REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

# CASE REPORT FORM DATA COMPLETION GUIDELINES

REMAP-CAP Case Report Form Data Completion Guidelines Version 14 dated 17 July 2024

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# 1. ABBREVIATIONS

| | |
|---|---|
| ABG | Arterial blood gas |
| AE | Adverse event |
| AIDS | Acquired immunodeficiency syndrome |
| ANZ | Australia and New Zealand |
| ANZICS CORE | Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation |
| APACHE | Acute Physiology and Chronic Health Evaluation |
| APD | Adult Patient Database |
| APS | Acute Physiology Score |
| AU | Australia |
| BAL | Bronchoalveolar lavage |
| β-hCG | Beta human chorionic gonadotropin |
| BiPAP | Bi-level positive airway pressure |
| Ca | Canada |
| CAP | Community-acquired pneumonia |
| CMP | Case Mix Programme |
| COPD | Chronic obstructive pulmonary disease |
| CPAP | Continuous positive airway pressure |
| CPE | Carbapenemase-producing Enterobacteriaceae |
| CRE | Carbapenem-resistant Enterobacteriaceae |
| CRF | Case report form |
| CT Scan | Computed tomography scan |
| CVS SOFA | Cardiovascular Sequential Organ Failure Assessment |
| DBP | Diastolic blood pressure |
| DOB | Date of birth |
| EARL | Ethical, administrative, regulatory and legal |
| $ECCO_2R$ | Extracorporeal carbon dioxide removal |
| ECMO | Extracorporeal membrane oxygenation |

| | |
|---|---|
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| ED | Emergency Department |
| EIA | Enzyme-linked immunoassay |
| ER | Emergency Room |
| ESBL | Extended spectrum beta-lactamase |
| ETT | Endotracheal tube |
| EU | European |
| $FiO_2$ | Fraction of inspired oxygen |
| FML | First, middle, last |
| GCP | Good Clinical Practice |
| GCS | Glasgow Coma Score |
| $HCO_3$ | Bicarbonate |
| HDU | High Dependency Unit |
| HFNP | High flow nasal prongs |
| HITH | Hospital in the home |
| HIV | Human immunodeficiency Virus |
| HREC | Human research ethics committee |
| hRSV | Human respiratory syncytial virus |
| IADLs | Instrumental activities of daily living |
| ICNARC | Intensive Care National Audit and Research Centre |
| ICU | Intensive Care Unit |
| IGRA | Interferon gamma release assay |
| IM | Intramuscular |
| IMV | Invasive mechanical ventilation |
| ITSC | International trial steering committee |
| IV | Intravenous |
| IRB | Institution Review Board |
| MAC | Mycobacterium avium complex |
| MAP | Mean arterial pressure |
| MERS-CoV | Middle East respiratory syndrome Coronavirus |

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|---|---|
| MoP | Manual of operations |
| MOTT | Mycobacteria other than tuberculosis |
| MRO | Multi-resistant organism |
| MRSA | Methicillin-resistant Staphylococcus aureus |
| NAT | Nucleic acid test |
| NG | Nasogastric |
| NHI | National Health Index |
| NHS | National Health Service |
| NJ | Nasojejunal |
| NIPPV | Non-invasive positive pressure ventilation |
| NIV | Non-invasive ventilation |
| NZ | New Zealand |
| $O_2$ | Oxygen |
| OG | Oral gastric |
| P:F Ratio | Ratio of Partial Pressure of Oxygen in Arterial Blood and Fraction of Inspired Oxygen Concentration |
| $PaO_2$ | Partial pressure of oxygen |
| PCR | Polymerase chain reaction |
| PCP | Pneumocystis carinii pneumonia |
| PEEP | Positive end expiratory pressure |
| PEG | Percutaneous endoscopic gastrostomy |
| PEJ | Percutaneous endoscopic jejunostomy |
| PI | Principal investigator |
| PJP | Pneumocystis jiroveci pneumonia |
| PLS | Primary lateral sclerosis |
| PSN | Participant study number |
| RAR | Response adaptive randomization |
| REMAP-CAP | Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia |
| RR | Respiratory rate |
| RRT | Renal replacement therapy |

| | |
|---|---|
| RSN | Registry study number |
| RSV | Respiratory syncytial virus |
| SAE | Serious adverse event |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| SBP | Systolic blood pressure |
| SLED | Slow low efficiency dialysis |
| SOP | Standard operating procedures |
| spp | Species |
| TdP | Torsades de pointes |
| TB | Tuberculosis |
| TEN | Toxic epidermal necrolysis |
| TT | Tracheostomy tube |
| UK | United Kingdom |
| UR | Unit record |
| VATS | Video-assisted thoroscopy |
| VRE | Vancomycin-resistant Enterococci |
| VT | Ventricular tachycardia |
| VZV | Varicella zoster virus |
| WHODAS | World Health Organization Disability Assessment Schedule |

## 2. CONTACT DETAILS

Contact the project managers any time if you have questions about the Case Report Form (CRF).

For questions related to the study database, contact info@remapcap.org

## 3. INTRODUCTION

This document provides instruction for the REMAP-CAP CRF and data definitions.

This document is to be used in conjunctions with the REMAP-CAP **Database User Guide**, which provides information to aid in the navigation of the regional REMAP-CAP databases, including:

- Participant enrolment and randomization
- Data Management

The Completion Guidelines are designed to accompany the CRF. The data definitions provide explanations of the CRF questions and should be used to collect data for the REMAP-CAP study.

The paper CRF may be used as a tool to collect data from the source documents and entered on the electronic CRF (eCRF).

### *3.1. Global Eligibility Website*

The global eligibility database URL is: https://remapcap.spinnakersoftware.com

### *3.2. eCRF Websites*

The Spiral database URL is: https://remapcap.spinnakersoftware.com

### *3.3. Patient Transfers*

**Patients transferred between REMAP-CAP participating hospitals**

If a patient is transferred from one REMAP-CAP participating hospital to another REMAP-CAP participating hospital the patient's eCRF should be transferred on the database to the receiving hospital, refer to the Database User Guide for instructions.

It is the responsibility of each participating hospital to complete data collection for the period while the patient was at their hospital. If data are missing contact the other hospital directly or the project manager. Contact details are provided in Section 2.

It is the responsibility of the randomizing site to complete post hospital follow-up for the patient, unless other arrangements have been made.

**Patients transferred to a non-REMAP-CAP participating hospital**

If a patient is transferred to a hospital not participating in REMAP-CAP it is the responsibility of the randomizing hospital to complete all data entry for the patient. Data collection stops at time of discharge from your hospital, you will only be asked to collect ultimate hospital discharge date.

# 4. COMMON FORMATTING

## *4.1. Date Format*

Date format is DD-MMM-YYYY for all date data points in the CRF. For example, 2nd February 2018 is 02-FEB-2018.

## *4.2. Time Format*

Time format to be used for all time data points is 24-hour format. For example, 6:05 pm = 18:05 hours. If you do not know an exact time, estimate to the nearest 15 minutes (e.g. 18:00, 18:15, 18:30, 18:45 or 19:00).

**Rule for midnight:**

- There is no 24:00 hrs.
- Do not round up times to 24:00 hrs, record 23:59 hrs if you are rounding to the closest hour.

## *4.3. Rounding numerical data*

If enough space is not provided in the eCRF to enter a full numerical value available, please round up or down as appropriate to fit the space available.

- Round the measurement up if equal to or greater than (≥) 5 or
- Round the measurement down if less than (<) 5 as appropriate

## *4.4. Study day definition*

A study day is defined as the chart day which corresponds with the site intensive care unit (ICU) daily flow/observation chart, regardless of the time that the flow chart begins. Daily data is therefore collected from one complete flow chart only.

Study day 1 commences at the time of randomization and concludes at the end of the ICU daily flow/observation chart for that day. In many ICUs this is a calendar day, but other definitions will be accommodated (e.g. 08:00 to 07:59 hrs the following day).

For patients randomized outside of ICU, study days are defined by the ICU chart day used by the site.

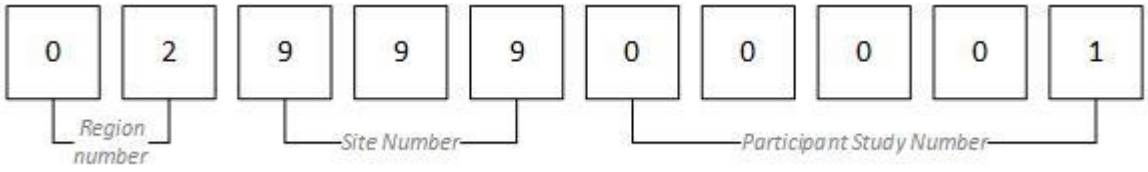
## 4.5. Missing Data

On the paper CRF and eCRF missing data is indicated by checking NOT RECORDED or NOT APPLICABLE, as relevant. This will ensure data queries are not raised unnecessarily.

## 4.6. Participant Study Number

The 10-digit Participant Study Number (PSN) is made up of the 2-digit region number, 3-digit site number plus the 5-digit patient number. The sequential patient number is allocated starting at 00001. The region number and 3-digit site number can be found in the Site File.

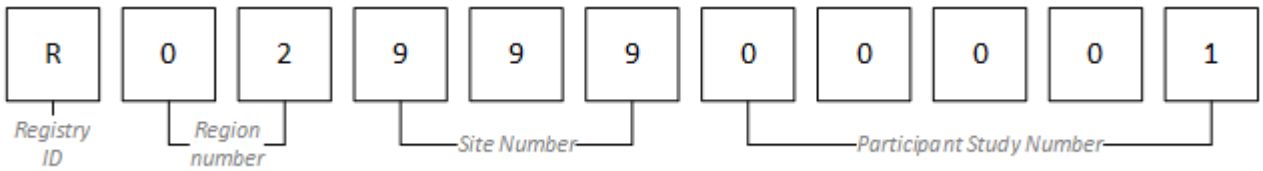
PSN example: Region 02, Site 999, the first patient's PSN will be 0299900001. There is no dash between the region number, the site number, and the sequential number.




## 4.7. Registry Study Number

The Registry Study Number (RSN) is made up of the Registry identifier (ID), a 2-digit region number, 3-digit site number plus a 5-digit patient number. The sequential RSN is allocated starting at 00001. The region and site number can be found in the Site File.

RSN example: Registry identifier is R, Region 02, Site 999, the first patient's RSN will be R0299900001. There is no dash in the RSN.




## 4.8. Paper CRF Instructions

***CRF Header***

If a paper CRF is used, complete the header of each paper CRF with:

- **Initials:** (ALL FORMS) the patient's initials in the format First, Middle, Last (FML). The patient does not have a middle name, use a dash (F-L)

- **PSN:** (ALL FORMS) the PSN is allocated by the database when the patient is randomized (see Section 4.7). The PSN will be displayed on the database and all participant documents.

***Empty variable box***

For variables entered in the variable boxes provided in the paper CRF fill all empty variable boxes with a zero (0). e.g. if the hours of ventilation the patient received that study day was 3 hours, the paper CRF data entry would be | 0 | 3 | hours

## 5. GENERAL DEFINITIONS

| | |
|---|---|
| Platform-randomized patient | • Patients allocated to an intervention within one or more REMAP-CAP domains. |
| Registry-only patient | • Patients meeting a minimum set of eligibility criteria but not allocated any interventions within available domains. |
| Home | • A place of residence, in which the patient is living independently, or with minimal assistance. This includes:<br>○ A patient who is homeless<br>○ A patient who is under Hospital in the Home (HITH) care<br>○ A patient who resides in University Halls of Residence or similar. |
| Nursing home | • A nursing home or long-term care facility resident refers to people who are living in a residential facility helping with activities of daily living (dressing, bathing, toileting, eating) on a regular basis because of chronic conditions, physical or mental disabilities.<br>• A nursing home / long-term care facility does not include**:**<br>○ Independent living in a retirement village<br>○ Hospital-in-the Home<br>○ Independent hostel or rest home living. |
| ICU | • An ICU is defined as a unit that provides specialized care for critically ill patients. These may also be known as Critical Care Units, or Intensive Treatment/Therapy Units. |

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| | • This definition includes High-Dependency Units (HDU) or other areas where patients are under the care of intensivists.<br>• During a pandemic the definition of an ICU includes a repurposed area that is capable of providing ICU-level care (NIV with a sealed mask, invasive mechanical ventilation, or vasopressors via continuous infusion).<br>• Areas that were not an ICU before a pandemic that were capable of providing NIV and continue to provide no more than NIV do not meet the definition of an ICU. |
| ICU Admission | • The time and date at which a patient physically arrives in the ICU.<br>• During a pandemic, for a patient admitted to a location that is not usually designated as an ICU, the time of ICU admission is the time of first administration of qualifying organ support (do not commence the eligibility process until patient has a qualifying organ failure support). |
| ICU Discharge | • The time and date at which a patient physically leaves the ICU.<br>• If a patient has been bed blocked or booked out of ICU, but physically remains in the ICU, then the patient is still defined as an ICU patient and daily data must be collected until they physically leave the ICU.<br>• During a pandemic ICU discharge is defined as the time at which a patient leaves an area in which ICU-level care (NIV with sealed mask, IMV, or vasopressor via continuous infusion) can be provided, either an area usually designated as an ICU or a new area where ICU-level care may be provided.<br>• If a patient with an endotracheal tube or tracheostomy tube in situ is transported directly from ICU to a location outside of the acute hospital (e.g. home) for the purposes of palliation, and the patient remains under the continued care of the ICU team, they are considered to remain admitted to ICU. For such patients, ICU discharge is the date and time that the ICU team ceased to provide care for the patient. |

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| Invasive Mechanical Ventilation | • Invasive mechanical ventilation includes any form of positive pressure ventilation above the expiratory pressure given during inspiration, delivered via an orotracheal, nasotracheal tube or tracheostomy tube (TT), with or without positive end expiratory pressure (PEEP).<br>• It includes, but is not limited to:<br>  ○ Assist Control Volume support<br>  ○ Assist Control Pressure support<br>  ○ Synchronized Intermittent Mechanical Ventilation, volume control with or without pressure support<br>  ○ Synchronized Intermittent Mechanical Ventilation, pressure control with or without pressure support<br>  ○ Pressure support (with no or without mandatory breaths)<br>  ○ Airway Pressure Release Ventilation<br>  ○ Pressure Regulated Volume Control<br>  ○ Adaptive Support Ventilation / Volume Support<br>  ○ High-frequency Oscillation (Jet) ventilation<br>  ○ Tube Compensation<br>  ○ Other invasive mode.<br>• Invasive Mechanical Ventilation <u>does not include:</u><br>  ○ T-piece<br>  ○ CPAP via TT (or endotracheal tube (ETT))<br>  ○ Direct Tracheal/Tracheostomy Interface/Connection<br>  ○ Swedish nose. |
| Illness severity state | • A **Moderate** illness severity state is defined by patients who do not require organ failure support in an ICU. This includes:<br>  ○ Patients not admitted to an ICU<br>  ○ Patients admitted to an ICU but not requiring organ failure support.<br>• **Severe** illness severity state is defined by patients who require organ failure support in an ICU. |

