The effect of corticosteroids, antibiotics, and anticoagulants on the development of post-COVID-19 syndrome in COVID-19 hospitalized patients 6 months after discharge: a retrospective follow up study.

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Abstract

Objective: To assess the effect of commonly used drugs in the treatment of hospitalized COVID-19 patients on the development of post-COVID-19 syndrome
Methods: Data from patients hospitalized in Medisch Spectrum Twente with an COVID-19 infection was collected from two separate databases, the MST ISARIC database containing the in-hospital electronic health records of COVID-19 patients and the Post-COVID cohort database containing patient follow-up data of the same patients. The aforementioned databases were then merged to determine the association between patient treatment with corticosteroids, antibiotics or anticoagulants during the hospital stay and the development of post-COVID-19 syndrome 6 months after hospital discharge.
Results: A total of 123 patients had ISARIC data and 6 months follow-up data available and fit the inclusion criteria. Out of these patients, 33 patients (26.8%) had developed and were still affected by post-COVID-19 syndrome 6 months after hospital discharge. Multivariate analysis showed that patients treated with corticosteroids were associated with a significantly lower chance (OR 0.34, 95% CI -2.12 to -0.02) of developing post-COVID-19 syndrome in contrast to antibiotics (OR 1.33, 95% CI -0.73 to 1.30) and anticoagulants (OR 0.60, 95% CI -1.66 to 0.63).
Conclusion: This study shows that corticosteroids have a significant protective effect on the development of post-COVID-19 syndrome in hospitalized patients. While anticoagulants also indicate a protective trend, this effect was not statistically significant. On the contrary, patients treated with antibiotics were shown to have increased chances of developing post-COVID-19 syndrome, although this effect was also not statistically significant.

Background

Severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2 which causes the Coronavirus disease (COVID-19) has taken the world by storm. The impact this virus has had on the global economy, education, travel, and healthcare has been astounding [1–3]. Although physicians initially had difficulty treating this disease, a more or less standardized treatment has been established. Corticosteroids and anticoagulants play an important role in this treatment and target key elements in the disease pathophysiology [4].

As higher incidences of venous thromboembolism (VTE) have been observed for COVID-19 hospitalized patients, varying from 2.6% to 15% for pulmonary embolisms (PE) and 4.6 to 12% for deep vein thrombosis (DVT), researchers have been prompted to investigate the underlying mechanism [5]. Although this mechanism has not yet been fully elucidated, COVID-19 is thought to cause an exaggerated inflammatory response which in turn leads to endothelial damage and activation of the coagulation cascade. Additionally, micro clotting has been observed in COVID-19 infected patients, hindering oxygen exchange [6]. Furthermore, the immobility of hospitalized patients further increases the risk of thrombotic complications, hence the administration of anticoagulants [7,8]. Aside from thrombotic complications, COVID-19 patients have been observed with higher levels of inflammatory indices such as C-reactive protein, neutrophils, and interleukins which in turn cause excessive release of pro inflammatory cytokines. These cytokines cause significant damage to the respiratory system leading to pulmonary infections, respiratory failure, and organ damage via immune and inflammatory mediated pathways [9,10]. Corticosteroids target these inflammatory pathways and have played a vital role in improving clinical outcomes and mortality in patients [11–13]. Another commonly used drug group in the treatment of COVID-19 patients are antibiotics. These drugs are primarily implemented to treat secondary infections and prevent superinfections which have accounted for a significant portion of COVID-19 deaths. That said, some COVID-19 hospitalized patients in severe health states have also been treated empirically with antibiotics, despite the lack of evidence for a beneficial effect [14].

Although healthcare workers have mainly been focused on the treatment of the acute phase, i.e., the viral infection and the associated health symptoms of COVID-19, it has now become apparent that after the initial infection a varying proportion of patients experience COVID-19 related symptoms for a prolonged period [15]. Due to the lack of a universally accepted definition among the scientific community and the ever-changing availability of information, these post-COVID conditions have been identified by various names. Long haul COVID, chronic COVID, post-acute COVID-19, long COVID, and post-COVID-19 syndrome are a few of the commonly used names. In this study, we have adopted the definitions of COVID conditions as described in the rapid guideline on post-COVID-19 conditions developed in collaboration with the National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), and the Royal College of General Practitioners (RCGP). Post-COVID-19 syndrome is defined as “signs and symptoms that develop during or after an infection consistent with COVID-19, present for more than 12 weeks and are not attributable to alternative diagnoses” [16].

As these post-COVID conditions are still in their infancy little is known about the underlying disease pathophysiology and epidemiology. The incidence rate of post-COVID-19 conditions varies widely per study, ranging from more than 30% to 76% after 6 months of symptom onset [17–21]. This variation can be attributed to differences in follow-up length, the definition of the post-COVID condition, and the population sample [15].

While much research has been done regarding the safety and efficacy of corticosteroids, antibiotics, and anticoagulants on the treatment of the acute phase of COVID-19 and its concomitant manifestations, little is known regarding the impact these medications have on the development of post-COVID-19 syndrome. Identifying the association between pharmacotherapy and the development of post-COVID-19 syndrome allows healthcare providers to make better-informed treatment choices and could contribute to overall patient well-being. Therefore, the aim of this study was to assess the effect of corticosteroids, anticoagulants, and antibiotics on the development of post-COVID-19 syndrome.

Methods

Study design

A single-center retrospective follow up study was conducted in which 2 separate databases; the MST ISARIC database which contains electronic health records of COVID-19 hospitalized patients and the Post-COVID cohort database which contains patient follow-up data were combined. Using the merged database, it is possible to determine the association between patient pharmacotherapy during the hospital stay and the development of post-COVID-19 syndrome 6 months after hospital discharge. Three drugs of interest were identified and analyzed, i.e., corticosteroids, antibiotics, and anticoagulants. Separate regression models were made to analyze each individual drug treatment. Drug class effects were measured without taking into account the dose variations or length of use as patients were treated according to the hospital protocol from which physicians rarely deviated.

Setting

The MST ISARIC database consists of retrospectively sourced patient data (March 2020 – September 2021) of 995 COVID-19 hospitalized patients from Medisch Spectrum Twente (MST), Enschede, the Netherlands. Patient data was collected from the time of the first admission with COVID-19 until the last discharge. This database was set up according to the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) rapid COVID-19 case report form (Annex 2).

