specimen Sampling, Storage Procedures and Transport

Appropriate selection and timely collection of high-quality specimens, proper storage procedures and comprehensive diagnostic testing will ensure the quality of data.

Local hospital protocols will be used to collect and handle specimens. Guidance on the collection of specimens from patients with emerging infections can be found on the WHO website.

In dealing with novel pathogens where little is known about transmissibility and/or virulence, great care must be exercised to ensure the safety of hospital staff and other patients. Strict adherence to collection protocols, biosafety and adequate personal protective equipment (PPE) is essential. Biosafety procedures will be as per local policy/guidance, will be in keeping with any national and/or international regulations, and will be applied to the collection, storage, transfer and laboratory handling of research samples.

Emerging or remerging pathogens may be classified as requiring BSL2, BSL3 or BSL4 safety management and guidelines should be consulted as per hospital protocol. In addition, an emergent agent may also be risk assessed as posing a threat to animal health, and may be regulated under the specified animal pathogens order as well. Laboratories planning to participate in the study should consider how they would fulfil a requirement to handle research samples in addition to clinical samples.

All samples collected must be labelled according to local hospital policy with appropriate identification (full patient identifiers) and hazard labelling and ideally marked 'ISARIC RESEARCH' with a solvent resistant marker. Samples will be processed as per Table 9 'Processing/storage'. Testing that cannot be done in country may be exported. Samples sent to laboratories other than those listed in the Protocol and Material Transfer Agreement will be anonymised with unique coded identifiers to protect the identity of the patient. National guidance must be adhered to for the transport of specimens

Clinical samples will be labelled with standard hospital information, including the date and sent with the standard lab request forms.

Residual volumes available after clinical and research testing is complete will be retained by the lab.

4.2 Additional Data Collection – Pharmacokinetic/Pharmacodynamics Studies

Where local resources allow, additional information and samples will be sought during treatment with antimicrobial or immunomodulatory therapies in order to investigate the relationship between dose and plasma drug concentrations, to determine the variability in pharmacokinetics in patients receiving these drugs, and to identify the key pharmacokinetic drivers of pharmacodynamic outcomes (measured using pathogen load, inflammatory markers, illness severity scores or drug toxicity). This information will be collected on the pharmacokinetics record form, and includes both the precise (to the minute) times of drug administration and the precise time of blood sampling.

Samples obtained will be split as required for pharmacokinetic/pharmacodynamic analysis of each antimicrobial or immunomodulatory therapy prescribed; the volume of blood to be drawn will not increase.

4.3 Sample Processing

Samples will only be processed if authorised biological containment and laboratory facilities appropriate to the relevant pathogen are available.

Table 9: Initial processing of biological samples

SAMPLE	INITIAL PROCESSING	ALIQUOTS	ULTIMATE USE
Blood (serum)	Centrifuge 1500g for 10mins.	Supernatant: freeze at -80°C*	Serology
		Supernatant: freeze at -80°C*	Circulating mediators by multiplex cytokine/chemokine assays and proteomics
		Supernatant: freeze at -80°C*	Mediators/proteomics other assays
Blood (EDTA)	Centrifuge 1500g for 10mins ideally at 4°C.	Supernatant: freeze at -80°C*	Serology
		Supernatant: freeze at -80°C*	Circulating mediators by multiplex cytokine/chemokine assays
		Supernatant: freeze at -80°C*	Other studies (eg pharmacokinetics/ pharmacodynamics)
		Cell pellet: freeze at -80°C*	High-throughput genotyping and/or high coverage genome sequencing
Blood (RNA tube)	No processing required. Freeze at -20°C	Where possible, freeze at -80°C* after 24hrs	Microarray analysis and/or RNA seq analysis of host and pathogen RNA
CSF (if acquired)	**Do not process at site**	Aliquot if safe to do so into 3 aliquots Freeze at -80°C*	Pathogen detection, quantification, viral genome sequencing and isolation
			Serology
			Circulating mediators by multiplex cytokine/chemokine assays and proteomics
Pathogen samples	**Do not process at site**	Freeze at -80 °C*	Pathogen detection, quantification and viral genome sequencing and isolation.