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| High-Flow Nasal Prongs | • High-flow oxygen delivered via nasal prongs or cannula by a specialized device. |
| Non-Invasive Ventilation | • Non-Invasive Ventilation (NIV) includes:<br>  ○ Continuous positive airways pressure (CPAP)<br>  ○ Bi-Level Positive Airway Pressure (BiPAP)<br>  ○ Non-Invasive Positive Pressure Ventilation (NIPPV)<br>• NIV does not include CPAP or BiPAP used solely for the management of pre-existing obstructive sleep apnea or other similar condition. |
| Renal Replacement Therapy | • Renal Replacement Therapy (RRT) includes any form of:<br>  ○ continuous hemofiltration, hemodialysis or hemodiafiltration<br>  ○ Intermittent hemodialysis<br>  ○ Slow Low Efficiency Dialysis (SLED).<br>• Peritoneal dialysis. |
| Vasopressor and inotrope | • A vasopressor is a pharmaceutical agent that causes vasoconstriction, thereby increasing blood pressure.<br>• An inotrope is a pharmaceutical agent that increases myocardial contractility.<br>• Examples of inotropes and vasopressors include:<br>  ○ Adrenaline / epinephrine<br>  ○ Noradrenaline/ norepinephrine<br>  ○ Dobutamine<br>  ○ Dopamine<br>  ○ Metamarinol (Aramine, Metaradrine, Metaramin, Pressonex)<br>  ○ Levosimendan (Simdax)<br>  ○ Milrinone (Primacor)<br>  ○ Vasopressin (Pitressin)<br>  ○ Phenylephrine<br>  ○ Ephedrine. |

# PATIENT SUMMARY PAGE

## General Guidance

- Complete these variables for all ***Platform-randomized and registry-only patients***.

| Question | Definition or Explanation of Question |
|---|---|
| Date of birth | • Date of birth, year of birth, or estimated age is entered on the eligibility form.<br>• If Date of Birth (DOB) was not entered in the Eligibility eCRF enter it on the Patient Summary Page.<br>• You are able to update incorrect date of birth, or age on the Patient Summary Page at any time.<br>• Date format is DD-MMM-YYYY (e.g. 07-JUN-1972). |
| ICU admission date & time | • ICU admission date & time is entered on the eligibility form<br>• You are able to update an incorrectly recorded date and time of ICU admission on the Patient Summary Page at any time.<br>• Date and time the patient was first admitted to any ICU during this hospital admission.<br>• If a patient was transferred to your ICU from another ICU, use the date and time the patient was admitted to the first hospital's ICU.<br>• During a pandemic, for a patient admitted to a location that is not usually designated as an ICU, the date and time of ICU admission is the date and time of first administration of qualifying organ support.<br>• ICU is defined in Section 5. General definitions. |
| Database Linkage | |
| APD Patient Identifier (ANZ only) | • The Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation (ANZICS CORE), Adult Patient Database (APD) patient identifier (PATIENTID) for all patients.<br>• The APD Number is known as the Patient ID and can be found in the Patient Details window on the AORTIC and COMET systems. It is usually auto generated by the APD data collection software. |

| | |
|---|---|
| | • There may be some delay in obtaining the APD number depending on local data collection practices at your site. If this number is not available at the time you collect other variables you can enter it into the eCRF at a later date.<br>• It is an alphabetic, alphanumeric or numeric string, with a maximum length of 12 digits. |
| National Health Index (NHI) number<br>(NZ sites only) | • Unique person identifier used within the New Zealand health system. It is technically not a number but rather an alphanumeric identifier consisting of 7 characters, with three letters and **four** numbers. If a patient also has a minor (supplementary) NHI number, only the major (primary) NHI number is required. |
| ICNARC Case Mix Programme Admission Number<br>(UK sites only) | • The patient's ICNARC case mix programme (CMP) admission number.<br>• This is a unique 8-digit number assigned to each patient admitted to the ICU. |
| Critical Care Asia Africa registry identifier<br>(CCAA sites only) | • The patient's Critical Care Asia (CCAA) registry identifier. |

# FORM 1: ELIGIBILITY

| Question | Definition or Explanation of Question |
|---|---|
| ***Eligibility assessment*** | |
| 1. Patient Demographics | |
| Patient initials | • In the format the First letter of the First, Middle, Last Name (FML) e.g. Donald Chow Yun-Fat = DCY<br>• If the patient does not have a middle name, use a dash (F-L) e.g. Vigdís Finnbogadóttir = V-F.<br>• If the patient has multiple first or middle names, use the first letter of the first and second name e.g. Geoffrey Arthur George Lucas = GAL<br>• If the patient has multiple last names (surnames) only enter the first initial of the first last name as it appears on the patient's medical record.<br>• It is important that the initials and date of birth are entered correctly and consistently, as this may prevent incorrect double-randomization of a patient.<br>• NOTE: In some locations you will not be asked to enter patients' initials, and in some regions this field is encrypted. Once entered, this data will not be displayed on the database and will not be accessible to the Sponsor. |
| | Example: First name: Lowitja, Middle name: nil, Last Name: O'Donoghue — Enter: L-O |
| | Example: First name: Anne, Middle name: nil, Last Name: Martínez García — Enter: A-M |
| | Example: First name: Arnoldo, Middle name: Thanh, Last name: Seefeldt- Groleau — Enter: ATS |
| | Example: First name: Ana, Middle name: María, Last name: O'Neill — Enter: AMO |
| Date of birth | • In some regions, you will only be asked to enter the patient's year of birth. |

| | |
|---|---|
| | • Format DD-MMM-YYYY (e.g. 07-JUN-1972).<br>• If exact date of birth is not known select UNKNOWN AT THIS TIME.<br>  ○ If UNKNOWN is checked, you will be asked to enter an estimated age before proceeding. For randomized participants, update DOB or age on the Patient Summary Page as soon as it is known. Refer to the relevant Database User Guide for instructions.<br>• There is no upper age limit for inclusion into the study. The lower age limit is 28 days old. However, the recruitment of pediatric patient is subject to ethical approvals in each jurisdiction and sites will have the option of which available domains and interventions will be offered to pediatric patients (if any).<br>• NOTE: In some locations this field is encrypted. Once this data is entered it will not be displayed on the database and will not be accessible to the Sponsor. |
| Estimated age | • If the patient's date of birth or year of birth is unknown, enter their estimated age in years.<br>• Do not round age up to the nearest year. For example, if the patient is 30 years and 11 months, enter 30 years.<br>• For patients who are randomized, you are able to update their estimated age on the Patient Summary Page at any time, as more information becomes available. |
| Infant age | • This field is only required if the patient's full date of birth is not entered, and their estimated age is less than 2 years.<br>• Enter the patient's age in months. Do not round up to the nearest month. For example, if a patient is 4 months and 3 weeks, enter 4 months.<br>• If the patient is less than one month old, enter 0 (zero) months. |
| Is the patient an adult in your jurisdiction | • This question only applies if a date of birth is entered and the patient is aged between 16 and 21 years old. |

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| | • An adult is defined by your HREC/IRB approval, irrespective of how it is classified at your hospital (e.g. if your hospital admits a 17 year-old to ICU as a child but you have HREC/IRB approval to enroll patients aged 16 and over this patient would be an adult in your jurisdiction).<br>• If a patient is aged <18 years and your site do not have any domains active in the Pediatric Strata, they will not be able to be randomized, despite being considered an adult. |
| Sex at birth | • Sex at birth is determined by physical sexual characteristics at the time of their birth (i.e. male or female).<br>• Intersex patients (i.e. individuals displaying both male and female physical sexual characteristics at birth) should be entered as the sex that they most identify with. |
| Was the patient randomized in this study in the last 90 days. | • If the patient is known to have been admitted to a hospital that is participating in this study in the last 90 days, check the patient's medical record for a previous randomization in this study.<br>• Patients randomized in REMAP-CAP, or another trial that will be analyzed in the same statistical model as REMAP-CAP, within the last 90 days are **NOT** eligible for re-randomization.<br>• If the patient has been randomized into another study that will be analyzed in the same statistical model as REMAP-CAP, answer "Yes".<br>  ○ Examples include the ASCOT Trial in Australia<br>  ○ If you are unsure whether another trial will be analyzed together with REMAP-CAP, contact your Regional Project Manager.<br>• Patients can be randomized more than once as long as 90 days have passed since the previous randomization (primary outcome from last randomization is known).<br>  ○ NOTE: In Germany, a patient who has been randomized into REMAP-CAP can never be re-randomized into this trial.<br>• If the patient was Registry-only during a previous hospital admission, they were not randomized. Check NO. |

| | |
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| | • This question is only displayed at sites where year of birth is entered. For sites that enter DOB and initials there is a database check of existing patients with the same DOB or initials. The research coordinator will need to confirm that this is not the same patient to proceed. |
| Where is the patient physically located | • Patient's physical location at the time of this eligibility assessment<br>• Only commence eligibility once the patient has been accepted for admission to the hospital<br>• If the patient is in an Emergency Department (ED) and accepted for hospital admission, specify the location to which the patient is intended to be transferred.<br>• ICU is defined in Section 5. General definitions. |
| 2. Platform Inclusion / Exclusion Criteria | |
| Is the patient a resident of a nursing home or long-term care facility | • Prior to this hospital admission the patient was a current resident of a nursing home or long-term care facility providing personal and nursing care.<br>• Nursing home is defined in Section 5. General definitions. |
| Prior to this illness was the patient known to be an inpatient in any healthcare facility within the last 30 days | • Prior to this hospital admission.<br>• An inpatient is a patient who is admitted to a healthcare facility to receive treatment and/or care that includes at least one night spent in hospital.<br>• Single-day admissions, including but not limited to surgery, endoscopy, diagnostic procedure, and dialysis are not an inpatient admission.<br>• A transfer from another acute hospital during this episode of CAP does not count as a prior inpatient admission |
| Does the patient have signs and/or symptoms that are consistent with lower | • Signs and symptoms of a lower respiratory tract infection include:<br>  ○ Acute onset of dyspnea (or acute increase in dyspnea)<br>  ○ Cough<br>  ○ Pleuritic chest pain |

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| respiratory tract infection | |
| Does the patient have radiological evidence of new onset infiltrate of infective origin | • Infiltrate is defined as one or more regions of interstitial and/or alveolar (air space) opacity on a plain chest x-ray or Computed Tomography Scan (CT scan) that is consistent with being caused by infection.<br>• For patients with pre-existing radiological changes, there should be evidence of new infiltrate (consolidation) before answering YES. |
| Is community-acquired respiratory tract infection (including due to COVID-19) the primary reason for this ICU admission | • This question only applies to patients currently in ICU at the time of this eligibility assessment.<br>• The treating clinician believes respiratory tract infection or complications of the respiratory tract infection (e.g. CAP, septic shock, respiratory failure, acute kidney injury, multiorgan failure from CAP) is the primary reason for the patient's ICU admission.<br>• Note that this includes viral pneumonia, including that caused by COVID-19 or influenza.<br>• ICU is defined in Section 5. General definitions. |
| Is community-acquired respiratory tract infection (including due to COVID-19) the primary reason for this hospital admission | • This question only applies to patients who are not in ICU at the time of this eligibility assessment.<br>• The treating clinician believes respiratory tract infection or complications of respiratory tract infection (e.g. CAP, septic shock, respiratory failure, acute kidney injury, multiorgan failure from CAP) is the primary reason for the patient's ICU admission.<br>• Note that this includes viral pneumonia, including that caused by COVID-19 or influenza.<br>• Hospital admission is defined in Section 5. General definitions. |
| What was the primary reason for admission | • This question is only required if community-acquired respiratory tract infection was not the primary reason for the patient's admission.<br>• This question should be answered based on the treating clinician's opinion. |

- Check the most appropriate reason, if the reason is not listed check other and specify in the text box.

| Primary Reason | Explanation |
|---|---|
| Aspiration | If there is known or suspected inhalation of a large volume of gastric contents and the inflammatory response to the aspiration, not primary infection of lung parenchyma, is the primary process.<br>Only check this option if there has been a witnessed or suspected episode of aspiration, or an episode that predisposes to aspiration such as documented coma.<br>A patient in which primary infection of the lung occurs in the context of micro-aspiration (e.g. hazardous alcohol consumption, esophageal disease, swallowing difficulties) is eligible for REMAP-CAP. |
| Exacerbation of asthma | The patient's predominant reason for this admission to ICU is airflow limitation.<br>Exacerbation of asthma is present if a patient has acute severe asthma, and there is also consolidation present on the chest X-ray, but the major clinical problem is the severity of the asthma (expiratory airflow limitation) and not the infection in the lung (such as impaired oxygenation or manifestations of sepsis or septic shock). If the patient meets this criterion, they are not eligible for REMAP-CAP.<br>A patient with mild airflow limitation or a history of asthma but who has CAP (with consolidation on chest X-ray) as their primary problem is eligible for REMAP-CAP. |

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| | Exacerbation of COPD | The patient's predominant reason for admission to ICU is airflow limitation and not respiratory tract infection.<br>Exacerbation of Chronic Obstructive Pulmonary Disease (COPD) is present if a patient has airflow limitation from COPD, and there is also consolidation present on the chest X-ray, but the major clinical problem is the severity of the COPD (expiratory airflow limitation) and not the infection in the lung (such as impaired oxygenation or manifestations of sepsis or septic shock). If the patient meets this criterion they are <u>not eligible</u> for REMAP-CAP.<br>A patient with mild airflow limitation or a history of COPD but who has a respiratory tract infection (with consolidation on chest X-ray) as their primary problem <u>is eligible</u> for REMAP-CAP. |
| | Heart failure | If cardiogenic or acute pulmonary edema is known or suspected to be the predominant process, even if antibiotics are being prescribed for treatment of CAP.<br>A patient with known impaired left ventricular function, valvular heart disease, or a history of cardiogenic or acute pulmonary edema, but who has clear clinical evidence of respiratory tract infection (i.e. focal consolidation), <u>is eligible</u> for REMAP-CAP. |
| | Chronic pneumonia, or strongly suspected fungal | The intention to request or the actual request for investigations for fungal infection or |

<table>
<tr><td></td><td>infection or tuberculosis infection</td><td colspan="2">tuberculosis, alone, is not sufficient to meet this criterion.</td></tr>
<tr><td></td><td></td><td>Chronic pneumonia</td><td>Is defined as symptoms attributable to pneumonia for more than 2 weeks.</td></tr>
<tr><td></td><td></td><td>Suspected fungal infection</td><td>Is defined as clinically suspected fungal infection (e.g. histoplasmosis or coccidiomycosis) in endemic areas and/or invasive fungal infection due to immunosuppression.</td></tr>
<tr><td></td><td></td><td>Suspected pulmonary tuberculosis</td><td>Is defined on clinical grounds where strong consideration is being given to commencing empiric anti-tuberculous therapy in addition to antibacterial agents.</td></tr>
<tr><td colspan="4">3. Platform and Domain Time-Window</td></tr>
<tr><td>When did this hospitalization start</td><td colspan="3">• Date and time the patient first <u>presented</u> from the community to an <u>emergency department</u> (ED) for this acute illness.<br>• If the patient was transferred from another hospital record the date and time they presented to the <u>first hospital's ED</u> (if known).<br>• If the patient presented to an ED multiple times prior to this hospital admission <u>only</u> enter the date and time the patient presented to the ED and was subsequently admitted as an in-patient for this hospital admission.<br>• If the patient is admitted from an outpatient clinic enter the date and time they were formally admitted to the hospital.<br>• If you are unsure what time they presented to the first hospital's ED enter 1 am on the day of admission (i.e. 01:00hrs).</td></tr>
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| When did ICU admission start | • This question only applies to patients located in an ICU at the time of eligibility assessment.<br>• Date and time the patient was first admitted to any ICU during this hospital admission.<br>• ICU is defined in Section 5. General definitions.<br>• If a patient was transferred to your ICU from another ICU use the date and time the patient was admitted to the first hospital's ICU.<br>• During a pandemic, for a patient admitted to a location that is not usually designated as an ICU, the date and time of ICU admission is the date and time of first administration of any qualifying organ support.<br>• For patients admitted to an area not usually designated as an ICU during a pandemic, do not commence the eligibility CRF until the patient has a qualifying organ failure.<br>• If the patient is still physically in the Emergency Department, enter the time that they were accepted for admission to ICU. However, if the patient has been transferred to ED at this hospital from ICU at another hospital, and is accepted for ICU admission at this hospital, enter the date and time of ICU admission at the previous hospital. |
| 4. Organ Failure and Strata Eligibility | |
| Has the patient received sustained organ failure support during this ICU admission | • This question only applies to patients who have already received an allocation to one or more domains in the Moderate illness severity state and are now being reassessed for eligibility for additional domains in the Severe illness severity state.<br>• Sustained organ support is defined as provision of any of the following for more than one continuous hour:<br>  ○ Continuous vasopressor and/or inotrope infusion<br>  ○ High-flow oxygen delivered via nasal prongs or cannula by a specialized device, with an FiO2 ≥ 0.4 and at a flow rate of at least 30 L/min (or at least 2 L/min/kg in children less than 15 kilograms) |