The Post COVID database is a separate COVID database that consists of 274 patients. This database was originally set up to follow COVID-19 patients' overall health and well-being after hospital discharge (September 2020 - present) using the short form Health survey 36 (SF-36), the EuroQol 5-dimension 5 level descriptive system (EQ-5D-5L), the Medical research council dyspnoe (MRC) survey and the short fatigue survey.

Study population

Health questionnaires were sent out to patients quarterly after discharge and focused on physical as well as mental well-being. Demographic information was acquired through a baseline questionnaire and partly through the MST ISARIC database. For the current study, questionnaires completed 6 months after hospital discharge were coupled via patient study number to the retrospectively collected ISARIC patient data and selected for analysis. By combining the two databases it is possible to determine which patients develop post-COVID-19 syndrome and the nature of the treatments and medications these patients have undergone while admitted to the hospital. Thus, making it possible to identify possible associations between drug treatments and the development of post-COVID-19 syndrome. The combined database consists of patients 18 years or older that were admitted to the hospital (MST) due to COVID-19 symptoms confirmed using a polymerase chain reaction (PCR) test, who have completed the informed consent form and have sufficient proficiency in the Dutch language.

Outcomes

Post-COVID-19 syndrome presence 6 months after hospital discharge was determined using the following questions out of the Post COVID database. Question 1: “In general, how would you describe your health at the moment?”. Question 2: “compared to one year ago, how would you rate your health in general now?”. Question 3: “during the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?”. Question 4: “For the following 4 statements regarding fatigue, please indicate how you have been feeling during the past 2 weeks”. Question 5: “have you felt downhearted or anxious?”. Question 6: “are you occasionally short of breath?”. Using the aforementioned questions, three definitions were created to determine post-COVID-19 syndrome status, each consisting of 4 questions. Definition 1 consist of question 1, 2, 3 and 4. Definition 2 consists of questions 1, 2, 3 and 5. Definition 3 consists of questions 1, 2, 3 and 6. If a patient fit one or more definitions based on the answers they provided, they were categorized as having post-COVID-19 syndrome. A combination of the first question being answered with “fair” or “poor” the second question with “Somewhat worse or much worse now than one year ago” and the third question with “slightly to very severe” combined with “mostly true” or “definitely true” for statements regarding experiencing fatigue and “mostly false” or “definitely false” for statement regarding being fit of the fourth question or “slightly to very severe” for the fifth or sixth questions prompted the patient to be categorized as having developed post-COVID-19 syndrome. The first 3 questions were chosen to capture the burden of post-COVID-19 symptoms and their effect on the physical, mental, and general health of patients. While the fourth, fifth and sixth questions are meant to encompass common symptoms of post-COVID-19 syndrome [22,23].

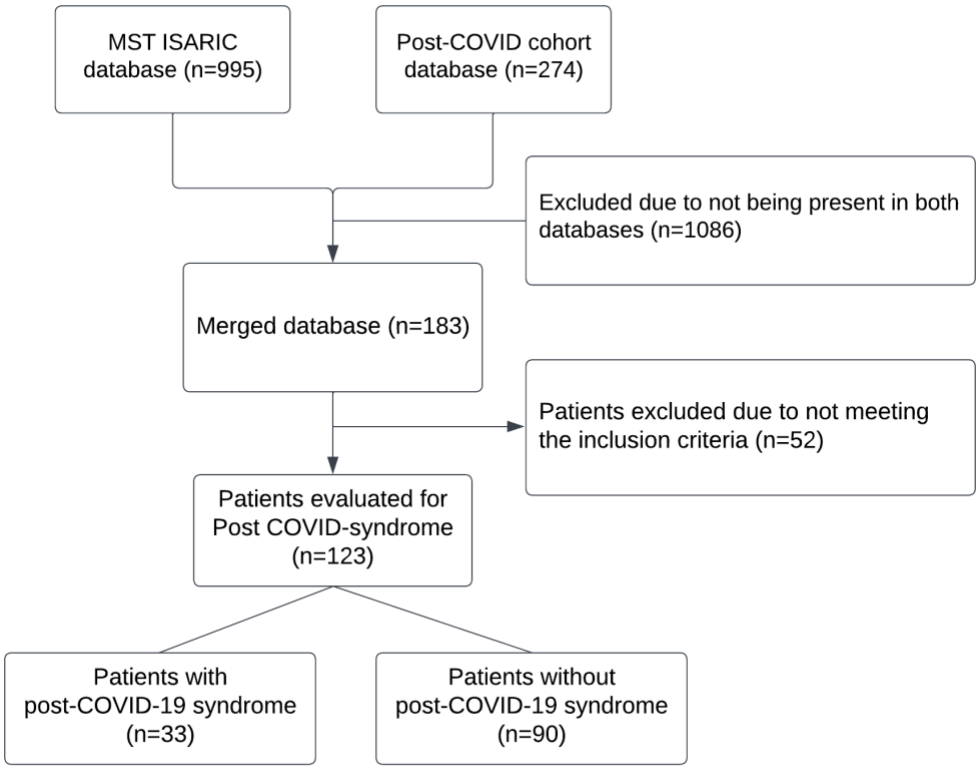

Figure 1: Flowchart of study design

Exposure

Exposure of interest were drug treatment with corticosteroids, antibiotics, or anticoagulants. According to the COVID-19 hospital protocol a respiratory rate greater than 25 breaths per minute, an oxygen requirement of more than 5 liters, or a rapidly increasing oxygen requirement prompted patients to receive 6mg dexamethasone daily for 10 days as per hospital protocol (Annex 1). If the patient is discharged from the hospital prior to these 10 days, dexamethasone was prescribed as home medication for the remaining days. Some patients received a different corticosteroid (hydrocortisone, methylprednisolone, and prednisolone) due to treatment for other illnesses.

Antibiotics were not incorporated into the COVID-19 hospital protocol but were administered preventively or on suspicion of a bacterial infection, ceftriaxone 2000mg was primarily used. A small group of patients received a different antibiotic (amoxicillin, amoxicillin/clavulanic acid, ceftazidime, ceftriaxone, ciprofloxacin, trimethoprim/sulfamethoxazole, doxycycline, and vancomycin) than ceftriaxone due to treatment for other illnesses.

Hospitalized patients with suspicion or confirmed COVID-19 were administered dalteparin 5000IE daily, while patients with a bodyweight of 100kg or more were given 7500IE daily. Only if the patients were already using certain anticoagulants was this deviated from.