*freeze at -80°C where possible, or at least at -20°C. If necessary (e.g.. weekends) store in refrigerator until processing.

4.4 Use of Stored Samples

Access to samples for additional analyses will be governed by a committee comprising the clinical lead investigators and scientific investigators for this study (the Data and Materials Access Committee), in collaboration with the individual recruiting sites. Linked anonymised data generated during the course of these studies may be shared between investigators. Each local site will hold their own data.

Where possible and within the constraints of international law and specific requirements of local ethical and institutional management approvals, data will be shared centrally within one master database held in Oxford, which will be fully compliant with standard data management processes and local regulations. This database will be held on servers. Access to data for outside investigators will be reviewed by the data and materials access committee.

Samples will only be stored in containment facilities that have appropriate biological safety measures in place and have received necessary authorisation to store samples (according to national regulations for the pathogen being studied).

4.5 Future Use of Samples

Samples collected will be used for the purpose of this study as stated in the protocol and consented for future use. The standard consent form will request consent from subjects for sample storage and/or export of specific samples to collaborating institutions for investigations that cannot be performed locally. Any proposed plans to use samples other than for those investigations detailed in this protocol will be submitted to the relevant ethics committees prior to any testing. Collaborating centres must have appropriate biological safety measures and regulatory approvals in place in order to receive samples.

Any database detailing clinical data will only identify participants by a participant number. Participant names or any other identifying details will NOT be included. Data may be used alone or in combination with data from related studies in secondary analyses. Data is hosted on REDCap, a secure web platform for building and managing online databases and surveys.

5. Medical Management and Safety Reporting

5.1 Medical Management

Medical management will be according to standard of care at the treating site and not a part of this research protocol. Research interventions include only collection of clinical information and specimens and therefore adverse event reporting is not applicable as there is no intervention.

6. Data Management

6.1 Data Collection

Clinical and laboratory data will be collected throughout the acute illness period according to local resources. Priority at all times will be given to the collection of clinical information. Research data will be integrated as much as possible with information available from hospital and regulatory files. Clinical data will be collected locally with the relevant CRF for SARI, VHF, CNS or other emerging infections of public health interest will be completed by a study staff as appropriate. The data will be anonymised at site and a study number issued.

6.2 Data Management

When available, data collected by staff at each site will be submitted electronically to a protected online database. Anonymised data may be entered by study staff in order to minimize the workload on site clinical staff. Quality checks will be built into the data management system and there will be quality control checks of critical data points entered into the CRFs to ensure standardization and validity of the data collected. Patients' identities will be protected and their information held securely. The records kept will not include any information that allows patients to be identified.

For the Clinical Characterisation Protocol 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 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 (enrolment log) is maintained locally and is not to be transferred to any other location. The sites will compile an enrolment log including the patient's name, date of birth, hospital identification number and unique study number. Subsequent data will be identified by the unique patient study number only. The enrolment log and study data will be kept separately.

6.3 Data Access and Data Sharing

This study will adhere to the research policies of ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium, www.isaric.org). A fundamental principle of this work is that clinical investigators contributing to research efforts, often in extremely difficult circumstances, must be given full recognition for their efforts and the opportunity to access data and samples. Ownership of any data transferred to the eCRF and centralized database 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.

Data and results from central laboratory analysis for individual patients will be available to the clinicians looking after those patients as soon as possible. Often, this may not be in time to affect treatment decisions. Research data will be shared with public health authorities as needed.

6.4 Data Quality

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

- A detailed data dictionary will define the data to be collected on the case report form;
- 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;

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.

6.4.1 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.

7. Ethical Considerations

This study is to be conducted during a disease outbreak or presentation of cases of disease of public health interest. This is a challenging research situation because this falls in the area between clinical care, public health and clinical research (WHO Ethical Review in Disease Outbreak Expert Meeting 2009). Normally research activities are defined by anything conducted outside standard clinical care. In these situations, there may be no definitive standard guidelines or treatment protocols and therefore there is often little difference between what can benefit the patients and what is very important for building knowledge on the pathogenesis of the disease to guide future treatment and management.