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| | ○ Non-invasive ventilation<br>○ Invasive mechanical ventilation |
| Date and time of commencement of sustained organ failure support during this ICU admission | • This question only applies to patients who have already received an allocation to one or more domains in the Moderate illness severity state and are now being reassessed for eligibility for additional domains in the Severe illness severity state, and who have received sustained organ failure support during this ICU admission.<br>• Enter the date and time that the patient first began receiving sustained organ failure support during this ICU admission<br>• Sustained organ support is defined as provision of any of the following for more than one continuous hour:<br>○ Continuous vasopressor and/or inotrope infusion<br>○ High-flow oxygen delivered via nasal prongs or cannula by a specialized device, with FiO2 ≥ 0.4 and at a flow rate of at least 30 L/min (or at least 2 L/min/kg in children less than 15 kilograms)<br>○ Non-invasive ventilation<br>○ Invasive mechanical ventilation |
| Is the patient receiving a continuous vasopressor and/or inotrope infusion | • At the time of eligibility assessment (now).<br>• If the patient is receiving one or more intravenous vasopressor agent(s) or inotrope agent(s) or both as an on-going infusion, check YES.<br>• If the patient is receiving intermittent doses of a vasopressor or inotrope, even if given frequently, check NO.<br>• Vasopressors and inotropes are defined in Section 5. General definitions. |
| Is the patient currently receiving High-Flow oxygen delivered via nasal prongs or cannula | • At the time of eligibility assessment (now)<br>• HFNP is defined as the provision of high-flow oxygen delivered via nasal prongs or cannula by a specialized device, with FiO2 ≥ 0.4 and at a flow |

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| | rate of at least 30 L/min (or at least 2 L/min/kg in children less than 15 kilograms). |
| Is the patient currently receiving NIV | • At the time of eligibility assessment (now).<br>• NIV is defined as the provision of positive inspiratory or expiratory pressure or both through the patient's own upper airway using a mask, helmet, or similar device.<br>• NIV full definition and examples are provided in Section 5. General definitions. |
| Is the patient receiving invasive mechanical ventilation | • At the time of eligibility assessment (now).<br>• Invasive Mechanical ventilation includes any form of positive pressure ventilation via an orotracheal, nasotracheal or TT, with or without PEEP.<br>• Also known as IMV.<br>• A full definition is provided in Section 5. General definitions.<br>• If the patient has undergone tracheal intubation and is receiving invasive mechanical ventilation check YES.<br>• If the patient is receiving long-term invasive ventilation, answer YES only if there is a significant increase in intensity of provision or IMV (e.g. a clinically significant increase in FiO2, PEEP, or inspiratory support) |
| Has an arterial blood gas been taken while the patient was mechanically ventilated | • This question only applies if the patient is receiving invasive mechanical ventilation at the time of eligibility assessment<br>• If an arterial blood gas (ABG) has not been performed since mechanical ventilation commenced, check NO.<br>• Only record if the ABG was performed as a part of routine clinical care.<br>• An ABG is not required for randomization to the Platform, but may be used to establish domain eligibility. |
| What was the $PaO_2$ on the most recent ABG | • This question is only required if an ABG was performed.<br>• The partial pressure of oxygen ($PaO_2$) measured on the most recent ABG analysis while the patient was invasively mechanically ventilated.<br>• If more than one ABG was drawn, use the most recent sample. |

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| | • Record the result and select the appropriate unit of measurement (mmHg or kPa). |
| What was the corresponding $FiO_2$ | • The fraction of inspired oxygen ($FiO_2$) (range 0.21 -1.0) the patient was receiving at the time that the ABG used to record the patient's $PaO_2$ in the previous question was obtained. |
| What was the corresponding PEEP | • The PEEP in $cmH_2O$ that the patient was receiving at the time that the ABG used to record the patient's $PaO_2$ and $FiO_2$ was obtained.<br>• If the patient was receiving invasive mechanical ventilation using APRV mode at the time that the ABG was obtained, select 'patient receiving APRV'. |
| Has the patient received invasive mechanical ventilation in an ICU during this acute hospital admission | • This question only applies to patients who are not in an ICU at the time of eligibility assessment or who are not currently receiving IMV<br>• Includes previous ICU admissions during this acute hospital admission<br>• IMV is defined in Section 5. General definitions.<br>• IMV provided in the operating room or for a procedure does not meet this criteria<br>• If the patient is receiving long-term invasive ventilation, answer YES only if there is a significant increase in intensity of provision of IMV (e.g. a clinically significant increase in FiO2, PEEP, or inspiratory support). |
| Is influenza infection suspected by the treating clinician or confirmed by microbiological testing | • At the time of eligibility assessment.<br>• If microbiological testing has confirmed the presence of influenza infection, select YES.<br>• If microbiological testing for influenza has not been performed or the results of microbiological testing are not available at the time of eligibility assessment, this question should be answered based on the treating clinician's opinion. |
| Does the patient have microbiologically | • At the time of eligibility assessment<br>• This question is only required if you have indicated that influenza infection is suspected or confirmed. |

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| confirmed influenza infection | • Answer YES if microbiological testing has confirmed the presence of influenza infection.<br>• Answer NO if microbiological testing has been conducted and is negative for influenza infection<br>• Answer NOT TESTED if microbiological testing for influenza has not been performed or the results of microbiological testing are not available at the time of eligibility assessment |
| Does the patient have clinically suspected or proven active pandemic infection | • This question is only required when the Pandemic Strata is active at a site<br>• At the time of eligibility assessment<br>• If microbiological testing has confirmed the presence of pandemic infection, select YES.<br>• If microbiological testing for pandemic infection has not been performed or the results of microbiological testing are not available at the time of eligibility assessment, this question should be answered based on the treating clinician's opinion.<br>• Clinically suspected means that the treating clinician considers pandemic infection is a likely diagnosis. Testing for pandemic infection for infection control reasons or to exclude an unlikely diagnosis is insufficient.<br>• Active means that the patient has current signs and symptoms attributed to pandemic infection. If the patient has suspected or proven pandemic infection but are asymptomatic and admitted for infection control reasons or because of another illness, answer NO.<br>• Patients admitted with another reason other than COVID-19, such as trauma or surgery, who were also found to have SARS-CoV-2 infection without associated acute illness that would require hospital admission do not meet the definition of active infection |
| Where was the suspected or proven | • This question only applies for patients with suspected or proven pandemic infection. |

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| pandemic infection acquired | • Select IN THE COMMUNITY if the pandemic infection was acquired prior to this hospital admission<br>  ○ Includes pandemic infection acquired in long-term healthcare facility or nursing home<br>  ○ Includes pandemic infection acquired during a previous hospital admission but discharged into the community before this current admission<br>• Select DURING THIS HOSPITAL ADMISSION if hospital-acquired or nosocomial infection pandemic infection is probable or proven |
| Signs or symptoms due to suspected or proven pandemic infection have been present for less than 14 days | • This question only applies to patients with suspected or proven pandemic infection acquired during this hospital admission<br>• Select YES if signs or symptoms of pandemic infection have been present for less than 14 days<br>• Select NO if signs or symptoms of pandemic infection have been present for more than 14 days |
| Samples for microbiological testing for SARS-CoV-2 | • This question only applies for patients with suspected or proven pandemic infection.<br>• If microbiological samples have been collected for testing for SARS-CoV-2 infection, select SAMPLES HAVE BEEN COLLECTED<br>• If microbiological samples have not yet been collected, but are planned to be collected select SAMPLES WILL BE COLLECTED<br>• If microbiological samples for testing for SARS-CoV-2 have not been collected and a decision has been made that such samples will not be collected, select SAMPLES WILL NOT BE COLLECTED |
| Has SARS-CoV-2 been confirmed by microbiological testing | • Any time during this acute illness<br>• If SARS-CoV-2 has been reported as isolated or detected on microbiological testing, select YES<br>• On pathology reports, SARS-CoV-2 may be documented as:<br>  ○ SARS-CoV-2<br>  ○ COVID-19 |

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| | ○ Novel Coronavirus<br>○ 2019-nCoV<br>• If no microbiological testing results are currently available, select NO |
| What is the date of first onset of clinical features of this acute illness | • This question is only required if the patient does have signs and/or symptoms that are consistent with lower respiratory tract infection<br>• Enter the date that the patient first experienced the symptoms of this acute illness.<br>• Symptoms may include coughing, sore throat, headache, nasal discharge/nasal congestion, feeling feverish or having chills, aches or pains of the muscles or joints, and fatigue.<br>• Use all available information to estimate the date of first symptom onset. For example:<br>○ If medical notes indicate that the patient was admitted with a "five-day history of cough", then enter the date five calendar days prior to the date of hospital admission.<br>○ If the participant states that they have had a fever for "around 3 or 4" days before coming to hospital, enter the calendar date four days prior to the date of hospital admission.<br>• Includes symptoms that first occur after hospital admission.<br>• If the patient does not have any signs or symptoms at this time, select "patient is asymptomatic"<br>• If no information is available, select NOT RECORDED |
| Is the patient expected to be discharged from this hospital admission today or tomorrow | • This question only applies for patients with suspected or proven pandemic infection.<br>• This question only applies to patients who are not in ICU at the time of this eligibility assessment<br>• Select YES if the patient is expected to be discharged from hospital later today or any time tomorrow<br>• If intended to be transferred to a non-REMAP-CAP participating hospital, answer YES. |

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<tr><td></td><td colspan="2"><ul><li>If intended to be transferred to a REMAP-CAP participating hospital, answer NO.</li><li>If appropriate, discuss participation with receiving REMAP-CAP participating hospital, particularly with respect to domain and intervention compatibility</li></ul></td></tr>
<tr><td rowspan="3">Is death deemed imminent and inevitable during the next 24 hours AND either the patient, substitute decision maker or attending physician is not committed to active treatment</td><td colspan="2">Select YES if the patient meets both of the criteria below:</td></tr>
<tr><td>Death deemed imminent and inevitable</td><td>The senior treating clinician believes there is no reasonable possibility of the patient surviving the next 24h.</td></tr>
<tr><td>No commitment to active treatment</td><td>A decision has been made to withhold a clinical treatment (or intensity of treatment) that would otherwise be indicated for the current severity of illness (e.g. the patient is hypotensive now and vasopressor will not be commenced or dose increased or patient has clinical indication for intubation now but will not be intubated).<br>If the goals of care are primarily aiming for patient comfort then this criterion is met.<br><br>If a ward patient is deemed not for escalation of intensity of treatment in the future, beyond the current level that is being received, this criterion is NOT met.</td></tr>
<tr><td colspan="3">5. Domain Inclusion / Exclusion Criteria</td></tr>
<tr><td colspan="3">Antibiotic Domain</td></tr>
<tr><td>What was the date & time of the first known intravenous antibiotic</td><td colspan="2"><ul><li>Date and time the patient received the first intravenous (IV) dose of an antibiotic for this illness (including if given in the community, if known).</li><li>If no IV antibiotic has been administered, check NOT GIVEN.</li></ul></td></tr>
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| administration for this illness | • If unsure what time of the day the first IV antibiotic was administered enter 1 am on the day you know an antibiotic was administered i.e. 01:00hrs.<br>• If a patient was transferred from another hospital enter the date and time they were given an IV antibiotic in the transferring hospital, if known.<br>• Only information easily available should be used (e.g. ED notes and observations, inpatient notes). |
| Do you suspect methicillin-resistant Staphylococcus aureus infection | • Methicillin-resistant staphylococcus aureus (MRSA) is defined as a staphylococcus aureus that is resistant to any of the following antibiotics:<br>  ○ methicillin<br>  ○ oxacillin<br>  ○ dicloxacillin<br>  ○ nafcillin<br>  ○ flucloxacillin.<br>• Patients with suspected MRSA infection are eligible for randomization to the Antibiotic, Macrolide Duration, and Corticosteroid domains, however an additional agent active against MRSA should be administered. |
| Is standard empiric antibiotic therapy for community-acquired pneumonia appropriate | • Standard empiric antibiotic therapy for CAP is defined as antibiotic therapy regarded as clinically appropriate before the potential availability of microbiological tests that allow guided antimicrobial therapy in accordance with local guidelines.<br>• The Antibiotic Domain allocates patients to various options that are regarded as acceptable standard empiric antibiotic therapy, noting that some additional agents can be added (e.g. vancomycin for MRSA), but not substituted, to ensure appropriate empiric therapy for each patient. |
| Please give a reason that standard empiric | • This question is only required if standard empiric antibiotic therapy is not appropriate. |

<table>
<tr><td rowspan="4">antibiotic therapy is not appropriate</td><td colspan="2">• Examples of when standard empiric antibiotic therapy is <u>not</u> appropriate or not sufficient include:</td></tr>
<tr><td>Primary Reason</td><td>Additional Information</td></tr>
<tr><td>There is sufficient microbiological information to guide specific antibacterial therapy</td><td>A microbiological result is available which indicates targeted antibacterial therapy, such as culture with sensitivities or polymerase chain reaction (PCR) of a known typical or atypical (e.g. Legionella) bacterial pathogen.<br>A positive test for influenza is not regarded as sufficient microbiological information to guide specific <u>antibacterial</u> therapy.<br>If this is selected, you will be asked to specify what information is available to guide antibacterial therapy.</td></tr>
<tr><td>Febrile neutropenia or significant immunosuppression</td><td>• Includes organ or bone marrow transplantation, human immunodeficiency virus (HIV) Infection with cluster of differentiation 4 (CD4) cell count <200 cells/µL, systemic immunosuppression, long term systemic corticosteroids).<br><br>This does not include neutropenia that is being attributed to the CAP (i.e. neutropenia secondary to severe sepsis).</td></tr>
<tr><td>Suspected infection with resistant bacteria (other than MRSA) where empiric agents in this study would not be expected to be active</td><td>Includes cystic fibrosis, bronchiectasis or other chronic suppurative lung disease where infection with Pseudomonas may be suspected.</td></tr>
<tr><td>Suspected or proven serious concomitant infection</td><td>e.g. meningitis</td></tr>
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| | Suspected melioidosis (during melioidosis season according to local guidelines) (Australian sites only) | Defined as the monsoonal period according to local guidelines, in sites located in tropical areas (defined in Australia as hospitals located north of a latitude of 21°S). |
| ***Corticosteroid Domain*** | | |
| Will the patient commence or continue (if already commenced) any of the following medications | • A systemic corticosteroid | • Other than as a REMAP-CAP allocated therapy<br>• Select this option if a systemic corticosteroid has been prescribed or will be prescribed for immediate commencement<br>• Includes only systemic corticosteroids administered enterally or parenterally<br>• Examples include systemic corticosteroids for the treatment of COVID-19 infection, continuation of long-term therapy, bronchospasm, or septic shock<br>• This question applies to patients being assessed for the Corticosteroid Domain, and all patients with proven or suspected pandemic infection<br>• This question applies across multiple domains with different response options. |
| Is the patient currently receiving some form of supplemental oxygen | • Supplemental oxygen includes supplemental oxygen at a FiO2 of > 0.21 delivered via simple facemask, low- or high-flow nasal oxygen, non-invasive ventilation, or invasive mechanical ventilation | |
| ***Influenza Antiviral Domain*** | | |