Variables

Six covariates were included in the association model, gender, age, body mass index (BMI), patient degree of illness, drug treatment, and comorbidity. Age was grouped into more or less equal group sizes to be able to identify trends in the data while BMI was grouped according to the World Health Organization (WHO) classification [24]. Patient degree of illness was determined using the National Early Warning Score 2 (NEWS 2) at hospital admission and could be categorized as low, low-medium, medium, and high [25]. Due to the relatively small sample size of the dataset, comorbidities were coded into the broadest parent term according to the International Statistical Classification of Diseases and Related Health Problems (ICD-11) after which the comorbidities were grouped into having a direct or indirect influence on COVID-19, based on literature and expert opinion. This was done to better capture the effect of the variable comorbidity by increasing the effect size of said variable. Diseases of the circulatory system, the respiratory system, the immune system, and endocrine, nutritional, or metabolic diseases were considered as having a potential direct influence on COVID-19. While diseases of the blood or blood-forming organs, the genitourinary system, the musculoskeletal system or connective tissue, the nervous system, neoplasms, sleep-wake disorders, factors influencing health status or contact with health services and mental, behavioral, or neurodevelopmental disorders were considered as having a potential indirect influence on COVID-19 [26,27].

Data analysis

To identify potential differences between the distributions of the COVID-19 drug treatment in non-post-COVID-19 syndrome and post-COVID-19 syndrome patients, Pearson's chi-squared test was used in combination with odds ratios to measure the effect size in the univariate analysis. Furthermore, using a binomial logistic regression, the association between corticosteroids, antibiotics, or anticoagulants and the development of the post-COVID-19 syndrome was determined. A p-value of 0.05 or lower was considered to be significant. Missing data was imputed using the expectation maximization method. A missing value of 5% or lower was considered to be acceptable for imputation. Furthermore, data imputation was only necessary in one case. Statistics were performed in R (version 4.0.3) and SPSS (version 28.0.1.0).

Ethical approval

Patients provided informed consent for the use of their data from the post COVID database. The institutional review board of MST approved of the use of the patient's data, as collected in the ISARIC database for COVID-19 related data.

Results

A total of 123 patients met the inclusion criteria of which, 33 patients (26.8%) had developed and were still affected by post-COVID-19 syndrome 6 months after hospital discharge (Table 1). The univariate analysis shows no statistically significant difference between the use of corticosteroids for patients who had and had not developed post-COVID-19 syndrome (p=0.14). The same results can be seen for patients treated with antibiotics (p=0.96) or anticoagulants (p=0.34).

Table 1 Characteristics of study population

	Total	**Post-COVID-19 syndrome**	**Non-post-COVID-19 syndrome**
Patients (%)	123	33 (26.8%)	90 (73.2%)
Gender (female) (%)	47 (38.2%)	17 (51.5%)	30 (33.3%)
Gender (male) (%)	76 (61.8%)	16 (48.5%)	60 (66.7%)
Age (years), mean ± SD	62.1 ± 9.5	58.5 ± 10.6	63.4 ± 8.8
Comorbidity (%)			
Direct influence on COVID-19[a]	85 (69.1%)	20 (60.6%)	65 (72.2%)
Indirect influence on COVID-19[b]	38 (30.9%)	13 (39.4%)	25 (27.8%)
Patient degree of illness[c] (%)			
Low	53 (43.1%)	14 (42.4%)	39 (43.3%)
Low-medium	8 (6.5%)	0 (0.0%)	8 (8.9%)
Medium	24 (19.5%)	6 (18.2%)	18 (20.0%)
High	38 (30.9%)	13 (39.4%)	25 (27.8%)
Drug treatment			
Antibiotics	94 (71.8%)	24 (72.7%)	65 (72.2%)
Anticoagulants	107 (81.7%)	25 (75.8%)	75 (83.3%)
Corticosteroids	78 (59.5%)	16 (48.5%)	57 (63.3%)
Antibiotic + anticoagulant	71 (57.7%)	18 (54.5%)	53 (58.9%)

Antibiotic + corticosteroids	53 (43.1%)	13 (39.4%)	40 (44.4%)
Anticoagulant + corticosteroid	64 (52.0%)	13 (39.4%)	51 (56.7%)
Antibiotic + anticoagulant + corticosteroid	46 (37.4%)	11 (33.3%)	35 (38.9%)
Hospital stay duration (days), mean ± SD	12.5 ± 11.3	10.2 ± 8.6	13.3 ± 12.1

[a]Diseases of the circulatory system, the respiratory system, the immune system, and endocrine, nutritional, or metabolic diseases

[b]Diseases of the blood or blood-forming organs, the genitourinary system, the musculoskeletal system or connective tissue, the nervous system, neoplasms, sleep-wake disorders, factors influencing health status or contact with health services and mental, behavioral, or neurodevelopmental disorders

[c]Determined using the NEWS-2 score

The multivariate analysis showed that corticosteroid treatment in patients hospitalized for COVID-19 was associated with a significantly smaller chance (OR 0.34, 95% CI -2.12 to -0.02, p = 0.04) of developing post-COVID-19 syndrome. Anticoagulant treatment in patients hospitalized for COVID-19 was associated with a smaller chance (OR 0.60, 95% CI -1.66 to 0.63, p = 0.37) of developing post-COVID-19 syndrome although this effect was not found to be significant. While antibiotic treatment in patients hospitalized for COVID-19 was associated with a greater chance (OR 1.33, 95% CI -0.73 to 1.30, p = 0.58) of developing post-COVID-19 syndrome compared to patients not treated with antibiotics, this effect was not significant.

Discussion

Patients treated with corticosteroids were associated with significantly lower incidences of post-COVID-19 syndrome. While patients treated with anticoagulants were also observed benefitting from a protective effect from developing post-COVID-19 syndrome, this effect was not significant. Antibiotic treatment on the other hand seemed to increase incidences of post-COVID-19 syndrome, although not significantly. Furthermore, no significant differences were shown between the administered drug treatment (corticosteroids, anticoagulants, or antibiotics) for patients who had and had not developed post-COVID-19 syndrome in the univariate analysis.

Although information regarding post-COVID-19 syndrome disease pathophysiology is scarce, corticosteroids' effect on this disease may be explained by the hyperactivation of (chronic) inflammatory and immunological pathways post-COVID-19 syndrome induces and the anti-inflammatory and immunomodulating mechanism of action of corticosteroids. Among others, Corticosteroids decrease the production of pro-inflammatory cytokines and chemokines, stimulate the release of anti-inflammatory cytokines, and suppress lymphocyte activation and production of immunoglobulins, which play important roles in the disease progression [15,28].