Medical management of participants in this study must never be compromised by study procedures. At all times, priority will be given to samples required for medical management. Research sampling should never compromise the quantity or quality of samples taken for medical management, nor create a significant diversion for clinical teams from the day-to-day care of the patients.

7.1 Regulations, Guidelines and Ethical Review

This study will be conducted in compliance with the principles set out in the Declaration of Helsinki. Where applicable, the principles of Good Clinical Practice (ICH 1996) and other applicable regulations and guidelines will be used to guide procedures and considerations.

This protocol will be reviewed and approved by the ethical and regulatory review boards required by the recruiting site and the study sponsor. No patients will be enrolled until all approvals have been obtained for the applicable site.

7.2 Informed Consent

Consent forms will be provided in plain English. Illiterate participants will have the consent form read in the presence of a witness, who will sign to verify the accurate reading of the form and agreement of the participant. For participants who cannot understand the language of the available forms, verified translations will be made when possible. If it is not possible to prepare a translation in a required language, verbal translation of the document and the consent discussion (if required) will be used. In this case, the translator may act as the witness for consent and sign the consent form so that patients who cannot read the language of the forms are not excluded from this research.

In the case of adult participants who are unable to give informed consent due to mental or physical status, the wishes of the participant may be declared by an appropriate consultee according to the site policy on obtaining consent for medical procedures. If, during the course of the study, the participant's status changes such that they are able to consider consent independently, informed consent must be discussed and obtained.

Parents or guardians of children under the age of 16 years old will give consent for their child. Study staff obtaining consent will consider the ability of the child to understand the principles of the study and will discuss the study with the child in age appropriate language. Where appropriate, children will be invited to give assent, which will be recorded on the informed consent form. The right to withdraw at any time without negative impact will be reinforced with the child and their parent/guardian. Should the UK rules on consent by young people for research purposes alter during the period of this study to allow consent by competent minors, then these new rules will be applied to this study without further amendment.

A copy of the informed consent form will be given to the person who gives consent.

7.3 Alternatives to Participation and Withdrawal

Prospective participants are freely able to decline participation in this study or to withdraw from participation at any point without suffering any implied or explicit disadvantage. All patients will be treated according to standard practice regardless of if they participate.

7.4 Risks to Participants

Inconvenience.

Participation in this research study poses a minimal risk of inconvenience through household visits and attendance of follow-up visits. Appropriate compensation for travel costs to attend follow-up visits and for time of attending visits will be given according to the standard policies of the sponsor.

Phlebotomy.

Participants may have blood drawn more often than is required for standard care. Phlebotomy can be associated with pain at the draw site and rarely with infection. Daily blood draw volumes have been restricted according to weight so that combined clinical and research sampling is within recommended limits. Discomfort will be minimized by having expert staff obtain blood samples, and by combining research sampling with routine clinical sampling, where possible, which normally occurs daily in acutely unwell patients in hospital.

Discomfort of respiratory swabs.

Collecting respiratory swabs may be cause transient discomfort. Discomfort and risk will be minimized by using experienced clinical staff at each site, and samples will be taken at the same time as clinical samples in order to minimize these risks.

Discomfort of lumbar puncture

Collection of cerebrospinal fluid with lumbar puncture will only be performed if clinically indicated, as decided by the responsible physician. Clinical investigations are the priority, with any remaining sample collected for use in research. Guidance on the safe recommended daily total volume of CSF to take in different age groups is provided (Table 7). Lumbar puncture can be associated with discomfort at the site of needle insertion, headache, and rarely bleeding or infection.

Incidental findings in genetic testing.

This study includes genetic testing to identify host genetic variants associated with disease progression or severity. There is a very small chance that these tests may result in the incidental discovery of information that is relevant to the participant's health. Since the samples will be analysed anonymously in batches, and generally in non-clinical laboratories with investigational

techniques, we will not attempt to identify and inform participants of any results from genetic tests. If we were to do so, there would be a considerable risk of accidental harm in the form of unnecessary anxiety and distress.