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| In the opinion of the treating clinician, how likely is it that this patient currently has a bacterial respiratory tract infection | • Select the option that best reflects the possibility of the patient having a bacterial respiratory tract infection, in the opinion of the treating clinician.<br>• Select CONFIRMED only if bacterial respiratory tract infection has been confirmed by microbiological testing. | |
| Is the patient currently receiving antibiotics for suspected or proven bacterial infection | • Select YES if the patient is currently receiving antibiotics for suspected or proven bacterial respiratory tract infection at the time of the eligibility assessment | |
| Will the patient commence or continue (if already commenced) any of the following medications | • An antiviral that is active against influenza, other than oseltamivir or baloxavir or both | • Other than as a REMAP-CAP allocated therapy<br>• Select this option if an antiviral against influenza has been prescribed or will be prescribed for immediate commencement<br>• Examples include zanamivir and peramivir<br>• This question applies across multiple domains with different response options. |
| Since admission to any hospital for this illness, has the patient received two or more doses of Oseltamivir (or any other neuraminidase inhibitor) or has | • Other neuraminidase inhibitors include Zanamivir and Peramivir. | |

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| already received one or more doses of baloxavir | | |
| ***Immunoglobulin Domain*** | | |
| Is the patient a participant in a trial where continuation of study assignment is required, or where ongoing activity of study drug is anticipated for: | • Any antibody therapy directed against COVID-19 | • For a patient randomized into a trial of therapies intended to be active against COVID-19 prior to ICU admission, refer to that study's protocol to determine if study assignment is required to continue in ICU.<br>• For trial medications that are ceased prior to or at the time of ICU admission, check whether study drugs are likely to continue to be active after cessation while the patient is in ICU.<br>• This includes assignment to "no treatment" interventions in open label studies<br>• This question applies across multiple domains with different response options. |
| Does the patient have a known condition or has received treatment resulting in ongoing immune suppression | Patient has an underlying immunodeficiency or has received recent immunosuppressant therapy, defined as:<br>• Immunosuppression:<br>○ Receiving or have received in the last three months non-biological oral immune modulating drugs (e.g. methotrexate >25 mg/week, azathioprine > 3.0 mg/kg/day, or 6-mercaptopurine > 1.5 mg/kg/day)<br>○ Receiving, or have received in the past three months, immunosuppressive chemotherapy<br>○ Received any form of chemotherapy in the last four weeks | |

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| | ○ Allogenic hematopoietic stem cell transplantation within the last 12 months or anytime if on-going treatment for chronic GVHD<br>○ CAR-T cell treatment within the last 12 months<br>○ Receiving or have received in the past 12 months immunosuppressive biological therapy (e.g. alemtuzumab, ofatumumab, or rituximab)<br>○ Organ transplantation recipients<br>○ Receiving other targeted cancer treatments which can affect the immune system, such as protein kinase inhibitors or PARP inhibitors<br>○ Receiving radiotherapy, including Myeloablative radiotherapy (e.g. prior to a stem cell transplant) or high-dose radiotherapy for lung cancer<br>○ Receiving high-dose steroid treatment (e.g. > 1.5 mg/kg methyl prednisolone or equivalent for ≥ 5 days)<br>○ Receiving long-term steroid treatment (e.g. > 20 mg/day of a systemic steroid)<br>• Immunosuppressive disease: the patient has one or more of the following diseases that are sufficiently advanced to suppress resistance to infection (excludes malignancy which has been in remission for five years or more)<br>○ Acquired Immunodeficiency Syndrome (AIDS)<br>○ Acute leukemia (including high-risk MDS)<br>○ Lymphoma<br>○ Myeloma<br>○ Metastatic cancer<br>○ Any other disease that is sufficiently advanced to suppress resistance to infection, for example:<br>▪ Primary or inherited immune deficiency syndromes, including B cell deficiencies (such as Bruton agammaglobulinemia), T cell deficiencies (such as |

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| | Wiskott Aldrich disease), or combined deficiencies (such as Common variable immunodeficiency)<br>▪ Secondary immune deficiency syndromes requiring treatment with regular IV immunoglobulin<br>▪ Aplastic anemia or other causes of chronic neutropenia or neutrophil dysfunction | |
| Is the patient known to have received treatment with polyclonal antibody therapy with the potential to be active against COVID-19 during this acute illness | • Polyclonal antibody therapy includes convalescent plasma and hyperimmunoglobulin against SARS-CoV-2<br>• Regular replacement immunoglobulin (intravenous or subcutaneous) does not meet this criteria | |
| ***Endothelial Domain*** | | |
| Is the patient receiving any of the following as a pre-hospitalization usual medication | • Imatinib, or another tyrosine kinase inhibitor targeting the same pathway as imatinib | • Other tyrosine kinase inhibitors targeting the same pathway as imatinib include dasatinib, nilotinib, ponatinib<br>• Indicate whether the patient was receiving any of the listed agents as a usual medication prior to this hospital admission<br>• This question applies across multiple domains with different response options |
| Will the patient commence or continue (if already commenced) any of | • Imatinib, or another tyrosine kinase inhibitor targeting the | • Other than as a REMAP-CAP allocated therapy<br>• Select this option if imatinib, or another tyrosine kinase inhibitor targeting the same pathway as |

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| the following medications | same pathway as imatinib | imatinib, has been prescribed or will be prescribed for immediate commencement<br>• Other tyrosine kinase inhibitors targeting the same pathway as imatinib include dasatinib, nilotinib, ponatinib<br>• |
| Does the patient have known severe liver disease | • Includes known portal hypertension, for example splenomegaly attributed to portal hypertension; varices demonstrated on endoscopy; or current or past episodes of hepatic encephalopathy severe enough to result in reduced level of consciousness.<br>• Any patient with Child-Pugh class C liver disease will meet this definition<br>• Abnormal liver function tests alone are not sufficient to meet this definition<br>• This question applies to patients being assessed for the Cysteamine Domain, or Endothelial Domain. | |
| Does the patient have an alanine aminotransferase or aspartate aminotransferase more than 5 times the upper limit of normal | • Select YES is the most recent alanine aminotransferase or aspartate aminotransferase recorded within the past 72 hours was greater than five times the upper limit of normal<br>• This question applies to patients being assessed for the Endothelial Domain, or Influenza Immune Modulation Domain. | |
| Does the patient have a bilirubin more than 3 times the upper limit of normal | • Select YES is the most recent bilirubin recorded within the past 72 hours was greater than three times the upper limit of normal | |

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| Does the patient have a platelet count < 50 x $10^9$ / L | • Select YES is the most recent platelet count recorded within the past 72 hours was less than 50 x $10^9$ / L | |
| Does the patient have a neutrophil count < 1.0 x $10^9$ / L | • Select YES is the most recent neutrophil count recorded within the past 72 hours was less than 1.0 x $10^9$ / L | |
| ***Influenza Immune Modulation Domain*** | | |
| Is the patient's respiratory tract infection the primary contributor for their requirement for this organ support | • Select YES if, in the opinion of the treating clinician, the patient's respiratory tract infection is the primary contributor for their current level of respiratory support.<br>• Answer NO if their current level of respiratory support is due primarily to other reasons. | |
| In the opinion of the treating clinician, how likely is it that this patient currently has a bacterial respiratory tract infection | • Select the option that best reflects the possibility of the patient having a bacterial respiratory tract infection, in the opinion of the treating clinician.<br>• Select CONFIRMED only if bacterial respiratory tract infection has been confirmed by microbiological testing. | |
| Is the patient currently receiving antibiotics for suspected or proven bacterial infection | • Select YES if the patient is currently receiving antibiotics for suspected or proven bacterial respiratory tract infection at the time of the eligibility assessment | |
| Is the patient receiving any of the following as a pre-hospital usual medication | • Tocilizumab<br>• Sarilumab<br>• Any other IL-6 receptor antagonist<br>• Baricitinib | • Indicate whether the patient was receiving any of the listed agents as a usual medication prior to this hospital admission |

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| | • Tofacitinib or another JAK inhibitor | • This question applies across multiple domains with different response options |
| Has the patient received any of the following during this hospitalization | • Tocilizumab<br>• Sarilumab<br>• Any other IL-6 receptor antagonist<br>• Baricitinib<br>• Tofacitinib or another JAK inhibitor | • Indicate whether the patient has received one or more doses of the following medications during this hospitalization |
| Does the patient have a known condition or has received treatment resulting in ongoing immune suppression | Patient has an underlying immunodeficiency or has received recent immunosuppressant therapy, defined as:<br>• Immunosuppression:<br>  ○ Receiving or have received in the last three months non-biological oral immune modulating drugs (e.g. methotrexate >25 mg/week, azathioprine > 3.0 mg/kg/day, or 6-mercaptopurine > 1.5 mg/kg/day)<br>  ○ Receiving, or have received in the past three months, immunosuppressive chemotherapy<br>  ○ Received any form of chemotherapy in the last four weeks<br>  ○ Allogenic hematopoietic stem cell transplantation within the last 12 months or anytime if on-going treatment for chronic GVHD<br>  ○ CAR-T cell treatment within the last 12 months<br>  ○ Receiving or have received in the past 12 months immunosuppressive biological therapy (e.g. alemtuzumab, ofatumumab, or rituximab)<br>  ○ Organ transplantation recipients<br>  ○ Receiving other targeted cancer treatments which can affect the immune system, such as protein kinase inhibitors or PARP inhibitors | |

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| | ○ Receiving radiotherapy, including Myeloablative radiotherapy (e.g. prior to a stem cell transplant) or high-dose radiotherapy for lung cancer<br>○ Receiving high-dose steroid treatment (e.g. > 1.5 mg/kg methyl prednisolone or equivalent for ≥ 5 days)<br>○ Receiving long-term steroid treatment (e.g. > 20 mg/day of a systemic steroid)<br>• Immunosuppressive disease: the patient has one or more of the following diseases that are sufficiently advanced to suppress resistance to infection (excludes malignancy which has been in remission for five years or more)<br>○ Acquired Immunodeficiency Syndrome (AIDS)<br>○ Acute leukemia (including high-risk MDS)<br>○ Lymphoma<br>○ Myeloma<br>○ Metastatic cancer<br>○ Any other disease that is sufficiently advanced to suppress resistance to infection, for example:<br>▪ Primary or inherited immune deficiency syndromes, including B cell deficiencies (such as Bruton agammaglobulinemia), T cell deficiencies (such as Wiskott Aldrich disease), or combined deficiencies (such as Common variable immunodeficiency)<br>▪ Secondary immune deficiency syndromes requiring treatment with regular IV immunoglobulin<br>• Aplastic anemia or other causes of chronic neutropenia or neutrophil dysfunction |
| Does the patient have confirmed invasive fungal or mycobacterial infection | • Select YES if, in the patient has microbiologically confirmed invasive fungal or mycobacterial infection; or if these are strongly suspected by the treating clinician.<br>• Examples of invasive fungal infections include any fungaemia (growth of a fungus such as a Candida species from a blood culture), invasive |

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| | aspergillosis (e.g. pulmonary aspergillosis), invasive mould infection (e.g. mucormycosis), Pneumocystis jirovecii pneumonia, and cryptococcal infection (e.g. cryptococcal pneumonia or meningitis). Do not select 'yes' if the patient has a fungal infection that is not invasive such as oral candidiasis, esophageal candidiasis, or fungal infection of the skin.<br>• Examples of mycobacterial infections include tuberculosis, leprosy, and non-tuberculous mycobacterial (NTM) infections such as Mycobacterium avium infection of the lungs. | |
| Will the patient commence or continue (if already commenced) any of the following medications | • Tocilizumab<br>• Baricitinib | • Other than as a REMAP-CAP allocated therapy<br>• Select this option if tocilizumab or sarilumab has been prescribed or will be prescribed for immediate commencement<br>• This question applies across multiple domains with different response options. |
| Does the patient have an alanine aminotransferase or aspartate aminotransferase more than 5 times the upper limit of normal | • Select YES is the most recent alanine aminotransferase or aspartate aminotransferase recorded within the past 72 hours was greater than five times the upper limit of normal<br>• This question applies to patients being assessed for the Endothelial Domain, and Influenza Immune Modulation Domain | |
| Height | • Record the patient's height and select the unit of measurement (cm or feet and inches).<br>• Height may be measured or estimated if it is not documented in the medical record.<br>• If estimated, estimate height during this hospital admission. | |

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| | • If not measured during this hospitalization, any measurement in the medical record taken whilst the patient was an adult (over the age of 18 years) can be used.<br>• If height is estimated and a measurement becomes available during this hospital admission, update the field.<br>• If estimated, document estimated height in the patient's medical record.<br>• This question is not required for pediatric participants. |
| Does the patient have a platelet count < 50 x $10^9$ / L | • Select YES is the most recent platelet count recorded within the past 72 hours was less than 50 x $10^9$ / L |
| Does the patient have a neutrophil count < 1.0 x $10^9$ / L | • Select YES is the most recent neutrophil count recorded within the past 72 hours was less than 1.0 x $10^9$ / L |
| Is the patient receiving renal replacement therapy | • Renal Replacement Therapy (RRT) includes any form of:<br>  ○ continuous hemofiltration, hemodialysis or hemodiafiltration<br>  ○ Intermittent hemodialysis<br>  ○ Slow Low Efficiency Dialysis (SLED).<br>  ○ Peritoneal dialysis. |
| Serum creatinine | • Enter the most recent serum creatinine measured during this hospital admission<br>• Serum creatinine is used together with the patient's age and height to estimate glomerular filtration rate (eGFR) to determine eligibility for the Influenza Immune Modulation Domain. |
| ***COVID-19 Antiviral (II) Domain*** | |
| Has SARS-CoV-2 infection been confirmed by positive rapid antigen test or polymerase chain | • Select YES if the patient has had a positive rapid antigen test or PCR test for SARS-CoV-2 within the last 7 calendar days. |

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| reaction test within the last 7 days | • If the patient has not had a RAT or PCR test for SARS-CoV-2 within the last seven days, or if all tests within this time period have been negative, select NO |
| Does the patient have a known condition or has received treatment resulting in ongoing immune suppression | Patient has an underlying immunodeficiency or has received recent immunosuppressant therapy, defined as:<br>• Immunosuppression:<br>○ Receiving or have received in the last three months non-biological oral immune modulating drugs (e.g. methotrexate >25 mg/week, azathioprine > 3.0 mg/kg/day, or 6-mercaptopurine > 1.5 mg/kg/day)<br>○ Receiving, or have received in the past three months, immunosuppressive chemotherapy<br>○ Received any form of chemotherapy in the last four weeks<br>○ Allogenic hematopoietic stem cell transplantation within the last 12 months or anytime if on-going treatment for chronic GVHD<br>○ CAR-T cell treatment within the last 12 months<br>○ Receiving or have received in the past 12 months immunosuppressive biological therapy (e.g. alemtuzumab, ofatumumab, or rituximab)<br>○ Organ transplantation recipients<br>○ Receiving other targeted cancer treatments which can affect the immune system, such as protein kinase inhibitors or PARP inhibitors<br>○ Receiving radiotherapy, including Myeloablative radiotherapy (e.g. prior to a stem cell transplant) or high-dose radiotherapy for lung cancer<br>○ Receiving high-dose steroid treatment (e.g. > 1.5 mg/kg methyl prednisolone or equivalent for ≥ 5 days)<br>○ Receiving long-term steroid treatment (e.g. > 20 mg/day of a systemic steroid)<br>• Immunosuppressive disease: the patient has one or more of the following diseases that are sufficiently advanced to suppress resistance |