Patients infected with COVID-19 have been observed developing micro clots which in turn obstruct capillaries, hinder oxygen exchange, and could cause post-COVID-19 related symptoms. This in turn may be a potential explanation for the seemingly protective effect against post-COVID-19 syndrome of anticoagulants [6]. In contrast to corticosteroids and anticoagulants, antibiotics seemed to increase the chances of developing post-COVID-19 syndrome. As antibiotics are not part of Medisch Spectrum Twente's COVID-19 treatment protocol, we can infer that patients who had received antibiotics were primarily treated for secondary infections which in turn suggests a graver patient health state. This is in line with our regression model which also shows a possible trend for higher chance of developing post-COVID-19 syndrome with increasing disease severity. However, this finding was not significant. Furthermore, some studies have better identified the role of the gut microbiome in COVID-19 patients, which show that antibiotics cause a dysbiosis in the gut microbiome which is closely involved in immune system regulation through the gut–lung axis and gut-brain axis amongst others. An imbalance can lead to more pro-inflammatory mediators and immune cell activation which in turn perpetuates the disease [29–32].

Besides the underlying disease mechanisms, the significance of these results may be explained by the discriminatory ability of the aforementioned drugs. When patients are admitted to MST due to COVID-19, anticoagulants are administered as per hospital protocol, whereas corticosteroids are only administered when certain patient criteria are met. These criteria, such as respiratory rate and oxygen requirement are directly linked to disease activity and therefore have a higher discriminatory ability.

Seeing as post-COVID-19 conditions had only just started to emerge at the commencement of this study, no treatment or predisposing factors for these conditions were known. We can therefore infer that the COVID-19 hospitalized patients were treated as per hospital protocol and thus received similar medical treatment, explaining why no differences were found in administered drug treatment among patients.

The current study has several limitations. Firstly, the included sample size was limited which has direct implications on the power of our study. Secondly, drug class effects were measured for each drug group without taking into account possible dose variations or treatment duration as patients were treated as per hospital protocol. Thirdly, comorbidities were grouped into having a direct or indirect influence on COVID-19. Due to the relatively small sample size, it was necessary to include limited disease groups so as to not skew the data. For this reason, based on literature review and expert opinion it was decided to only include a select few disease groups as these were considered to be the most impactful on COVID-19 severity.

This study provides more insight into the effect of commonly used drug treatments for COVID-19 hospitalized patients on the development of post-COVID-19 syndrome. Although corticosteroids are primarily used for the treatment of COVID-19 hospitalized patients fitting certain respiratory criteria, this study shows corticosteroids reducing the probability of developing post-COVID-19 syndrome. The observed protective effect is a new and unexpected

finding which may have implications for daily practice in healthcare in relation to post COVID-19 syndrome prevention. Although the results indicate the added value of using corticosteroids for the prevention of post-COVID-19 syndrome, it is equally important not to overuse these drugs given the immunosuppressive effects and the development of infections. For this reason, more studies are needed to not only substantiate these findings but also to find an optimal treatment dose and length for corticosteroids.

Conclusion

COVID-19 hospitalized patients in MST underwent the same treatments as per hospital protocol. No distinction was made between patients with predisposing factors for post-COVID-19 syndrome. Corticosteroids have shown a significant protective effect on the development of post-COVID-19 syndrome in this study. While anticoagulants have also shown a similar protective effect, this effect is not significant. Conversely, treatment with antibiotics has shown to increase hospitalized patients' chances of developing post-COVID-19 syndrome while this effect is also not significant. Further research is required to validate these findings and to yield improved prevention and management strategies for post-COVID-19 syndrome.

Conflicts of interest

None.

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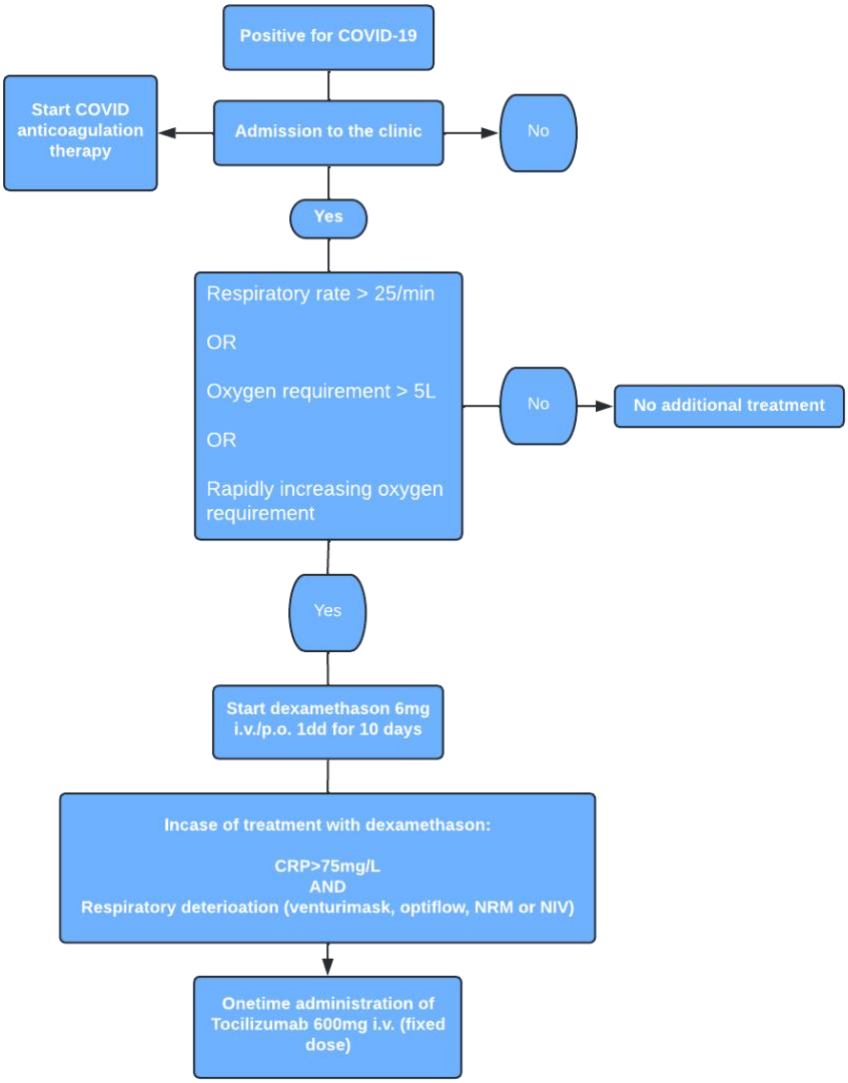
Annex 1 – MST COVID-19 treatment protocol



Annex 2 – ISARIC rapid case record form

Global COVID-19 Clinical Platform

NOVEL CORONAVIRUS (COVID-19) - RAPID VERSION

DESIGN OF THIS CASE RECORD FORM (CRF)

This CRF has 3 modules:

Module 1 to be completed on the first day of admission to the health centre.