Specific risks for VHF patients

Participants with VHF may be at increased risk of bleeding from venepuncture sites. The decision to perform venepuncture for research purposes will only be performed following discussion with the attending clinician and only if venepuncture is deemed not to pose unacceptable risk to the patient and/or staff. When at risk venepuncture will be minimised by limiting research venepuncture to coincide with clinical venepuncture.

7.5 Benefits to Participants

There will be no direct benefit to research participants. The study may include biological sampling in addition to sampling required for medical management. The results of the tests done on these samples may not contribute to improving the participant's health. The results of this study will not be available in time to contribute to the participant's care. Where possible, test results with potential relevance to patient care will be informed to the participant and/or treating doctor. The feasibility of this will depend on local resources. Some assays cannot immediately benefit the patient because data will need to be pooled with others, or because the assays take time.

7.6 Participation in Other Research Studies / Co-enrolment

Particularly in the case of emerging infections, it is likely that other research projects, including clinical trials, will also recruit participants in this study. In fact, it is important that they do so, and great effort has been expended to ensure that this observational study is compatible with, and complementary to, other possible research projects.

7.7 Confidentiality

This study will be conducted by clinical staff and those involved in the study will ensure that each study participant's privacy and confidentiality is maintained. Participants will not be identified in any published reports of this study. All records will be kept confidential to the extent provided by international and local law. All laboratory specimens, evaluation forms, reports, study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party.

Paper and electronic medical records may be accessed during the study to confirm, verify or complete clinical information provided in the case report form.

Site files will at all times be accessible only to clinical and research staff. Consent will be sought for investigators to access patient data. Local research staff will access personal information, but all data will be pseudo-anonymised before transfer by eCRF.

It is important that data generated now is not destroyed unnecessarily, since they will be of considerable potential value to future generations faced with similar outbreaks of infectious disease. Electronic data and electronic copies of paper documents will be stored for at least 5 years.

7.8 Custody of Data and Samples

Custody of site data will remain with the responsible physician at the site. Samples may be shipped (depending upon pathogen of interest) to a reference laboratory for analysis as approved by the appropriate ethics/institutional review committee. Any residual sample will remain in the custody of the site until use can be decided upon.

7.9 Additional Ethical Considerations

Recruitment of critically ill patients who are not able to consent. This is a ubiquitous problem in acute and critical care research and there is a clear legal framework under which these patients may be recruited to research studies. In all cases, efforts will be made to obtain informed consent from patients early in the course of illness, before critical illness interferes with their capacity to make decisions and to confirm consent at the earliest point in recovery. This principle applies equally to adults and children.

Perceived coercion because of individual responsibilities to society, and the implications of this research for public health. We are sensitive to the fact that some patients or their representatives may feel under an unusually strong moral obligation to participate given the nature of this research

and the wide, and often inaccurate, publicity surrounding emerging infections. In view of this, we have tried to make both the potential benefits and limitations of this simple observational study clear in the information sheet. In the informed consent form we also stress that participation is entirely voluntary and there is no penalty of any kind for declining to join the study.

Balance between public health and research. Patients with emerging infections are commonly the subject of public health investigations. The work proposed here is research and will be clearly presented as such. There is no primary gain to the patient from participating. In designing and describing this research we are clear that, in accordance with the guiding principles of Good Clinical Practice, the needs and autonomy of the individual are paramount and the potential benefits to wider society do not take precedence.

Risks to clinical and research staff treating the participants. Staff who enrol, examine and take samples from study patients are at risk of infection. Care of study participants will require increased sampling and contact frequency added to normally heavy clinical workloads. All staff must be trained in recognised infection control measures and have ready access to appropriate personal protective equipment. In collaboration with the public health authorities, there will be on-going communication with hospital staff to ensure the appropriate training is given, to support the work and to ensure that there is no excess burden on the health system. Where appropriate, dedicated research staff will be available to support the study activities.