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| | to infection (excludes malignancy which has been in remission for five years or more)<br>○ Acquired Immunodeficiency Syndrome (AIDS)<br>○ Acute leukemia (including high-risk MDS)<br>○ Lymphoma<br>○ Myeloma<br>○ Metastatic cancer<br>○ Any other disease that is sufficiently advanced to suppress resistance to infection, for example:<br>▪ Primary or inherited immune deficiency syndromes, including B cell deficiencies (such as Bruton agammaglobulinemia), T cell deficiencies (such as Wiskott Aldrich disease), or combined deficiencies (such as Common variable immunodeficiency)<br>▪ Secondary immune deficiency syndromes requiring treatment with regular IV immunoglobulin<br>• Aplastic anemia or other causes of chronic neutropenia or neutrophil dysfunction |
| Has the patient received more than 24 hours of an antiviral agent intended to be active against SARS-CoV-2 within the past 7 days | • Includes antiviral agents received in the community prior to this hospital admission. |
| Has the patient received supplemental oxygen on this calendar day | • "On the day of eligibility assessment" means any time after midnight on that calendar day.<br>• For example, if a patient was receiving oxygen via nasal prongs at 2L/min at 03:00, and at 04:30 it was removed, and the eligibility assessment is being completed at 11:45, this patient would not be eligible for the No Antiviral intervention. |

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| | • The indication for the supplemental oxygen is not relevant to this question.<br>• Patients on long term domiciliary oxygen who continue on that in hospital will be considered to be receiving supplemental oxygen. |
| Does the patient have an alanine aminotransferase or aspartate aminotransferase more than 5 times the upper limit of normal | • Select YES is the most recent alanine aminotransferase or aspartate aminotransferase recorded within the past 72 hours was greater than five times the upper limit of normal<br>• This question applies to patients being assessed for the Endothelial Domain, or Influenza Immune Modulation Domain |
| Is the patient receiving renal replacement therapy | • Renal Replacement Therapy (RRT) includes any form of:<br>○ continuous hemofiltration, hemodialysis or hemodiafiltration<br>○ Intermittent hemodialysis<br>○ Slow Low Efficiency Dialysis (SLED).<br>○ Peritoneal dialysis. |
| Serum creatinine | • Enter the most recent serum creatinine measured during this hospital admission<br>• Serum creatinine is used together with the patient's age and height to estimate glomerular filtration rate (eGFR) to determine eligibility for the Influenza Immune Modulation Domain. |

| 6. Intervention Contraindications | | |
|---|---|---|
| Is the patient pregnant and/or breastfeeding | All other sites | • This question will only be required for female patients aged 12 - 55 years.<br>• Pregnancy is confirmed by one or more of:<br>  ○ An ultrasound or other imaging<br>  ○ A urine or blood Beta Human Chorionic Gonadotropin (β-hCG test)<br>  ○ A clinical diagnosis<br>• If a female is <u>not known</u> to be pregnant or breastfeeding and they are of childbearing potential check UNKNOWN.<br>• NOTE: A female under 55 years old with no documented evidence of menopause, hysterectomy, surgical sterilization is of child-bearing potential. |
| | German sites | • This question is required for all female patients.<br>• Pregnancy is confirmed with a urine or blood β-hCG test. |
| Does the patient have a contraindication to | • A contraindication is defined as any clinical reason why a specific medication should not be administered. | |

<table>
<tr><td rowspan="4">any of the following medications</td><td colspan="2"><ul><li>It includes, but is not limited to, any and all adverse drug reactions known from the patient’s history and/or medication chart or concomitant clinical condition or history of a condition that precludes administration of a medication.</li></ul></td></tr>
<tr><td>Penicillins</td><td><ul><li>Include any contraindication documented in the patient’s medical record, irrespective of the severity.</li><li>NOTE: any history of the following related to penicillin or any beta-lactam:<ul><li>Anaphylaxis</li><li>Penicillin induced autoimmune hemolytic anemia</li><li>Penicillin induced interstitial nephritis</li><li>Stevens-Johnson Syndrome</li><li>Toxic Epidermal Necrolysis</li><li>Other non-life-threatening adverse drug reactions such as rash.</li></ul></li></ul></td></tr>
<tr><td>Cephalosporins</td><td><ul><li>Include any contraindication documented in the patient’s medical record, irrespective of the severity.</li><li>NOTE: any history of the following related to cephalosporin or any beta-lactam:<ul><li>Anaphylaxis</li><li>Cephalosporin induced autoimmune hemolytic anemia</li><li>Cephalosporin induced interstitial nephritis</li><li>Stevens-Johnson Syndrome</li></ul></li></ul></td></tr>
</table>

| | | |
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| | | ○ Toxic Epidermal Necrolysis<br>○ Other non-life-threatening adverse drug reactions such as rash. |
| | Quinolones | Include any contraindication documented in the patient's medical record, irrespective of the severity. |
| | Macrolides | Include any contraindication documented in the patient's medical record, irrespective of the severity. |
| | Any corticosteroid | Include any contraindication documented in the patient's medical record, irrespective of the severity. |
| | Oseltamivir | Include any contraindication documented in the patient's medical record, irrespective of the severity. |
| | Baloxavir | Include any contraindication documented in the patient's medical record, irrespective of the severity. |
| | Transfusion of blood products | Includes:<br>• Known history of moderate or severe allergy or transfusion reaction to blood components<br>• Known history of transfusion-related lung injury<br>• Known objection to receiving plasma products |

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| | Imatinib | Includes:<br>• Known hepatitis B or C<br>• Currently receiving strong CYP3A4 inhibitors (e.g. -azoles, erythromycin) or inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin)<br>• Currently receiving a calcineurin inhibitor (e.g. cyclosporine, tacrolimus, everolimus, or sirolimus) |
| | Tocilizumab | Includes:<br>• Known adverse drug reaction<br>• AST / ALT level more than 5 times the upper limit of normal range, or<br>• Platelet count < 50 x $10^9$ / L |
| | Baricitinib | Includes:<br>• Known adverse drug reaction |
| | Enteral nirmatrelvir / ritonavir | Includes:<br>• Known adverse drug reaction<br>• The patient is unable to take, tolerate or absorb oral or enteral medications, or<br>• Receipt of a concomitant drug with a high-risk interaction with nirmatrelvir / ritonavir which cannot be ceased or substituted |
| | Intravenous remdesivir | Includes:<br>• Known adverse drug reaction<br>• No venous access is available and none can be created |

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| | In the opinion of the treating clinician, is the patient at very high risk for progression to severe COVID-19 | • Patients at high risk include those who:<br>  ○ have not completed at least a primary course of vaccination; OR<br>  ○ do not have a history of previous COVID-19 infection; OR<br>  ○ who may not have responded well to vaccination (e.g., are immunocompromised)<br>• "Very high risk for progression to severe COVID-19" includes patients who have had previous severe COVID-19 pneumonitis requiring admission to ICU, or other patients for whom the clinician lacks equipoise to randomize to no antiviral treatment<br>• Selecting "Yes" will exclude the patient from receiving the 'no antiviral' intervention in the COVID-19 Antiviral II Domain. |
| | Is nirmatrelvir- ritonavir available for administration to this patient, if they are assigned to this intervention | • Different healthcare providers may have specific criteria to allow access to nirmatrelvir- ritonavir. This question confirms whether this patient satisfies such criteria for access. If your patient would satisfy the local access criteria but nirmatrelvir-ritonavir is contraindicated due to drug interactions, please answer YES to this question. |
| | Is remdesivir available for administration to this patient, | • Different healthcare providers may have specific criteria to allow access to |

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| | if they are assigned to this intervention | remdesivir. This question confirms whether this patient satisfies such criteria for access. If your patient would satisfy the local access criteria but remdesivir is contraindicated (eg hepatic or renal failure), please answer YES to this question. |
| 7. Consent | | |
| Have you gained consent from the participant/legal representative or, in Germany, do you have permission to enroll the patient without prior consent into at least one domain | | • This question is only required at sites where prospective consent is required prior to randomization.<br>• Select YES – AGREED if consent has been obtained from the participant or their legal representative.<br>• In Germany, select YES – AGREED if the patient or their legal representative are not able to provide consent at this time and an independent physician has given consent for the patient to be enrolled into the trial.<br>• Select NO – DECLINED if the patient, their legal representative, or (in Germany) an independent physician has declined to consent to enroll the patient in this trial.<br>• Select NOT YET if no one has been approached to provide consent for participation in this trial.<br>  ○ If NOT YET is selected, the patient will be deemed to be "consent pending", and may be eligible for the trial if consent is obtained within the eligibility time-window. Please return to this page and update consent information as soon as possible to complete eligibility assessment. |
| At this time is the patient sufficiently capable of providing informed consent to participate or have | | • This question only applies at sites where, for patients who are not competent to consent, prospective agreement to participate is not required prior to enrollment for patients.<br>• Select YES if the patient is competent to consent |

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| you gained consent from a proxy/legal representative | • If the patient does not have capacity to consent, select YES if a suitable proxy or legal representative has already been approached to provide consent, regardless of the outcome of this consent discussion<br>• If the patient is not competent to consent, and consent has not been gained from a proxy or legal representative, tick NO and this will allow you to proceed.<br>• It is important to consider if the patient is competent prior to randomization. It is not sufficient that a patient can sign a consent form, they must be capable of understanding their participation and making an informed choice regarding a decision to take part in the study.<br>• If the patient is capable of providing consent, speak to a Research Coordinator or the Principal Investigator at your site before approaching the patient.<br>• You are able to save the eCRF while you obtain consent. Follow the instructions provided on the eCRF and document the patient's unique eligibility assessment code. |
| Is there agreement to participate in at least one domain | This question only applies if the patient was capable of providing agreement.<br>Please select from the following options:<br>• Yes – Agreed<br>• No – Declined<br>• Not Yet<br>• Not in the patient's best interests |
| Which domains have been consented to | • This question only applies if the answer to the previous question is "Yes – Agreed".<br>• Select "Yes – Agreed" or "No – Declined" for each available domain.<br>• Select "Not in the patient's best interests" if the patient was not approached for consent for a domain because the clinician had determined that participation in that domain was not in their best interests. |

| 8. Best Interest | |
|---|---|
| In the opinion of the treating clinician allocation to any of the Antibiotic Domain options above is appropriate for this patient | • The information you have provided indicates that this patient is eligible for the Antibiotic Domain.<br>• By checking YES, you are confirming that the treating clinician believes that all of these options are equally clinically appropriate for this patient and that there is no other treatment option that the treating clinician believes to be superior to any of these options. |
| In the opinion of the treating clinician allocation to any of the Macrolide Duration Domain options above is appropriate for this patient | • The information you have provided indicates that this patient is eligible for the Macrolide Duration Domain.<br>• By checking YES, you are confirming that the treating clinician believes standard course (3-5 days) or long course (14 days) of Macrolide treatment are equally appropriate for this patient.<br>• Patients allocated to standard course macrolide can have the macrolide extended if microbiological results become available indicating a longer course of macrolide is required.<br>• Considerations should include risk of ventricular rhythm disturbance and QT prolongation. |
| In the opinion of the treating clinician allocation to any of the Corticosteroid Domain options above is appropriate for this patient | • The information you have provided indicates that this patient is eligible for the Corticosteroid Domain.<br>• By checking YES, you are confirming that the treating clinician believes that all of these options are equally clinically appropriate for this patient and that there is no other treatment option that the treating clinician believes to be superior to any of these options.<br>• Considerations should include recent upper gastrointestinal bleeding, co-existing immunosuppression, and prior use of etomidate. |
| In the opinion of the treating clinician allocation to any of the Influenza Antiviral Domain options | • The information that you have provided indicates that the patient is eligible for the Antiviral Domain.<br>• By checking YES, you are confirming that the treating clinician believes that all of these options are equally clinically appropriate for this |

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| above is appropriate for this patient | patient and that there is no other treatment option that the treating clinician believes to be superior to any of these options. |
| In the opinion of the treating clinician allocation to any of the Immunoglobulin Domain options above is appropriate for this patient | • The information that you have provided indicates that the patient is eligible for the Immunoglobulin Domain<br>• By checking YES, you are confirming that the treating clinician believes that all of these options are equally clinically appropriate for the patients and that there is no other treatment option that the treating clinician believes to be superior to any of these options. |
| In the opinion of the treating clinician allocation to any of the Endothelial Domain options above is appropriate for this patient | • The information that you have provided indicates that the patient is eligible for the Endothelial Domain<br>• By checking YES, you are confirming that the treating clinician believes that all of these options are equally clinically appropriate for the patient and that there is no other treatment option that the treating clinician believes to be superior to any of these options. |
| In the opinion of the treating clinician allocation to any of the Influenza Immune Modulation Domain options above is appropriate for this patient | • The information that you have provided indicates that the patient is eligible for the Influenza Immune Modulation Domain<br>• By checking YES, you are confirming that the treating clinician believes that all of these options are equally clinically appropriate for the patient and that there is no other treatment option that the treating clinician believes to be superior to any of these options. |
| In the opinion of the treating clinician allocation to any of the COVID-19 Antiviral (II) Domain options above is appropriate for this patient | • The information that you have provided indicates that the patient is eligible for the COVID-19 Antiviral (II) Domain<br>• By checking YES, you are confirming that the treating clinician believes that all of these options are equally clinically appropriate for the patient and that there is no other treatment option that the treating clinician believes to be superior to any of these options. |

## REGISTRY PATIENTS

### General Guidance

- The following questions apply only to patients with community-acquired pneumonia who are otherwise not eligible for the platform.

| Question | Definition or Explanation of Question | |
|---|---|---|
| At any time in the first 48 hour of the ICU admission did the patient receive any of the following | This set of questions only apply if the current eligibility assessment occurs after the REMAP-CAP organ failure time-window has closed. | |
| | A continuous vasopressor and/or inotrope infusion | • If a patient received a continuous infusion at any time during the first 48 hours of their ICU admission check YES.<br>• The infusion must have been administered for at least one continuous hour. If the ICU Chart only records hourly interventions the treatment must have been recorded for at least two consecutive hours.<br>• If the patient received intermittent doses of a vasopressor or inotrope, even if given frequently, check NO.<br>• Vasopressors and inotropes are defined in Section 5. General definitions. |
| | High-Flow Nasal Prongs | • If a patient has received high-flow oxygen therapy at any time during the first 48 hours of their ICU admission, check YES.<br>• The high-flow oxygen therapy must have been administered for at least one continuous hour. If the ICU chart only records hourly interventions the |

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| | | treatment must have been recorded for at least two consecutive hours.<br>• HFNP is defined as the provision of high-flow oxygen delivered via nasal prongs or cannula by a specialized device, with an FiO2 ≥ 0.4 and at a flow rate of at least 30 L/min (or at least 2 L/min/kg in children less than 15 kilograms). |
| | NIV | • If a patient received non-invasive ventilation at any time during the first 48 hours of their ICU admission check YES.<br>• The NIV must have been administered for at least one continuous hour. If the ICU Chart only records hourly interventions the treatment must have been recorded for at least two consecutive hours.<br>• NIV is defined as the provision of positive inspiratory or expiratory pressure or both through the patient's own upper airway using a mask, helmet, or similar device.<br>• NIV full definition and examples are provided in Section 5. General definitions. |
| | Invasive mechanical ventilation | • If a patient received invasive mechanical ventilation at any time during the first 48 hours of their ICU admission check YES. |

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| | | • The invasive mechanical ventilation must have been administered for at least one continuous hour. If the ICU Chart only records hourly interventions the treatment must have been recorded for at least two consecutive hours.<br>• Invasive mechanical ventilation includes any form of positive pressure ventilation via an orotracheal, nasotracheal or tracheostomy tube, with or without PEEP.<br>• Also known as IMV.<br>• A full definition is provided in Section 5. General definitions. |