Module 2 to be completed on first day of admission to ICU or high dependency unit. Module 2 should also be completed daily for as many days as resources allow. Continue to follow-up patients who transfer between wards.

Module 3 to be completed 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 retrospectively if the patient is enrolled after the admission date.
- Participant Identification Numbers consist of a site code and a participant number. You can obtain a site code and register 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, you can assign numbers in blocks or incorporate 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.
- Data are entered to the central electronic REDCap database at https://ncov.medsci.ox.ac.uk or to your site/network's independent database. Printed paper CRFs may be used and the data can be typed into the electronic database afterwards.
- Complete every section. Questions marked "If yes,…" should be left blank when they do not apply (i.e. when the answer is not yes).
- Selections with square boxes (☐) are single selection answers (choose one answer only).
- Selections with circular boxes (**O**) are multiple selection answers (choose all that apply).
- Mark 'Unknown' for any data that are not available or unknown.
- Avoid recording data outside of the dedicated areas.
- If using paper CRFs, we recommend writing clearly in ink, using BLOCK-CAPITAL LETTERS.
- Place an (X) in the boxes to mark the 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 can be stored by the institution responsible for them. All data should be transferred to the 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 can support the establishment of locally hosted databases.
- Please contact us at ncov@isaric.org. If we can help with databases, if you have comments and to let us know that you are using the forms.

PARTICIPANT ID I___I I___I I___I I___I I___I -- I___I I___I I___I I___I

MODULE1: complete on admission/enrolment

Site name _____ **Country** _____

Date of enrolment [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

CLINICAL INCLUSION CRITERIA

Proven or suspected infection with pathogen of Public Health Interest ☐Yes ☐No

One or more	|	A history of self-reported feverishness or measured fever of ≥ 38°C	☐Yes ☐No
of these	|	Cough	☐Yes ☐No
during this	|	Dyspnoea (shortness of breath) OR Tachypnoea*	☐Yes ☐No
illness	|	Clinical suspicion of ARI despite not meeting criteria above	☐Yes ☐No

** respiratory rate ≥50 breaths/min for <1 year; ≥40 for 1-4 years; ≥30 for 5-12 years; ≥20 for ≥13 years*

Is COVID-19 the reason for hospital admission?
☐Yes, COVID-19 is the reason for hospital admission
☐No, the patient is admitted to hospital for a reason other than COVID-19

DEMOGRAPHICS

Sex at Birth ☐Male ☐Female ☐Not specified **Date of birth** [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_][_Y_][_Y_]
If date of birth is unknown, record: **Age** [___][___]years OR [___][___]months
Healthcare Worker? ☐Yes ☐No ☐Unknown **Laboratory Worker?** ☐Yes ☐No ☐Unknown
Pregnant? ☐Yes ☐No ☐Unknown ☐N/A **If yes: Gestational weeks assessment** [___][___] weeks

PREVIOUS COVID-19 INFECTIONS

Has the patient had COVID-19 previously?
☐ No ☐ Yes - once previously ☐ Yes - twice previously ☐ Yes - three times previously
(there is more space on the eCRF to capture this)

First COVID-19 infection:
When did their first COVID infection occur? (MM/YYY) _____
Was their first COVID infection confirmed by testing:
☐Yes, confirmed by testing ☐No, not confirmed by testing
Were they admitted to hospital for their first infection of COVID? ☐Yes ☐No

Second COVID-19 infection:
When did their second COVID infection occur? (MM/YYY) _____
Was their second COVID infection confirmed by testing:
☐Yes, confirmed by testing ☐No, not confirmed by testing
Were they admitted to hospital for their second infection of COVID? ☐Yes ☐No

If data on this patient was previously recorded in this study, record the Participant Identification Number (PIN) previously used in the section below

RE-ADMISSION AND PREVIOUS PIN

Was the patient admitted previously or transferred from any other facility during this illness episode?
☐YES-admitted previously to this facility ☐YES–transferred from other facility ☐NO ☐Unknown
Number of previous admissions for this infection: _____
Has this patient's data been previously collected under a different patient number?: ☐YES ☐NO ☐Unknown
If YES, Participant Identification Number (PIN): _____

PARTICIPANT ID [___][___][___][___][___][___] -- [___][___][___][___][___][___]

MODULE1: complete on admission/enrolment

SYMPTOM ONSET AND ADMISSION *(first available data at presentation/admission)*

Symptom onset (date of first/earliest symptom) [D_D_]/[M_M_]/[2_2_0_0_Y_Y_]
Admission date at this facility [D_D_]/[M_M_]/[2_2_0_0_Y_Y_]
Temperature [___].[___]°C **Heart rate** [___][___][___]beats/min
Respiratory rate [___][___]breaths/min
BP [___] [___] [___](systolic) [___][___][___](diastolic) mmHg **Severe dehydration** ☐Yes ☐No ☐Unknown
Sternal capillary refill time >2seconds ☐Yes ☐No ☐Unknown
Oxygen saturation: [___][___]% on ☐room air ☐oxygen therapy ☐Unknown **A V P U** (circle one)
Glasgow Coma Score (GCS /15) [___][___] **Malnutrition** ☐Yes ☐No ☐Unknown
Mid-upper arm circumference [___][___][___]mm **Height:** [___] [___] [___]cm **Weight**: [___][___][___]kg

CO-MORBIDITIES *(existing prior to admission) (Unk = Unknown)*

Chronic cardiac disease *(not hypertension)*	☐Yes ☐No ☐Unk	Diabetes	☐Yes	☐No	☐Unk
Hypertension	☐Yes ☐No ☐Unk	Current smoking	☐Yes	☐No	☐Unk
Chronic pulmonary disease	☐Yes ☐No ☐Unk	Tuberculosis	☐Yes	☐No	☐Unk
Asthma	☐Yes ☐No ☐Unk	Asplenia	☐Yes	☐No	☐Unk
Chronic kidney disease	☐Yes ☐No ☐Unk	Malignant neoplasm	☐Yes	☐No	☐Unk
Chronic liver disease	☐Yes ☐No ☐Unk	Other	☐Yes	☐No	☐Unk
Chronic neurological disorder	☐Yes ☐No ☐Unk	If yes, specify:			
HIV	☐Yes-on ART ☐Yes-not on ART ☐No ☐Unknown				