7.10 Scientific and Peer Review

The proposed research is the product of several years of discussion within a group of international experts who were brought together following the 2009 influenza pandemic to plan the global research response to future severe and emerging infections: the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC). ISARIC working group 3 (genomics, pathogenesis and pharmacology) comprised senior clinical scientists from 5 continents working together to promote and harmonise observational research during outbreaks of severe infectious disease.

Appendix 1: Test Activation Guidance – Internal Pilot Study

For maintenance of the Clinical Characterisation Protocol. **To be used in combination with this protocol.**

Appendix 2: Full biological sampling schedules (Tier 1 and Tier 2 schedule 2-11)

An online interactive presentation of the information contained in the following tables is available at: https://isaric.net/ccp/

Tier 1 (1 sample set)

		Serial samples.															
	Recruitment	Week 1						Week 2								Further samples	Convalescent samples
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Weekly until max 100 days	3 months and 6 months after recruitment
Any weight	R																
Sample priority	1																

Tier 2, schedule 2

		Serial samples.															
	Recruitment	Week 1						Week 2								Further samples	Convalescent samples
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Weekly until max 100 days	3 months and 6 months after recruitment
Any weight	R		S														
Sample priority	1		2														

Tier 2, schedule 3

		Serial samples.															
	Recruitment	Week 1						Week 2								Further samples	Convalescent samples
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Weekly until max 100 days	3 months and 6 months after recruitment
Any weight	R		S						S								
Sample priority	1		2						3								

Tier 2, schedule 4

		Serial samples.															
	Recruitment	Week 1						Week 2								Further samples	Convalescent samples
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Weekly until max 100 days	3 months and 6 months after recruitment
Any weight	R		S						S								C
Sample priority	1		2						3								4

Tier 2, schedule 5

		Serial samples.															
	Recruitment	Week 1						Week 2								Further samples	Convalescent samples
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Weekly until max 100 days	3 months and 6 months after recruitment
Any weight	R		S		S				S								C
Sample priority	1		2		5				3								4

Tier 2, schedule 6

		Serial samples.															
	Recruitment	Week 1						Week 2								Further samples	Convalescent samples
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Weekly until max 100 days	3 months and 6 months after recruitment
Any weight	R		S		S				S							S	C
Sample priority	1		2		5				3							6	4

Tier 2, schedule 7

		Serial samples.															
	Recruitment	Week 1						Week 2								Further samples	Convalescent samples
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Weekly until max 100 days	3 months and 6 months after recruitment
>40kg	R		S		S		S		S							S	C
20 to 40kg	R		S		S		S		S							S	C
10 to 20kg	R		S		S		S		S							S	C
4 to 10kg	R		S		S		P		S							S	C
<4kg	R		S		S		P		S							S	C
Sample priority	1		2		5		7		3							6	4

Tier 2, schedule 8

		Serial samples.															
	Recruitment	Week 1						Week 2								Further samples	Convalescent samples
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Weekly until max 100 days	3 months and 6 months after recruitment
>40kg	R		S		S		S		S		S					S	C
20 to 40kg	R		S		S		S		S		S					S	C
10 to 20kg	R		S		S		S		S		S					S	C
4 to 10kg	R		S		S		P		S		P					S	C
<4kg	R		S		S		P		S		P					S	C
Sample priority	1		2		5		7		3		8					6	4

Tier 2, schedule 9

		Serial samples.															
	Recruitment	Week 1						Week 2								Further samples	Convalescent samples
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Weekly until max 100 days	3 months and 6 months after recruitment
>40kg	R		S		S		S		S		S				S	S	C
20 to 40kg	R		S		S		S		S		S				S	S	C
10 to 20kg	R		S		S		S		S		S				S	S	C
4 to 10kg	R		S		S		P		S		P				P	S	C
<4kg	R		S		S		P		S		P				P	S	C
Sample priority	1		2		5		7		3		8				9	6	4