# FORM 1B: MACROLIDE REVEAL

## General Guidance

- This page applies for all patients eligible for the Macrolide Duration Domain
- Macrolide Duration allocation can only be revealed between time of randomization and the end of study day 5
- In all regions except the UK, agreement must be obtained from the patient or their proxy before Macrolide Duration allocation can be revealed

| Question | Definition or Explanation of Question |
|---|---|
| Is the patient's pneumonia due to microbiologically proven or strongly suspected infection with Legionella or another atypical organism | • Select YES if the patient's pneumonia is suspected or confirmed to be caused by Legionella or another atypical organism that may require an extended course of Macrolide. |
| Has macrolide been ceased for more than 36 hours | • Select YES if the patient has not received a macrolide for any period of 36 hours or more since randomization in the Antibiotic Domain. |
| Agreement to participate in the Macrolide Duration Domain has been obtained | • Indicate whether the patient or their proxy has agreed to participation in the Macrolide Duration domain.<br>• Note that this question is not required for sites in the UK. |
| In the opinion of the treating clinician, allocation to any of the Macrolide Duration Domain options below is appropriate for the patient | • By checking YES, you are confirming that the treating clinician believes standard course (3-5 days) or long course (14 days) of Macrolide treatment are equally appropriate for this patient.<br>• Patients allocated to standard course macrolide can have the macrolide extended if microbiological results become available indicating a longer course of macrolide is required.<br>• Considerations should include risk of ventricular rhythm disturbance and QT interval prolongation. |

# FORM 1C: DOMAIN REVEAL

## General Guidance

- This page applies for all patients eligible for the Antibiotic Domain, Corticosteroid Domain, Influenza Antiviral Domain, Anticoagulation Domain, and Endothelial Domain.
- Allocation in the Antibiotic, Corticosteroid, Influenza Antiviral, , and Endothelial Domains can only be revealed between time of randomization and the end of the eligibility time windows for these domains
    - For patients randomized to these domains in the Moderate illness severity state, reveal of allocation status can only occur up to 48 hours after randomization.

| Question | Definition or Explanation of Question |
|---|---|
| Has agreement to participate in the Domain been obtained | • Select YES if informed consent for participation in this domain has been obtained in accordance with ethical and regulatory approvals at your site |
| In the opinion of the treating clinician, allocation to any of the Domain options below is appropriate for this patient | • By checking YES, you are confirming that the treating clinician believes that all of these options are equally clinically appropriate for the patients and that there is no other treatment option that the treating clinician believes to be superior to any of these options. |

# FORM 1D: IMMUNOGLOBULIN DOMAIN REVEAL

## General Guidance

- This page applies for all patients eligible for the Immunoglobulin Domain
- Allocation in this domain can only be revealed between time of randomization and the end of the domain eligibility time window

| Question | Definition or Explanation of Question |
|---|---|
| SARS-CoV-2 infection is confirmed | • If SARS-CoV-2 has been reported as isolated or detected on microbiological testing, select YES<br>• On pathology reports, SARS-CoV-2 may be documented as:<br>  ○ SARS-CoV-2<br>  ○ COVID-19<br>  ○ Novel Coronavirus<br>  ○ 2019-nCoV |
| Is the patient known to have received treatment with monoclonal antibody therapy active against SARS-CoV-2 during this acute illness | • Select YES if the patients is known to have received treatment with monoclonal antibody therapy with the potential to be active against SARS-CoV-2 at any time during this acute illness<br>• Includes prior to hospital admission during this acute illness<br>• Examples of monoclonal antibody therapy include:<br>  ○ Bamlanivimab / etesevimab<br>  ○ Casirivimab / imdevimab (also known as REGEN-COV or Ronapreve)<br>  ○ Sotrovimab |
| Can two units of high-titre convalescent plasma be made available for administration to this participant if they are assigned to this intervention | • Select YES only once the availability of two units of high titre convalescent plasma has been confirmed.<br>• Please confirm availability of high titre convalescent plasma with your blood service in your region or hospital blood bank.<br>• If two units of high titre convalescent plasma are not available, the participant's allocation in this domain cannot be revealed. |

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| Has the clinical team agreed not to administer convalescent plasma if this patient is allocated 'no convalescent plasma' | • Select YES if the clinical team caring for the participant have agreed not to administered convalescent plasma if the participant is allocated to the 'no convalescent plasma' intervention within this domain.<br>• If the treating clinical team cannot agree to withhold convalescent plasma if the participant is allocated to the 'no convalescent plasma' intervention, select NO. The participant's allocation in this domain will not be revealed. |
| Has agreement to participate in the Immunoglobulin Domain been obtained | • Select YES if informed consent for participation in this domain has been obtained in accordance with ethical and regulatory approvals at your site |
| In the opinion of the treating clinician is allocation to any of the immunoglobulin domain options below appropriate for this patient | • By checking YES, you are confirming that the treating clinician believes that all of these options are equally clinically appropriate for the patients and that there is no other treatment option that the treating clinician believes to be superior to any of these options. |

## FORM 1E: INFLUENZA IMMUNE MODULATION DOMAIN REVEAL

### General Guidance

- This page applies for all patients eligible for the Influenza Immune Modulation Domain
- Allocation in this domain can only be revealed up to 48 hours after randomisation

| Question | Definition or Explanation of Question |
|---|---|
| Does the patient have microbiologically confirmed influenza infection | • At the time of eligibility assessment<br>• This question is only required if you have indicated that influenza infection is suspected or confirmed.<br>• Answer YES if microbiological testing has confirmed the presence of influenza infection.<br>• Answer NO if microbiological testing has been conducted and is negative for influenza infection<br>• Answer NOT TESTED if microbiological testing for influenza has not been performed or the results of microbiological testing are not available at the time of eligibility assessment |
| Has SARS-CoV-2 infection been confirmed by microbiological testing | • If SARS-CoV-2 has been reported as isolated or detected on microbiological testing, select YES<br>• On pathology reports, SARS-CoV-2 may be documented as:<br>  ○ SARS-CoV-2<br>  ○ COVID-19<br>  ○ Novel Coronavirus<br>  ○ 2019-nCoV |
| Has agreement to participate in the Influenza Immune Modulation Domain been obtained | • Select YES if informed consent for participation in this domain has been obtained in accordance with ethical and regulatory approvals at your site |
| In the opinion of the treating clinician is allocation to any of the Influenza Immune Modulation Domain options | • By checking YES, you are confirming that the treating clinician believes that all of these options are equally clinically appropriate for the patients and that there is no other treatment |

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| below appropriate for this patient | option that the treating clinician believes to be superior to any of these options. |

## FORM 1F: COVID-19 ANTIVIRAL (II) DOMAIN REVEAL

### General Guidance

- This page applies for all patients eligible for the COVID-19 Antiviral (II) Domain
- Allocation in this domain can only be revealed up to 48 hours after randomisation

| Question | Definition or Explanation of Question |
|---|---|
| Has SARS-CoV-2 infection been confirmed by positive rapid antigen testing or polymerase chain reaction test within the last 7 days | • Select YES if the patient has had a positive rapid antigen test or PCR test for SARS-CoV-2 within the last 7 calendar days.<br>• If the patient has not had a RAT or PCR test for SARS-CoV-2 within the last seven days, or if all tests within this time period have been negative, select NO |
| Serum creatinine | • Enter the most recent serum creatinine measured during this hospital admission<br>• Serum creatinine is used together with the patient's age and height to estimate glomerular filtration rate (eGFR) to determine eligibility for the Influenza Immune Modulation Domain. |
| Is the patient receiving renal replacement therapy | • Renal Replacement Therapy (RRT) includes any form of:<br>○ continuous hemofiltration, hemodialysis or hemodiafiltration<br>○ Intermittent hemodialysis<br>○ Slow Low Efficiency Dialysis (SLED)<br>○ Peritoneal dialysis. |
| In the opinion of the treating clinician, is the patient at very high risk for progression to severe COVID-19 | • Patients at high risk include those who:<br>○ have not completed at least a primary course of vaccination; OR<br>○ do not have a history of previous COVID-19 infection; OR<br>○ who may not have responded well to vaccination (e.g., are immunocompromised)<br>• "Very high risk for progression to severe COVID-19" includes patients who have had previous severe COVID-19 pneumonitis |

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| | requiring admission to ICU, or other patients for whom the clinician lacks equipoise to randomize to no antiviral treatment<br>• Selecting "Yes" will exclude the patient from receiving the 'no antiviral' intervention in the COVID-19 Antiviral II Domain. |
| Is nirmatrelvir-ritonavir available for administration to this patient, if they are assigned to this intervention | • Different healthcare providers may have specific criteria to allow access to nirmatrelvir- ritonavir. This question confirms whether this patient satisfies such criteria for access. If your patient would satisfy the local access criteria but nirmatrelvir-ritonavir is contraindicated due to drug interactions, please answer YES to this question. |
| Is remdesivir available for administration to this patient, if they are assigned to this intervention | • Different healthcare providers may have specific criteria to allow access to remdesivir. This question confirms whether this patient satisfies such criteria for access. If your patient would satisfy the local access criteria but remdesivir is contraindicated (e.g. hepatic or renal failure), please answer YES to this question. |
| Has agreement to participate in the COVID-19 Antiviral (II) Domain been obtained | • Select YES if informed consent for participation in this domain has been obtained in accordance with ethical and regulatory approvals at your site |
| In the opinion of the treating clinician is allocation to any of the COVID-19 Antiviral (II) Domain options below appropriate for this patient | • By checking YES, you are confirming that the treating clinician believes that all of these options are equally clinically appropriate for the patients and that there is no other treatment option that the treating clinician believes to be superior to any of these options. |

# FORM 2: BASELINE

## General Guidance

- Complete this form for all ***Platform*** patients.
- Baseline is defined as prior to or at the time of randomization.
- Source data is the medical record, ED notes and observations, inpatient notes, online pathology and radiological reports, ICU flow charts, past medical records (for past medical conditions).
- Patients who receive an allocation to a domain while in the Moderate illness severity state and later receive an allocation to another domain while in the Severe illness severity state will complete two baseline forms, one relating to each randomization.

| Question | Definition or Explanation of Question | |
|---|---|---|
| ***Platform*** | | |
| 1. Hospital & ICU Admission Source | | |
| Hospital admission source | • Check one option.<br>• Usual residence immediately prior to this hospital admission.<br>• This question is not required for pediatric participants. | |
| | Home / community | Defined in Section 5. General Definitions. |
| | Assisted living not in own home | A patient living in a hostel / rest home such as a retirement village or other facility that does not meet the definition of nursing home. Includes:<br>• Independent living in a retirement village<br>• Independent living in a hostel or rest home<br>• People living in a Community Mental Health Rehabilitation Service or similar. |
| | Nursing home / chronic care / palliative care | • Nursing home is defined in Section 5. General Definitions.<br>• Includes short term rehabilitation or respite care.<br>• If selected complete the Platform Protocol Deviation CRF. |

<table>
<tr><td>Hospital admission date & time</td><td colspan="2"><ul><li>Hospital admission date and time is defined in Eligibility CRF, Section 2 Inclusion / Exclusion criteria.</li></ul></td></tr>
<tr><td>Patient location at baseline</td><td colspan="2"><ul><li>This question is only required when the Pandemic Strata is active at the site</li><li>Physical ICU is an area normally designated as any form of ICU. This includes being cared for in an ICU that does not normally care for medical or respiratory failure patients, such as a surgical ICU, cardiothoracic ICU, or neurosurgical ICU</li><li>An area not designated as an ICU includes an area of the hospital that was not designated as an ICU outside of a pandemic. Examples may include a High Dependency Unit that is not usually staffed by ICU specialists, a Coronary Care Unit, post-operative recovery room, operating theatre, or general ward area.</li></ul></td></tr>
<tr><td rowspan="4">ICU admission source</td><td colspan="2"><ul><li>Check one option.</li><li>The patient’s clinical location immediately prior to this ICU admission.</li><li>During a pandemic if the patient is located in an area that is not usually designated as an ICU, admission source is the location immediately prior to the location in which enrolment occurred.</li><li>This question is not required for pediatric participants.</li></ul></td></tr>
<tr><td>Emergency Department – same hospital</td><td>ED is also known as an Emergency Room (ER).<br>Refers to the ED at this hospital.</td></tr>
<tr><td>ICU/HDU – same hospital</td><td>Refer to ICU definition in Section 5. General definitions.<br>This option should only be selected if you have two or more separate ICUs in this hospital.</td></tr>
<tr><td>Ward – same hospital</td><td>Any area within the hospital (including the coronary care unit and day care facility) is considered a (general) ward.<br>Include a HDU that is not managed by an intensivist.</td></tr>
</table>

| | | |
|---|---|---|
| | ED - other hospital | Transferred from another hospital's ED if the patient was never admitted to the other hospital prior to the transfer. |
| | ICU/HDU– other hospital | Transferred from an ICU in another hospital.<br>Refer to ICU definition in Section 5. General definitions. |
| | Ward - other hospital | Transferred from any area in another hospital excluding the ICU or ED.<br>Includes a HDU that is not managed by an intensivist. |
| Patient location at baseline | • Refer to ICU definition in Section 5. General definitions.<br>• Ward is defined as Any area within the hospital (including the coronary care unit and day care facility) is considered a (general) ward. This includes a HDU that is not managed by an intensivist<br>• Select Emergency Department (ED) if the patient was in emergency department at the time of randomization. Note that only patients who have been accepted for hospital admission are eligible for randomization. | |
| 2. Demographics | | |
| Height | • Record the patient's height and select the unit of measurement (cm or feet and inches).<br>• Height may be measured or estimated if it is not documented in the medical record.<br>• If estimated, estimate height during this hospital admission.<br>• If not measured during this hospitalization, any measurement in the medical record taken whilst the patient was an adult (over the age of 18 years) can be used.<br>• If height is estimated and a measurement becomes available during this hospital admission, update the field.<br>• If estimated, document estimated height in the patient's medical record.<br>• This question is not required for pediatric participants. | |

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| Weight | • Record the patient's weight and select the unit of measurement (kg or lbs).<br>• Weight may be measured or estimated if it is not documented in the medical record.<br>• If weight is estimated, estimate weight at the time of randomization.<br>• If not measured prior to randomization, any measurement in the medical record taken within the last 2 months can be used.<br>• If estimated, document estimated weight in the patient's medical record |
| Pregnant at hospital admission | • This question will only appear for female patients aged 12 - 55 years.<br>• Defined as pregnancy status at time of first hospital admission for this illness.<br>• Pregnancy status at hospital admission may be confirmed by one or more of:<br>  ○ An ultrasound or other imaging<br>  ○ A urine or blood β-hCG test<br>  ○ A clinical diagnosis<br>• If there is documented evidence of menopause, hysterectomy, or surgical sterilization, check NO.<br>• If pregnancy status was not confirmed at the time of hospital admission, check NO. |
| Gestation in weeks | • This question will only appear for pregnant patients.<br>• Enter the approximate gestation in weeks at the time of hospital admission. |
| Postpartum at hospital admission | • This question will only appear for female patients aged 55 years or younger who were not pregnant.<br>• The postpartum period is defined as within 6-weeks after the birth of the child. |

| 3. Environmental Risk Factors | |
|---|---|
| Current tobacco smoker | • Defined as smoking immediately prior to the onset of this illness (includes smoking of any quantity).<br>• Tobacco smoking includes:<br>  ○ Manufactured (packet) cigarettes<br>  ○ Roll-your-own cigarettes<br>  ○ Cigars<br>  ○ Pipes.<br>• Tobacco smoking does not include:<br>  ○ Chewing tobacco<br>  ○ Smoking of non-tobacco products<br>  ○ Electronic cigarettes & vaporizers.<br>• If smoking status is not available, check NOT RECORDED.<br>• This question is not required for pediatric participants. |
| History of hazardous alcohol consumption | • If the medical record or other source includes a reference to hazardous alcohol intake, or similar terms in the year prior to this hospital admission, check YES.<br>• If only an amount of alcohol consumption is recorded, hazardous alcohol consumption is defined as:<br>  ○ Men who consume more than 8 standard drinks a day on average OR more than 56 standard drinks in a week<br>  ○ Women who consume more than 4 standard drinks a day on average OR more than 28 standard drinks in a week.<br>• If hazardous alcohol consumption status is not available, check NOT RECORDED.<br>• This question is not required for pediatric participants. |
| Patient is a healthcare worker | • This question is only required when the pandemic strata is active at a site. |

| | |
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| | • Answer YES if the patient is a healthcare worker who has had direct contact with patients who have suspected or confirmed pandemic infection within the 21 days prior to this hospital admission<br>• This question is not required for pediatric participants. |
| 4. Past Medical History | |
| Chronic respiratory or pharyngeal neuromuscular weakness | • Weakness sufficient to have resulted in documented or implied functional impairment of <u>one or both</u> of respiratory muscle strength or laryngeal protective mechanisms.<br>• Associated conditions include:<br>  ○ Stroke with swallowing difficulty<br>  ○ Cerebral palsy<br>  ○ Motor Neuron Disease includes Lou Gehrig's disease (aka Amyotrophic lateral sclerosis, Progressive Muscular Atrophy, Progressive Bulbar Palsy and Primary Lateral Sclerosis)<br>  ○ Muscular dystrophy<br>  ○ Myotonic dystrophy<br>  ○ Chronic demyelinating polyneuropathy<br>  ○ Current (not recovered) Guillain–Barré syndrome<br>  ○ Bulbar neuromuscular weakness (including stroke).<br>• If unknown check NO. |
| Diabetes | • Check <u>one</u> option.<br>• Documented clinical diagnosis of diabetes mellitus prior to randomization.<br>• A patient with documented Type 1 or Type 2 diabetes who is also pregnant <u>does not have gestational diabetes</u>.<br>• Check NOT DIAGNOSED WITH DIABETES if there is no history of diabetes in the medical record.<br>• Check NOT DIAGNOSED WITH DIABETES in patients who have an elevated blood glucose level due to critical illness but did not have a diagnosis of diabetes prior to this hospital admission. |