PRE-ADMISSION & CHRONIC MEDICATION **Were any of the following taken within 14 days of admission?**

Angiotensin converting enzyme inhibitors (ACE inhibitors)? ☐Yes ☐No ☐Unknown
Angiotensin II receptor blockers (ARBs)? ☐Yes ☐No ☐Unknown
Non-steroidal anti-inflammatory (NSAID)? ☐Yes ☐No ☐Unknown

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

History of fever	☐Yes ☐No ☐Unk	Lower chest wall indrawing	☐Yes	☐No	☐Unk
Cough	☐Yes ☐No ☐Unk	Headache.	☐Yes	☐No	☐Unk
with sputum production	☐Yes ☐No ☐Unk	Altered consciousness/confusion	☐Yes	☐No	☐Unk
with haemoptysis	☐Yes ☐No ☐Unk	Seizures	☐Yes	☐No	☐Unk
Sore throat	☐Yes ☐No ☐Unk	Abdominal pain	☐Yes	☐No	☐Unk
Runny nose (rhinorrhoea).	☐Yes ☐No ☐Unk	Vomiting / Nausea	☐Yes	☐No	☐Unk
Wheezing	☐Yes ☐No ☐Unk	Diarrhoea	☐Yes	☐No	☐Unk
Chest pain.	☐Yes ☐No ☐Unk	Conjunctivitis	☐Yes	☐No	☐Unk
Muscle aches (myalgia)	☐Yes ☐No ☐Unk	Skin rash	☐Yes	☐No	☐Unk
Joint pain (arthralgia).	☐Yes ☐No ☐Unk	Skin ulcers	☐Yes	☐No	☐Unk
Fatigue / Malaise	☐Yes ☐No ☐Unk	Lymphadenopathy	☐Yes	☐No	☐Unk
Shortness of breath .	☐Yes ☐No ☐Unk	Bleeding (Haemorrhage).	☐Yes	☐No	☐Unk
Inability to walk	☐Yes ☐No ☐Unk	If bleeding: specify site(s):			

Other ☐Yes ☐No ☐Unk If yes, specify: _____

PARTICIPANT ID [___][___][___][___][___][___] -- [___][___][___][___][___][___]

MODULE1: complete on admission/enrolment

VACCINATIONS

Covid-19 vaccination ☐YES ☐NO ☐Unk

Date of first vaccine :[D_D_]/[M_M_]/[2_2_0_0_Y_Y_] Date: ☐actual ☐estimated
Type of first vaccine: ☐Pfizer/BioNTech | ☐AstraZeneca/University of Oxford (Covishield in India) | ☐Moderna ☐Novavax | ☐Janssens (Johnson & Johnson) | ☐Sinopharm | ☐Sinovac | ☐Sputnik V ☐Covaxin | ☐CanSinoBIO | ☐Unknown | ☐other, please specify _____

Date of second vaccine :[D_D_]/[M_M_]/[2_2_0_0_Y_Y_] Date: ☐actual ☐estimated
Type of second vaccine: ☐Pfizer/BioNTech | ☐AstraZeneca/University of Oxford (Covishield in India) | ☐Moderna ☐Novavax | ☐Janssens (Johnson & Johnson) | ☐Sinopharm | ☐Sinovac | ☐Sputnik V ☐Covaxin | ☐CanSinoBIO | ☐Unknown | ☐other, please specify _____

Date of third vaccine :[D_D_]/[M_M_]/[2_2_0_0_Y_Y_] Date: ☐actual ☐estimated
Type of third vaccine: ☐Pfizer/BioNTech | ☐AstraZeneca/University of Oxford (Covishield in India) | ☐Moderna ☐Novavax | ☐Janssens (Johnson & Johnson) | ☐Sinopharm | ☐Sinovac | ☐Sputnik V ☐Covaxin | ☐CanSinoBIO | ☐Unknown | ☐other, please specify _____

Influenza vaccination within the last 6 months: ☐YES ☐NO ☐Unknown
Date of influenza vaccine :[D_D_]/[M_M_]/[2_2_0_0_Y_Y_] Date: ☐actual ☐estimated

MEDICATION ***Is the patient CURRENTLY receiving any of the following?***

Oral/orogastric fluids? ☐Yes ☐No ☐ Unknown **Intravenous fluids?** ☐Yes ☐No ☐Unknown
Antiviral? ☐Yes ☐No ☐Unknown **If yes:** ORibavirin OLopinavir/Ritonavir ONeuraminidase inhibitor
OInterferon alpha OInterferon beta OOther, specify: _____
Corticosteroid? ☐Yes ☐No ☐Unknown **If yes,** route: OOral OIntravenous OInhaled
If yes, please provide agent and maximum daily dose: _____
Antibiotic? ☐Yes ☐No ☐Unknown **Antifungal agent?** ☐Yes ☐No ☐Unknown
Antimalarial agent? ☐Yes ☐No ☐Unknown **If yes,** specify: _____
Experimental agent? ☐Yes ☐No ☐Unknown **If yes,** specify: _____
Non-steroidal anti-inflammatory (NSAID) ☐Yes ☐No ☐Unknown
Angiotensin converting enzyme inhibitors (ACE inhibitors) ☐Yes ☐No ☐Unknown
Angiotensin II receptor blockers (ARBs) ☐Yes ☐No ☐Unknown

SUPPORTIVE CARE ***Is the patient CURRENTLY receiving any of the following?***

ICU or High Dependency Unit admission? ☐Yes ☐No ☐Unknown
Oxygen therapy? ☐Yes ☐No ☐ Unknown **If yes**, complete all below
O_2 flow: ☐1-5 L/min ☐6-10 L/min ☐11-15 L/min ☐>15 L/min ☐Unknown
Source of oxygen: ☐Piped ☐Cylinder ☐Concentrator ☐Unknown
Interface: ☐Nasal prongs ☐HF nasal cannula ☐Mask ☐Mask with reservoir ☐CPAP/NIV mask ☐Unknown
Non-invasive ventilation? *(e.g.BIPAP/CPAP)* ☐Yes ☐No ☐N/A
Invasive ventilation *(Any)*? ☐Yes ☐No ☐ Unknown **Inotropes/vasopressors?** ☐Yes ☐No ☐Unknown
Extracorporeal (ECMO) support? ☐Yes ☐No ☐ Unknown **Prone position?** ☐Yes ☐No ☐ Unknown