Tier 2, schedule 10

		Serial samples.															
	Recruitment	Week 1						Week 2								Further samples	Convalescent samples
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Weekly until max 100 days	3 months and 6 months after recruitment
>40kg	R		S		S		S		S		S		S		S	S	C
20 to 40kg	R		S		S		S		S		S		S		S	S	C
10 to 20kg	R		S		S		S		S		S		S		S	S	C
4 to 10kg	R		S		S		P		S		P		S		P	S	C
<4kg	R		S		S		P		S		P		S		P	S	C
Sample priority	1		2		5		7		3		8		10		9	6	4

Tier 2, schedule 11

		Serial samples.															
	Recruitment	Week 1						Week 2								Further samples	Convalescent samples
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Weekly until max 100 days	3 months and 6 months after recruitment
>40kg	R	P	S	P	S	P	S	P	S	P	S	P	S	P	S	S	C
20 to 40kg	R	P	S	P	S	P	S	P	S	P	S	P	S	P	S	S	C
10 to 20kg	R	P	S	P	S	P	S	P	S	P	S	P	S	P	S	S	C
4 to 10kg	R	P	S	P	S	P	P	P	S	P	P	P	S	P	P	S	C
<4kg	R	P	S	P	S	P	P	P	S	P	P	P	S	P	P	S	C
Sample priority	1	11	2	11	5	11	7	11	3	11	8	11	10	11	9	6	4

Key

R: recruitment samples including pathogen samples

S: serial samples including pathogen samples

P: research pathogen samples only

C: convalescent samples

In the event that local resource limitations require sampling frequency to decrease, samples will be prioritised as shown (1=highest priority). Serial sampling will stop when acute illness resolves, or a patient is discharged from hospital: next samples taken will be the blood sample at 3 months and 6 months post recruitment.

Appendix 3: Example logistics guidance document for recruiting sites

ISARIC/WHO Clinical Characterisation Protocol UK (Scotland)

Recruitment Procedures for FRONTLINE CLINICAL RESEARCH STAFF

A virtual site visit is available at **https://isaric.net/4c/virtual_site_visit**

Aim: recruit hospitalised cases of *confirmed* COVID-19, as early as possible.

Consent: once the form is signed by a participant it is hazardous. To record consent, we suggest an independent witness observes the completed form then signs a fresh copy outside of the isolation area. Telephone proxy consent is acceptable if relatives are unable to attend the hospital.

Sampling pack will be sent from [**hq_contact_details**]. This will contain blood RNA tubes, "SAM" strips for nasal sampling, "Oracol" swabs for oral fluid collection, barcode labels and CatB shipment containers.

Obtain samples according to the schedule. You can find out which tier you are operating at in the front page of the site file.

*If you have capacity to recruit at **TIER 2**:*

Day	**1**	2	**3**	4	5	6	7	8	**9**		**28 days after recruitment**
Samples	**R**		**S**						**S**		**C**
Sample priority	1		2						3		4

R: recruitment sample; S: serial sample; C: convalescent sample.

If for any reason a sample cannot be collected on a given day, collect at the next opportunity.

If unable to collect all planned samples, 'sample priority' denotes the relative priority of each set of samples.

If patient is discharged before day 9, the day 9 sample set can be omitted.

*Or if your centre is recruiting at **TIER 1**:*

Day	**1**	2	3	4	5	6	7	8	9		28 days after recruitment
Samples	**R**										
Sample priority	1										

Case report form data should be entered electronically at **https://ncov.medsci.ox.ac.uk/** using the REDCap platform. Complete the *core form* on day 1, the *daily form* on alternate days thereafter and the *outcome form* on discharge/death.

OBTAINING SAMPLES

Prior to donning PPE and entering isolation, label sample collection containers as follows:

(i) 5 digit site code + 4 digit patient code (see below) – using a solvent resistant marker
(ii) "ISARIC" – using a solvent resistant marker
(iii) unique barcode label **(not for clotted or EDTA blood tubes)**

Ensure labels do not cover the whole tube: a clear window into the full length of the tube is essential for processing.

All samples should be double-bagged after collection and handled per local clinical and laboratory procedures. PATHOGEN samples should be doubled bagged separately from the BLOOD samples. This is because PATHOGEN samples will go straight to freezer storage without further handling to comply with PHE Guidance, while some BLOOD samples will require processing before storage.