<table>
<tr><td>Chronic kidney disease</td><td colspan="2"><ul><li>Check one option.</li><li>Determined from the most recent stable serum creatinine in the year prior to this hospital admission, except in patients who were receiving chronic dialysis prior to this hospital admission.</li><li>If there is only one serum creatinine available, assume that this value is stable.</li><li>If an arteriovenous fistula or shunt has been placed in readiness for chronic dialysis but dialysis has not commenced, check ABNORMAL RENAL FUNCTION NOT NORMALLY RECEIVING DIALYSIS.</li></ul></td></tr>
<tr><td></td><td>Normal renal function</td><td>Normal renal function is defined as creatinine level of:<ul><li>MALES: < 130µmol/L (1.5 mg/dL)</li><li>FEMALES: < 100 µmol/L (1.1 mg/dL).</li></ul></td></tr>
<tr><td></td><td>Abnormal renal function not normally receiving dialysis</td><td>In patients not receiving chronic dialysis prior to this hospital admission, abnormal renal function is defined as a creatinine level of:<ul><li>MALES: ≥130 µmol/L (1.5 mg/dL)</li><li>FEMALES: ≥100 µmol/L (1.1 mg/dL).</li></ul></td></tr>
<tr><td></td><td>Normally receiving dialysis</td><td>The patient was receiving chronic hemodialysis or peritoneal dialysis prior to this hospital admission.</td></tr>
<tr><td></td><td>Not recorded</td><td>No information prior to this hospital admission.</td></tr>
<tr><td>Respiratory co-morbidities</td><td colspan="2"><ul><li>Check all that apply.</li><li>A respiratory co-morbidity is defined as being present and diagnosed prior to this hospital admission.</li></ul></td></tr>
<tr><td></td><td>Asthma</td><td>Asthma requiring inhalers.</td></tr>
<tr><td></td><td>Bronchiectasis</td><td>Diagnosis of bronchiectasis in medical records.</td></tr>
<tr><td></td><td>COPD</td><td>Diagnosis of COPD in medical record.<br>This option is not available for pediatric participants.</td></tr>
</table>

| | | |
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| | Interstitial lung disease | Interstitial lung disease is defined as a group of disorders that cause progressive scarring of lung tissue, including:<br>• Idiopathic pulmonary fibrosis<br>• Other idiopathic interstitial pneumonias<br>• Interstitial lung disease associated with systemic diseases/connective tissue diseases e.g., rheumatoid arthritis, scleroderma, sarcoidosis. |
| | Primary lung cancer | • Current diagnosis of primary lung cancer documented in medical records.<br>• Does not include:<br>  ○ Resection of primary lung cancer without recurrence<br>  ○ Secondary (metastatic) cancer of the lung.<br>• This response option is not required for pediatric participants. |
| | Chronic lung disease of prematurity (not asthma) | • Current diagnosis of chronic lung disease of prematurity (not including asthma) documented in medical records.<br>• This response option is only available for pediatric participants |
| | Other | Any other respiratory co-morbidity which can be associated with severe functional respiratory impairment including (but not limited to):<br>• Primary pulmonary hypertension<br>• Severe restrictive lung disease, including kyphoscoliosis or morbid obesity with documented severe respiratory impairment |

| | | |
|---|---|---|
| | | • Cystic fibrosis<br>• Severe respiratory neuromuscular weakness. |
| | None | Nil recorded in the medical record prior to this hospital admission. |
| Severe respiratory co-morbidity | • This question will only appear if a respiratory co-morbidity was indicated in the previous question.<br>• A severe respiratory co-morbidity is defined as:<br>  ○ Chronic respiratory disease resulting in severe exercise restriction (unable to climb stairs or perform household duties) OR<br>  ○ Documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (mean > 40 mmHg). | |
| Immunosuppressive treatment | • The patient has received therapy that has suppressed resistance to infection prior to this hospital admission, includes:<br>  ○ Immunosuppression, chemotherapy within 4 weeks of admission<br>  ○ Radiation<br>  ○ High-dose steroid treatment (e.g. >1.5mg/kg methyl prednisolone or equivalent for ≥5 days)<br>  ○ Long-term treatment steroid treatment (e.g. >20 mg/day of a steroid). | |
| Specify | • This question only applies to patients randomized to the Immunoglobulin Domain who have received immunosuppressive treatment<br>• Select all therapies that apply<br>• Immunosuppressive therapy includes (not limited to)<br>  ○ Chemotherapy within 4 weeks of admission<br>  ○ High dose steroid treatment (>1.5mg/kg methyl prednisolone or equivalent for ≥5 days)<br>  ○ Long-term steroid treatment (e.g. > 20mg/day of a steroid)<br>  ○ High dose radiotherapy (e.g. for lung cancer)<br>  ○ Anti- CD20 antibodies (e.g. rituximab, obinutuzumab, ocrelizumab) | |

<table>
<tr><td></td><td colspan="2">
<ul>
<li>Bruton’s Tyrosine Kinase Inhibitors (e.g. ibrutinib, acalabrutinib, zanubrutinib)</li>
<li>Allogeneic stem cell transplant in the last 12 months or anytime if on-going treatment for chronic GVHD</li>
<li>Autologous stem cell transplant in the last 6 months</li>
<li>Solid organ transplant</li>
<li>Chimeric antigen receptor T-cell (CAR-T) therapy</li>
<li>Other immunosuppressive biological therapies</li>
</ul>
</td></tr>
<tr><td>Immunosuppressive disease</td><td colspan="2">
<ul>
<li>Check <u>all</u> that apply.</li>
<li>The patient has one or more disease(s) that is sufficiently advanced to suppress resistance to infection.</li>
<li>If the <u>cancer or hematological malignancy</u> has been in <u>remission for 5 years</u> or more, they are <u>no longer considered co-morbidities</u>.</li>
</ul>
</td></tr>
<tr><td></td><td>AIDS</td><td>
<ul>
<li>Acquired immunodeficiency syndrome (AIDS)</li>
<li>Any clinical syndrome of <u>AIDS-HIV positive with AIDS defining complications</u> (e.g. Pneumocystis carinii pneumonia, Kaposi’s sarcoma, lymphoma, tuberculosis or Toxoplasma infection).</li>
</ul>
</td></tr>
<tr><td></td><td>Acute leukemia</td><td>Any type of acute leukemia, including acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL).</td></tr>
<tr><td></td><td>Chronic lymphocytic leukemia</td><td>Chronic lymphocytic leukemia (CLL).</td></tr>
<tr><td></td><td>Lymphoma</td><td>Any type of lymphoma.</td></tr>
<tr><td></td><td>Metastatic cancer</td><td>Proven distant metastases (not regional lymph nodes or contiguous spread) by surgery, CT scan or other method.</td></tr>
<tr><td></td><td>Myeloma</td><td>Multiple myeloma.</td></tr>
<tr><td></td><td>Aplastic anemia</td><td>Any severity of aplastic anemia</td></tr>
<tr><td></td><td>Severe chronic neutropenia</td><td>Any type of severe chronic neutropenia, including congenital, autoimmune, or idiopathic</td></tr>
<tr><td></td><td>Myelodysplastic syndrome</td><td>Any myelodysplastic syndrome (MDS). Includes chronic myelomonocytic leukemia (CMML), atypical chronic</td></tr>
</table>

| | | |
|---|---|---|
| | | myeloid leukemia (aCML), or unclassifiable myelodysplastic/myeloproliferative neoplasms (MDS/MPN) |
| | Primary or inherited immune deficiency | Including B-cell deficiencies (such as Bruton agammaglobulinemia), T-cell deficiencies (such as Wiskott Aldrich disease), or combined deficiencies (such as common variable immunodeficiency) |
| | Secondary immunodeficiency syndromes | Including any condition that requires regular immunoglobulin replacement therapy (either intravenous [IVIG] or subcutaneous [ScIG]) |
| | Other | Any other disease that is sufficiently advanced to suppress resistance to infection. |
| | None | Nil recorded in the medical record prior to this hospital admission. |
| Other APACHE II co-morbidities | Check all that apply.<br>This question is not required for pediatric participants. | |
| | Chronic cardiovascular disease | New York Heart Association Class IV Heart Failure: angina or other symptoms at rest or on minimal exertion (whilst getting dressed or during self-care). Unable to carry out any physical activity without discomfort. If physical activity is undertaken, discomfort increases. |
| | Cirrhosis | • Biopsy or imaging proven cirrhosis and documented portal hypertension OR<br>• Episodes of past upper gastrointestinal bleeding attributed to portal hypertension.<br><br>If the patient has a functioning liver transplant do not check this box. |
| | Hepatic failure | Episodes of hepatic failure and/or encephalopathy or coma. |
| | None of the above | Nil recorded in the medical record prior to this hospital admission. |

<table>
<tr><td>Clinical Frailty Score</td><td colspan="2">
<ul>
<li>Check one option.</li>
<li>Clinical frailty status may be obtained from the medical record or the patient directly, or other sources, if easily accessible.</li>
<li>Other information including employment, recreational activities, and performance of activities of daily living can be used.</li>
<li>For assistance refer to the Clinical Frailty Score in Appendix 1.</li>
<li>This question is not required for pediatric participants.</li>
</ul>
Scoring frailty in people with dementia:
<ul>
<li>The degree of frailty corresponds to the degree of dementia. Common symptoms of mild dementia include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.</li>
<li>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.</li>
<li>In severe dementia, they cannot do personal care without help.</li>
</ul>
<table>
<tr><td>Very fit<br>score ①</td><td>People who are robust, active, energetic and motivated. These people commonly exercise regularly.</td></tr>
<tr><td>Well<br>score ②</td><td>People who have no active disease symptoms but exercise less regularly than those in group 1. They often exercise or are very active occasionally (e.g. seasonally).</td></tr>
<tr><td>Managing Well<br>score ③</td><td>People whose medical problems are well controlled, but are not regularly active beyond walking.</td></tr>
<tr><td>Vulnerable<br>score ④</td><td>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.</td></tr>
<tr><td>Mildly Frail<br>score ⑤</td><td>These people often have more evident slowing, and need help in higher order instrumental activities of daily living (IADLs) (e.g. finances, transportation, heavy housework, medications). Typically, mild frailty</td></tr>
</table>
</td></tr>
</table>

| | | |
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| | | progressively impairs shopping, walking outside alone, meal preparation and house work. |
| | Moderately Frail score ⑥ | People need help with all outside activities and with keeping house. Inside, they often have problems with stairs, need help with bathing and may need minimal assistance with dressing. |
| | Severely Frail score ⑦ | Completely dependent for personal care (resulting from physical or cognitive issues). But seem stable and not at high risk of dying within the next 6 months. |
| | Very Severely Frail score ⑧ | Completely dependent, approaching end of life. Typically, they could not recover even from a minor illness. |
| | Terminally ill Score ⑨ | Approaching the end of life. This category applies to people with a life expectancy < 6 months who are not otherwise evidently frail. |
| COVID-19 vaccination prior to this acute illness | • This question only applies to patients with suspected or confirmed pandemic infection<br>• Check 'YES' if this patient has received at least one dose of a WHO-approved COVID-19 vaccine prior to this acute illness.<br>• Check 'NO' if it is known that this patient has not received any dose of a WHO-approved COVID-19 vaccine.<br>• Check 'UNKNOWN' if information on this patient's vaccination status is unavailable. | |
| Specify | • This question is only required for patients who have received at least one dose of a WHO-approved COVID-19 vaccine<br>• Select 'Partial course received' if the patient has received a vaccination but has not completed the full course as per current WHO-approved recommendations for that vaccine at least two weeks prior to this acute illness onset | |

| | |
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| | • Select 'Full course completed' if the patient has completed the full course as per current WHO-approved recommendations for that vaccine at least two weeks prior to this acute illness onset<br>• Select 'Full course completed with booster dose' if the patient has completed the full course as per WHO-approved recommendations and an additional dose of vaccine<br>• Select 'Unknown' if information on how many vaccine doses the patient has received is unavailable. |
| Have SARS-CoV-2 anti-spike antibodies been detected | • Select “not tested” if only nucleocapsid protein antibodies have been tested for |

## 5. APACHE II

**General Guidance**

- APACHE II is only required for patients located in an ICU at the time of randomization.
- APACHE II is not required for pediatric participants.
- An APACHE II calculator is available on the ANZ + Ca REMAP-CAP database for assistance. Use of the online calculator is encouraged, but not mandatory.
- A worksheet is provided in the REMAP-CAP study tools.
- The APACHE II score is derived from 3 scoring systems:
    - Part A – Acute Physiology Score – data collected and scored by the site research staff.
    - Part B – Age Points – **calculated by the study database.**
    - Part C – Chronic Health Points – **calculated by the study database**.
- A patient may not have been in ICU for the 24 hours prior to randomization. If so, please use any available values from the pre-ICU medical records (e.g. Emergency Department charts, operating and recovery room charts, ambulance reports, ward charts etc.).
- If medical records are not available because the patient was not under medical care prior to their ICU admission, please use any available values within 24 hours prior to randomization to derive the score (e.g. community health medical notes and laboratory samples).

<table>
<tr><td rowspan="2">APACHE II acute physiology score</td><td colspan="2"><ul><li>For each of the 12 physiological variables, check the <u>most deranged</u> value (i.e. associated with the highest score) over the 24-hour period prior to randomization.</li><li>The most deranged value will be the value that is associated with the highest point score assigned by APACHE II. For example, if their temperature in the last 24 hours has been as high as 40°C and as low as 33°C, check the box in the column that assigns 3 points in the ‘high abnormal range’ column because 40°C attracts 3 points while 33°C attracts 2 points.</li><li>Whenever possible, try to obtain a score for each physiological variable.</li><li>If one of the 12 variables are not available, assign 0 points and make a note of this absence on the APACHE II worksheet or database. The assumption is that a test or measurement was not ordered because patient status did not warrant investigation (rather than the data were missing).</li><li>For exact non-integer data that is not found in any of the given ranges, round the figure up or down to the nearest whole number. Round up for numbers ≥0.5; round down for numbers <0.5. e.g.:<ul><li>a calculated mean arterial pressure (MAP) of 129.7 is rounded up to 130</li><li>a calculated MAP of 129.5 is rounded up to 130</li><li>a calculated MAP of 129.4 is rounded down to 129</li></ul>This must be followed for every patient to ensure consistency.</li><li>If you are using the APACHE II worksheet <u>keep the completed worksheet</u> for each patient, as it may be reviewed during study monitoring visits.</li></ul></td></tr>
<tr><td>Temperature</td><td><ul><li>This should be a core temperature measurement (such as rectal, tympanic, esophageal or via pulmonary artery catheter).</li><li>If an oral or axillary temperature is available add 0.5°C to the oral or axillary temperature.</li></ul></td></tr>
</table>

<table>
<tr><td></td><td></td><td colspan="2">

- Temperatures recorded when the patient is being actively cooled should not be included.