PARTICIPANT ID [___][___][___][___][___][___] -- [___][___][___][___][___][___]

MODULE1: complete on admission/enrolment

LABORATORY RESULTS ON ADMISSION (*record units if different from those listed)*

Parameter	Value*	Not done	Parameter	Value*	Not done
Haemoglobin (g/L)		☐	Creatinine (µmol/L)		☐
WBC count (x10⁹/L)		☐	Sodium (mEq/L)		☐
Haematocrit (%)		☐	Potassium (mEq/L)		☐
Platelets (x10⁹/L)		☐	Procalcitonin (ng/mL)		☐
APTT/APTR		☐	CRP (mg/L)		☐
PT (seconds)		☐	LDH (U/L)		☐
INR		☐	Creatine kinase (U/L)		☐
ALT/SGPT (U/L)		☐	Troponin (ng/mL)		☐
Total bilirubin (µmol/L)		☐	ESR (mm/hr)		☐
AST/SGOT (U/L)		☐	D-dimer (mg/L)		☐
Urea (BUN) (mmol/L)		☐	Ferritin (ng/mL)		☐
Lactate (mmol/L)		☐	IL-6 (pg/mL)		☐

PARTICIPANT ID [___][___][___][___][___][___] -- [___][___][___][___][___][___]

MODULE 2: follow-up (frequency of completion determined by available resources)

Date of follow up [D_D_]/[M_M_]/[2_2_0_0_Y_Y_]

VITAL SIGNS *(record most abnormal value between 00:00 to 24:00)*

Temperature [___][___].[___]°C **Heart rate** [___][___][___]beats per min **Respiratory rate** [___][___]breaths/min
BP [___] [___] [___](systolic) [___][___][___](diastolic) mmHg **Severe dehydration** ☐Yes ☐No ☐Unknown
Sternal capillary refill time >2seconds ☐Yes ☐No ☐Unknown **GCS/15** [___][___]
Oxygen saturation [___][___][___]% on ☐ room air ☐ oxygen therapy ☐Unknown **A V P U** (circle one)

DAILY CLINICAL FEATURES *(Unk = Unknown)*

Cough and sputum production	☐Yes ☐No ☐Unk		Seizures	☐Yes ☐No ☐Unk	
Sore throat	☐Yes ☐No ☐Unk		Vomiting / Nausea	☐Yes ☐No ☐Unk	
Chest pain	☐Yes ☐No ☐Unk		Diarrhoea	☐Yes ☐No ☐Unk	
Shortness of breath	☐Yes ☐No ☐Unk		Conjunctivitis	☐Yes ☐No ☐Unk	
Confusion	☐Yes ☐No ☐Unk		Myalgia	☐Yes ☐No ☐Unk	
			Other, specify:	☐Yes ☐No ☐Unk	

LABORATORY RESULTS (*record units if different from those listed)*

Parameter	Value*	Not done	Parameter	Value*	Not done
Haemoglobin (g/L)		☐	Creatinine (µmol/L)		☐
WBC count (x10⁹/L)		☐	Sodium (mEq/L)		☐
Haematocrit (%)		☐	Potassium (mEq/L)		☐
Platelets (x10⁹/L)		☐	Procalcitonin (ng/mL)		☐
APTT/APTR		☐	CRP (mg/L)		☐
PT (seconds)		☐	LDH (U/L)		☐
INR		☐	Creatine kinase (U/L)		☐
ALT/SGPT (U/L)		☐	Troponin (ng/mL)		☐
Total bilirubin (µmol/L)		☐	ESR (mm/hr)		☐
AST/SGOT (U/L)		☐	D-dimer (mg/L)		☐
Urea (BUN) (mmol/L)		☐	Ferritin (ng/mL)		☐
Lactate (mmol/L)		☐	IL-6 (pg/mL)		☐

MEDICATION ***Is the patient CURRENTLY receiving any of the following?***

Oral/orogastric fluids? ☐Yes ☐No ☐ Unknown **Intravenous fluids?** ☐Yes ☐No ☐Unknown
Antiviral? ☐Yes ☐No ☐Unknown **If yes:** ORibavirin OLopinavir/Ritonavir ONeuraminidase inhibitor
OInterferon alpha OInterferon beta OOther, specify: _____
Corticosteroid? ☐Yes ☐No ☐Unknown **If yes,** route: OOral OIntravenous OInhaled
If yes, please provide agent and maximum daily dose: _____
Antibiotic? ☐Yes ☐No ☐Unknown **Antifungal agent?** ☐Yes ☐No ☐Unknown
Antimalarial agent? ☐Yes ☐No ☐Unknown **If yes,** specify: _____
Experimental agent? ☐Yes ☐No ☐Unknown **If yes,** specify: _____
Non-steroidal anti-inflammatory (NSAID) ☐Yes ☐No ☐Unknown
Angiotensin converting enzyme inhibitors (ACE inhibitors) ☐Yes ☐No ☐Unknown
Angiotensin II receptor blockers (ARBs) ☐Yes ☐No ☐Unknown

SUPPORTIVE CARE ***Is the patient CURRENTLY receiving any of the following?***

ICU or High Dependency Unit admission? ☐Yes ☐No ☐Unknown
Oxygen therapy? ☐Yes ☐No ☐Unknown **If yes,** complete all below:
O_2 flow volume: ☐1-5 L/min ☐6-10 L/min ☐11-15 L/min ☐>15 L/min ☐Unknown
Source of oxygen: ☐Piped ☐Cylinder ☐Concentrator ☐Unknown
Interface: ☐Nasal prongs ☐HF nasal cannula ☐Mask ☐Mask with reservoir ☐CPAP/NIV mask ☐Unknown
Non-invasive ventilation? *(e.g. BIPAP, CPAP)* ☐Yes ☐No ☐Unknown
Invasive ventilation *(Any)*? ☐Yes ☐No ☐Unknown **Inotropes/vasopressors?** ☐Yes ☐No ☐Unknown
Extracorporeal (ECMO) support? ☐Yes ☐No ☐Unknown **Prone position?** ☐Yes ☐No ☐ Unknown
Renal replacement therapy (RRT) or dialysis? ☐Yes ☐No ☐Unknown