The 'Transport of Samples' form should be filled out for each sample set with *study number*, *collection date*, *timepoint*, *samples obtained* and the *unique barcodes* corresponding to each sample (stick in copy of barcode sticker).

Biological samples to collect

Weight	Samples at recruitment (R)	Serial samples (S)	Convalescent samples (C)
>40kg	• **9ml** (3x3ml) EDTA blood • 3ml clotted blood • 3ml blood in RNA tube • Oral Fluid (Oracol swab) • Research pathogen samples	• **3ml** EDTA blood • 3ml clotted blood • 3ml blood in RNA tube • Oral Fluid (Oracol swab) • Research pathogen samples	• 3ml EDTA blood • 3ml clotted blood • 3ml blood in RNA tube • Oral Fluid (Oracol swab) • Research pathogen samples
20 to 40kg	• 6ml (3x2ml) EDTA blood • 3ml clotted blood • 3ml blood in RNA tube • Oral Fluid (Oracol swab) • Research pathogen samples	• 1ml EDTA blood • 2ml blood in RNA tube • Oral Fluid (Oracol swab) • Research pathogen samples	• 1ml EDTA blood • 3ml clotted blood • 2ml blood in RNA tube • Oral Fluid (Oracol swab) • Research pathogen samples
10 to 20kg	• 2ml (2x1ml) EDTA blood • 2ml clotted blood • 2ml blood in RNA tube • Oral Fluid (Oracol swab) • Research pathogen samples	• 1ml EDTA blood • 1ml blood in RNA tube • Oral Fluid (Oracol swab) • Research pathogen samples	• 1ml EDTA blood • 1ml clotted blood • 1ml blood in RNA tube • Oral Fluid (Oracol swab) • Research pathogen samples
4 to 10kg	• 1ml EDTA blood • 1ml clotted blood • 1ml blood in RNA tube • Oral Fluid (Oracol swab) • Research pathogen samples	• 1ml EDTA blood • Oral Fluid (Oracol swab) • Research pathogen samples	• 1ml EDTA blood • 1ml clotted blood • Oral Fluid (Oracol swab) • Research pathogen samples
< 4kg	• 0.5ml EDTA blood • 0.1ml clotted blood • 0.5ml blood in RNA tube • Oral Fluid (Oracol swab) • Research pathogen samples	• 0.2ml EDTA blood • Oral Fluid (Oracol swab) • Research pathogen samples	• 0.2ml EDTA blood • 0.2ml clotted blood • Oral Fluid (Oracol swab) • Research pathogen samples
PATHOGEN SAMPLES MUST BE DOUBLE BAGGED SEPERATELY FROM BLOOD SAMPLES. THESE ARE: 2. Throat swab in viral transport medium (VTM) 3. Nasal SAM strip* 4. Nasopharyngeal aspirate (NPA) in universal container OR (if NPA impossible) flocked throat swab in VTM 5. In all intubated patients with SARI or respiratory infection: endotracheal aspirate in universal container 6. Urine (~10ml in sterile universal container, if available) 7. Rectal swab (in VTM) or stool (~10ml in sterile universal container/stool specimen container, if available)			

*A video demonstrating correct use of nasal SAM strips can be found here: **www.jove.com/video/56413**

Sample identifiers

All data records entered on the REDCap system must be anonymised using a **five-digit site code** then **sequential four-digit patient number** e.g. 0001 and so on.