MODULE 3: complete at discharge/death

DIAGNOSTIC/PATHOGEN TESTING

Chest X-Ray /CT performed? ☐Yes ☐No ☐Unknown **If Yes: infiltrates present?** ☐Yes ☐No ☐Unknown
Was pathogen testing done during this illness episode? ☐Yes ☐No ☐Unknown **If yes**, complete all below:

Influenza virus: ☐Positive ☐Negative ☐Not done **If positive,** type _____
Coronavirus: ☐Positive ☐Negative ☐Not done **If positive:** ☐MERS-CoV ☐SARS-CoV-2 ☐Other _____
Other respiratory pathogen: ☐Positive ☐Negative ☐Not done **If positive,** specify _____
Viral haemorrhagic fever: ☐Positive ☐Negative ☐Not done **If positive,** specify virus _____
Other pathogen of public health interest detected: If yes, specify: _____
Falciparum malaria: ☐Positive ☐Negative ☐Not done **Non-falciparum malaria:** ☐Positive ☐Negative ☐Not done
HIV: ☐Positive ☐Negative ☐Not done

COMPLICATIONS: At any time during hospitalisation did the patient experience:

Shock	☐Yes ☐No ☐Unknown	Bacteraemia	☐Yes ☐No ☐Unknown
Seizure	☐Yes ☐No ☐Unknown	Bleeding	☐Yes ☐No ☐Unknown
Meningitis/Encephalitis	☐Yes ☐No ☐Unknown	Endocarditis	☐Yes ☐No ☐Unknown
Anaemia	☐Yes ☐No ☐Unknown	Myocarditis/Pericarditis	☐Yes ☐No ☐Unknown
Cardiac arrhythmia	☐Yes ☐No ☐Unknown	Acute renal injury	☐Yes ☐No ☐Unknown
Cardiac arrest	☐Yes ☐No ☐Unknown	Pancreatitis	☐Yes ☐No ☐Unknown
Pneumonia	☐Yes ☐No ☐Unknown	Liver dysfunction	☐Yes ☐No ☐Unknown
Bronchiolitis	☐Yes ☐No ☐Unknown	Cardiomyopathy	☐Yes ☐No ☐Unknown
Acute Respiratory Distress Syndrome	☐Yes ☐No ☐Unknown	Other If Yes, specify	☐Yes ☐No ☐Unknown _____

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

Oral/orogastric fluids? ☐Yes ☐No ☐Unknown **Intravenous fluids?** ☐Yes ☐No ☐Unknown
Antiviral? ☐Yes ☐No ☐Unknown **If yes:** ○Ribavirin ○Lopinavir/Ritonavir ○Neuraminidase inhibitor ○Interferon alpha ○Interferon beta ○Other, specify: _____
Antibiotic? ☐Yes ☐No ☐Unknown **If yes,** specify: _____
Corticosteroid? ☐Yes ☐No ☐Unknown **If yes,** route: ○Oral ○Intravenous ○Inhaled
If yes, specify agent and maximum daily dose: _____
Antifungal agent? ☐Yes ☐No ☐Unknown **If yes,** specify: _____
Antimalarial agent? ☐Yes ☐No ☐Unknown **If yes,** specify: _____
Experimental agent? ☐Yes ☐No ☐Unknown **If yes,** specify: _____
Non-steroidal anti-inflammatory (NSAID) ☐Yes ☐No ☐Unknown **If yes,** specify: _____

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

ICU or High Dependency Unit admission? ☐Yes ☐No ☐ Unknown **If yes,** total duration: _____days
Date of ICU admission:[_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] ☐N/A
Date of ICU discharge:[_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] ☐In ICU at outcome ☐N/A
Oxygen therapy? ☐Yes ☐No ☐Unknown **If yes, complete all:** **Total duration**: _____days
O_2 flow volume: ○1-5 L/min ○6-10 L/min ○11-15 L/min ○>15 L/min
Source of oxygen: ○Piped ○Cylinder ○Concentrator
Interface: ○Nasal prongs ○HF nasal cannula ○Mask ○Mask with reservoir ○CPAP/NIV mask
Non-invasive ventilation? *(e.g. BIPAP, CPAP)* ☐Yes ☐No ☐ Unknown **If yes,** total duration: _____days
Invasive ventilation *(Any)***?** ☐Yes ☐No ☐Unknown **If yes,** total duration: _____days
Extracorporeal (ECMO) support? ☐Yes ☐No ☐Unknown **If yes,** total duration: _____days
Prone position? ☐Yes ☐No ☐ Unknown **If yes,** total duration: _____days
Renal replacement therapy (RRT) or dialysis? ☐Yes ☐No ☐Unknown
Inotropes/vasopressors? ☐Yes ☐No ☐Unknown **If yes,** total duration: _____days

MODULE 3: complete at discharge/death

OUTCOME

Is the patient infected with a variant of concern (VOC) ?

☐ Unknown
☐ No: Variant is known and no VOC identified
☐ Yes: Delta - B.1.617.2, identified Oct 2020
☐ Yes: Omicron, B.1.1.529, identified Nov 2021
☐ Yes: Alpha - B.1.1.7, identified in UK Sept 2020
☐ Yes: Beta - B.1.351, identified in South Africa May 2020
☐ Yes: Gamma - P.1, identified in Brazil Nov 2020
☐ Yes: Epsilon - B.1.427/B.1.429, identified in USA Mar 2021
☐ Yes: Zeta - P.2, identified in Brazil Apr 2020
☐ Yes: Eta - B.1.525, identified in Multiple Countries Dec 2020
☐ Yes: Theta - P.3, identified in Philippines Jan 2021
☐ Yes: Iota - B.1.526, identified in USA Nov 2020
☐ Yes: Kappa - B.1.617.1, identified in India Oct 2020
☐ Yes: Lambda - C.37, identified in Peru Dec 2020
☐ Yes: Mu - B.1.621, identified in Colombia Jan 2021
☐ Yes: A variant not listed above

Please check the REDCAP database for variants not listed above. New variants will be added to the database as they are identified.

If omicron variant was identified, what method was used to identify it?

☐Genomic sequencing ☐S-gene target failure (SGTF) testing ☐PCR genotyping ☐Unknown or untested

Outcome: ☐Discharged alive ☐Hospitalized ☐Transfer to other facility ☐Death ☐Palliative discharge ☐Unknown

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

If Discharged alive: Ability to self-care at discharge versus before illness: ☐Same as before illness ☐Worse ☐Better ☐Unknown