Local sample log

Please maintain an electronic log of samples obtained (patient study number, sample type, date obtained, timepoint)

Sample types

Clotted blood
(gold Vacutainer or brown Monovette)
Provided by site

EDTA blood
(purple Vacutainer or red Monovette)
Provided by site

Blood in RNA tube
(Tempus tube)
Provided in recruitment pack

Nasal SAM strip
(Synthetic absorptive matrix)
Provided in recruitment pack

Saliva
(Oracol S14 Plus swab)
Provided in recruitment pack

Nasopharyngeal, throat or rectal swabs
(swab in virus transport medium) Provided by site

Respiratory secretions and urine
(universal container)
Provided by site

Stool
(universal container)
Provided by site

For practical or logistic questions please contact Clark Russell

The Roslin Institute, University of Edinburgh

clark.russell@ed.ac.uk

ISARIC/WHO Clinical Characterisation Protocol UK (Scotland)

Information for LABORATORY STAFF

Processing and storage of samples at site laboratory

Sample	Instructions for site laboratory
Pathogen samples[a] **Nasal SAM strips Oracol swabs**	**No processing required. Do not open bags.** Store at -80°C[b]
Clotted blood	Centrifuge 1500g for 10mins, ideally at +4°C. → **serum** (3x 1mL aliquots; store -80°C[b])
EDTA blood	Centrifuge 1500g for 10mins, ideally at +4°C. → **plasma** (3x 1mL aliquots; store -80°C[b]) → **cell pellet** (1x 1mL aliquot; store -80°C[b]) leave the cell pellet in the EDTA tube and store -80°C[b]
Blood in Tempus RNA tube	**No processing required.** Freeze at -20°C; transfer to -80°C after 24h where possible.

[a]Pathogen samples: swabs in VTM, respiratory secretions, urine or stool.

[b]Freeze at -80°C where possible, or at least at -20°C.

Samples may be stored at +4°C out of hours and at weekends prior to processing and freezing.

Aliquots must be stored in screw-cap vials, not flip-top tubes.

Label aliquots with:

(i) 5 digit site code + 4 digit patient code – using a solvent resistant marker
(ii) "ISARIC" – using a solvent resistant marker
(iii) **"S"** = serum; **"P"** = plasma; **"C"** = cell pellet – using a solvent resistant marker
(iv) unique barcode label

Please do not label samples with any patient identifiable information.

Specimen handling

PHE have issued guidance on appropriate biosafety levels for handling specimens from patients with COVID-19: https://www.gov.uk/government/publications/wuhan-novel-coronavirus-guidance-for-clinical-diagnostic-laboratories/wuhan-novel-coronavirus-handling-and-processing-of-laboratory-specimens

- **Section 5.1** Processing of respiratory tract specimens, faecal specimens, urine specimens, and tissue specimens in which virus has not been inactivated should be conducted at BSL3. No such processing is required for this protocol. **These samples should remain double bagged and frozen pending transport to the MRC-University of Glasgow Centre for Virus Research.**
- Section 5.2 **Accordingly, processing of whole blood, including aliquoting of serum and plasma can be conducted at BSL2**, as long as it is consistent with the terms of the local risk assessment.

- Section 6 **Manual centrifugation of specimens with infectious potential must be performed using sealed centrifuge rotors or sample cups. Rotors or cups should be loaded and unloaded in a Microbiology Safety Cabinet.**

Thus, blood from COVID-19 patients participating in the CCP-UK study may be spun and aliquoted in usual BSL2 laboratories.

Preparation of samples for onward transport

PATHOGEN samples should already be labelled, double-bagged, and frozen. Frozen **BLOOD** samples (RNA tube, 6 aliquots and EDTA cell pellet) should be double bagged together. BLOOD and PATHOGEN samples should be placed together into the sealable UN3373 compliant plastic pod and frozen. We suggest for convenience all samples are stored and frozen in this pod prior to collection when the pod should be placed in the cardboard container supplied with it. Please ensure that the outer surfaces of the pods are decontaminated with suitable disinfectant (eg 70% IMS or 1% Virkon) prior to packing into the cardboard container.

It is a legal requirement that each shipment includes a **list** placed between the secondary container and outer packing listing the summary details of each pod. This is a legal requirement under the Carriage of Dangerous Goods and Use of Transportable Pressure Equipment Regulations 2009. Complete and include the ***Transport of Samples form*** with patient number, collection date and attach copies of each barcode used. The third copy of the barcode may be used for local records such as CRF or consent form if appropriate.

Label the outer transport container with the sender's and recipient's name and address. If pre-printed labels are not supplied the recipient details are as follows:

[**hq_contact_details**]