</td></tr>
<tr><td></td><td>MAP</td><td colspan="2">If the MAP is not calculated by monitoring equipment, use the manual sphygmomanometer recording of systolic (SBP) and diastolic blood pressure (DBP) to obtain MAP using the equation:<br>$$\boldsymbol{MAP = \frac{(DBP \times 2) + SBP}{3}}$$</td></tr>
<tr><td></td><td>Respiratory Rate (RR)</td><td colspan="2">For ventilated patients: the RR is the combined total of spontaneous and ventilator/mechanical breaths.</td></tr>
<tr><td></td><td>Oxygenation</td><td colspan="2">

- The $FiO_2$ here is expressed as a proportion of a unit e.g. $FiO_2$ 100% = 1 and $Fi0_2$ 60% = 0.6
- If the $FiO_2$ is greater than (≥) 50% (0.50), record the most deranged value for the A – $aDO_2$. Equation:

$$\boldsymbol{AaDO_2 = (713 \times FiO_2) - \left(\frac{pCO_2}{0.8}\right) - (paO_2)}$$

- If the $FiO_2$ is less than 50% record the $PaO_2$ (arterial oxygen pressure).

**For $O_2$ delivered by mask or low-flow nasal prongs, see conversion chart below:**

<table>
<tr><td>Nasal Cannula</td><td>1L/pm = 24%<br>2L/pm = 28%<br>3L/pm = 32%<br>4L/pm = 36%</td></tr>
<tr><td>Hudson Oxygen Mask</td><td>5 – 6L/ pm = 40%<br>6 – 7L/ pm = 50%<br>7 – 8L/ pm = 60%</td></tr>
<tr><td>High Concentration Mask</td><td>8 – 15L/pm = 60 – 80%</td></tr>
</table>

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| | | Partial Re-breathing Mask | 8 – 15L/pm = 60 – 80% |
| | | Non-Rebreathing Mask | 8 – 15L/pm = 90 - 99% |
| | Arterial pH | If ABGs have not been performed prior to randomization or are unavailable, choose the most deranged value for serum venous bicarbonate ($HCO_3$) in place of the arterial pH. | |
| | Serum Sodium | • Record in mmol/L.<br>• Missing values are treated as normal (no points assigned).<br>• An ABG machine measured sodium may be used but only if a laboratory measured serum value is not available. | |
| | Serum Potassium | • Record in mmol/L.<br>• Missing values are treated as normal (no points assigned).<br>• An ABG machine measured potassium may be used but only if a laboratory measured serum value is not available. | |
| | Serum creatinine | • For creatinine score, acute renal failure is defined as any elevated creatinine value that is <u>not</u> within the normal range designated by the APACHE system.<br>• If this criterion is met and the patient does <u>not</u> have chronic renal failure. They have acute renal failure.<br>• Patients with acute renal failure double the creatinine points in the APACHE score. | |

<table>
<tr><td rowspan="4"></td><td>Hematocrit</td><td colspan="2"><ul><li>Enter as percentage (%).</li><li>Missing values are treated as normal (no points assigned).</li></ul></td></tr>
<tr><td>White blood count</td><td colspan="2">Missing values are treated as normal (no points assigned).</td></tr>
<tr><td>Glasgow Coma Score (GCS)</td><td colspan="2"><ul><li>Subtract the GCS score from 15 to arrive at a score on the APACHE II worksheet.</li><li>The total GCS is the sum of the scores for the three GCS components: eye opening, verbal and motor.</li><li>The lowest GCS during the 24 hours prior to randomization should be recorded, provided the patient is free from the effects of sedative, paralyzing or neuromuscular blocking agents.</li><li>If not clearly documented in medical record, ancillary information should be used to provide the best estimate of pre-sedation GCS.</li><li>Missing values are treated as normal (no points assigned).</li></ul>NOTE:<br>The pre-sedation GCS does not need to be from the 24 hours prior to randomization. You should go back as far as necessary to the time at which the patient was first sedated and identify the GCS at the time of/just prior to sedation.</td></tr>
<tr><td>Paralyzed/Sedated patients:</td><td>The GCS taken at the time of or just prior to sedation should be recorded, even if it is more than 24 hours prior to randomization.</td></tr>
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| | | | |
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| | | Transfer/Retrieval patients: | The GCS determined by the medical/paramedical assessment prior to intubation/sedation should be recorded. |
| 6. Interventions & Physiology at Baseline | | | |
| Creatinine | • Taken from <u>serum or plasma samples</u>.<br>• If a laboratory measured serum or plasma value is <u>not available,</u> an ABG machine measured creatinine may be used.<br>• Only use samples collected during this hospital admission prior to randomization (closest to randomization).<br>• Select the unit of measurement and record the result in the appropriate box.<br>• If creatinine was not measured, check NOT RECORDED. | | |
| Platelet count | • Enter platelet count in cells x $10^9$ /L.<br>• Taken from laboratory sample.<br>• Only use results from samples collected during this hospital admission prior to randomization (closest to randomization).<br>• If platelet count was not measured, check NOT RECORDED. | | |
| Bilirubin level | • Taken from serum or plasma samples.<br>• Only use results from samples collected during this hospital admission prior to randomization (closest to randomization).<br>• Select the unit of measurement and record the result in the appropriate box.<br>• If bilirubin level was not measured, check NOT RECORDED. | | |
| Lactate | • If a laboratory measured serum value is not available, a <u>venous or arterial measurement from an ABG machine or laboratory is acceptable</u>.<br>• Enter lactate in mmol/L. | | |

| | |
|---|---|
| | • Only use samples collected during this hospital admission prior to randomization (closest to randomization).<br>• If lactate was not measured, check NOT RECORDED. |
| $FiO_2$ at time of ABG or capillary blood gas | • If an ABG was entered in the Eligibility eCRF the study database will pre-fill with what was entered. Check the pre-filled data, if it is not correct update this field with the correct information.<br>• Record the $FiO_2$ (range 0.21 - 1.0) the patient was receiving at the time the ABG was taken. The most recent ABG prior to randomization should be used.<br>• For pediatric patients, if no ABG has been taken, record the FiO2 the patient was receiving at the time of the latest capillary blood gas. The most recent capillary blood gas prior to randomization should be used.<br>• Only use a sample collected during this hospital admission prior to randomization.<br>• If multiple ABGs or capillary blood gases were taken between hospital admission and randomization use the sample collected closest to randomization.<br>• If no ABG or capillary blood gas was collected prior to randomization enter the $FiO_2$ the patient received immediately prior to randomization.<br>For $O_2$ delivered by mask or low-flow nasal prongs, refer to conversions in Section 5: APACHE II: Oxygenation. |
| Corresponding $PaO_2$ | • If an ABG or capillary blood gas was entered in the Eligibility eCRF the study database will pre-fill with what was entered. Check the pre-filled data, if it is not correct update this field with the correct information and if promoted check confirm.<br>• Enter the $PaO_2$ on the ABG or capillary blood gas collected at the same time as the $FiO_2$.<br>• Select the unit of measurement and enter the result in the appropriate box. |

| | |
|---|---|
| | • If no ABG or capillary blood gas was collected prior to randomization check NOT RECORDED. |
| Corresponding SpO2 | • If an ABG or capillary blood gas was entered in the Eligibility eCRF the study database will pre-fill with what was entered. Check the pre-filled data, if it is not correct update this field with the correct information and if promoted check confirm.<br>• Enter the $SpO_2$ on the ABG or capillary blood gas collected at the same time as the $FiO_2$.<br>• Select the unit of measurement and enter the result in the appropriate box.<br>• If no ABG or capillary blood gas was collected prior to randomization check NOT RECORDED. |
| Corresponding PEEP | • If an ABG or capillary blood gas was entered in the Eligibility eCRF the study database will pre-fill the answer to this question. Check the pre-filled data, if it is not correct update this field with the correct information and if promoted check confirm.<br>• The PEEP the patient received at the time the ABG or capillary blood gas used above was collected.<br>• If no ABG or capillary blood gas was collected enter PEEP at the time of randomization.<br>• If the patient is receiving invasive mechanical ventilation or NIV and the PEEP/CPAP is set to 0, enter 0.<br>• If the patient was receiving High-Flow oxygen at the time of the ABG or capillary blood gas, enter the PEEP as zero (i.e. 0).<br>• If the patient is not receiving invasive mechanical ventilation, NIV, or HFNP, check NOT RECORDED.<br>• If the patient was receiving invasive mechanical ventilation using APRV mode at the time that the ABG was obtained, select 'patient receiving APRV'. |

<table>
<tr><td>Glasgow Coma Scale score</td><td colspan="3"><ul><li>Enter the GCS recorded closest to randomization but prior to the administration of sedative agents.</li><li>The pre-sedation GCS does not need to be from the 24 hours prior to randomization. You should go back as far as necessary to the time at which the patient was first sedated and identify the GCS at the time of/just prior to sedation.</li></ul></td></tr>
<tr><td rowspan="5">Extended Cardiovascular SOFA score</td><td colspan="3"><ul><li>Use MAP value and corresponding dose of inotropes and/or vasopressors documented during this hospital admission prior to randomization (closest to randomization).</li></ul></td></tr>
<tr><td>Score 0</td><td colspan="2">Both of the following criteria are met:<ol><li>MAP equal to or higher than (≥) 70 mm Hg or 9.33 kPa for all recordings<br>AND</li><li>No inotrope/vasopressor support received.</li></ol></td></tr>
<tr><td>Score 1</td><td colspan="2">Both of the following criteria are met:<ol><li>Patient’s MAP is less than (<) 70 mmHg or 9.33 kPa<br>AND</li><li>No inotrope/vasopressor support received</li></ol></td></tr>
<tr><td>Score 2</td><td colspan="2">Any of the following inotrope/vasopressor(s) were administered as an infusion for at least one hour at the indicated dose:</td></tr>
<tr><td></td><td>Inotrope/Vasopressor</td><td>Dose required</td></tr>
<tr><td></td><td>Dopamine</td><td>Equal to or less than (≤) 5 µg/kg/min</td></tr>
<tr><td></td><td>Dobutamine</td><td>any dose</td></tr>
<tr><td></td><td>Levosimendan (Simdax)</td><td>any dose</td></tr>
<tr><td></td><td>Milrinone (Primacor)</td><td>any dose</td></tr>
</table>

<table>
<tr><td></td><td>Score 3</td><td colspan="2">Any of the following vasopressors were administered as an infusion for at least one hour at the indicated dose:</td></tr>
<tr><td></td><td></td><td>Inotrope/Vasopressor</td><td>Dose required</td></tr>
<tr><td></td><td></td><td>Epinephrine / Adrenaline</td><td>Equal to or less than (≤) 0.1 µg/kg/min</td></tr>
<tr><td></td><td></td><td>Dopamine</td><td>Greater than (>) 5 µg/kg/min<br>AND<br>Equal to or less than (≤) 15 µg/kg/min</td></tr>
<tr><td></td><td></td><td>Norepinephrine / Noradrenaline</td><td>Equal to or less than (≤) 0.1 µg/kg/min</td></tr>
<tr><td></td><td></td><td>Metaraminol<br>(Aramine, Metaradrine, Metaramin, Pressonex)</td><td>any dose</td></tr>
<tr><td></td><td></td><td>Phenylephrine</td><td>any dose</td></tr>
<tr><td></td><td></td><td>Vasopressin (Pitressin)</td><td>any dose</td></tr>
<tr><td></td><td>Score 4</td><td colspan="2">Any of the following vasopressors were administered as an infusion for at least one hour at the indicated dose:</td></tr>
<tr><td></td><td></td><td>Inotrope/Vasopressor</td><td>Dose required</td></tr>
<tr><td></td><td></td><td>Epinephrine / Adrenaline</td><td>Greater than (>) 0.1 µg/kg/min<br>AND<br>Equal to or less than (≤) 0.3 µg/kg/min</td></tr>
<tr><td></td><td></td><td>Dopamine</td><td>Greater than (>) 15 µg/kg/min</td></tr>
<tr><td></td><td></td><td>Norepinephrine / Noradrenaline</td><td>Greater than (>) 0.1 µg/kg/min<br>AND</td></tr>
</table>

| | | | |
|---|---|---|---|
| | | | Equal to or less than (≤) 0.3 µg/kg/min |
| | Score 4+ | Any of the following vasopressors were administered as an infusion for at least one hour at the indicated dose: | |
| | | Inotrope / Vasopressor | Dose required |
| | | Epinephrine / Adrenaline | Greater than (>) 0.3 µg/kg/min |
| | | Norepinephrine / Noradrenaline | Greater than (>) 0.3 µg/kg/min |
| Extended Cardiovascular Pediatric SOFA score | • Use MAP value and corresponding dose of inotropes and/or vasopressors documented during this hospital admission prior to randomization (closest to randomization).<br>• Only required for pediatric patients. | | |
| | Score 0 | Age | MAP |
| | | < 1 Month | ≥ 46 mmHg |
| | | 1 – 11 months | ≥ 55 mmHg |
| | | 12 – 23 months | ≥ 60 mmHg |
| | | 24 – 59 months | ≥ 62 mmHg |
| | | 60 – 143 months | ≥ 65 mmHg |
| | | 144 – 216 months | ≥ 67 mmHg |
| | | > 216 months | ≥ 70 mmHg |
| | Score 1 | Age | MAP |
| | | < 1 Month | < 46 mmHg |
| | | 1 – 11 months | < 55 mmHg |
| | | 12 – 23 months | < 60 mmHg |
| | | 24 – 59 months | < 62 mmHg |

| | | | |
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| | | 60 – 143 months | < 65 mmHg |
| | | 144 – 216 months | < 67 mmHg |
| | | > 216 months | < 70 mmHg |
| | Score 2 | Any of the following vasopressors were administered as an infusion for at least one hour at the indicated dose: | |
| | | Inotrope / Vasopressor | Dose required |
| | | Dopamine hydrochloride | ≤ 5 µg/kg/min |
| | | Dobutamine hydrochloride | Any |
| | Score 3 | Any of the following vasopressors were administered as an infusion for at least one hour at the indicated dose: | |
| | | Inotrope / Vasopressor | Dose required |
| | | Dopamine hydrochloride | > 5 µg/kg/min and ≤ 15 µg/kg/min |
| | | Epinephrine / Adrenaline | ≤ 0.1 µg/kg/min |
| | | Norepinephrine / Noradrenaline | ≤ 0.1 µg/kg/min |
| | Score 4 | Any of the following vasopressors were administered as an infusion for at least one hour at the indicated dose: | |
| | | Inotrope / Vasopressor | Dose required |
| | | Dopamine hydrochloride | > 15 µg/kg/min |
| | | Epinephrine / Adrenaline | > 0.1 µg/kg/min and ≤ 0.3 µg/kg/min |
| | | Norepinephrine / Noradrenaline | > 0.1 µg/kg/min and ≤ 0.3 µg/kg/min |
| | Score 4+ | Any of the following vasopressors were administered as an infusion for at least one hour at the indicated dose: | |

<table>
<tr><td></td><td></td><td>Inotrope / Vasopressor</td><td>Dose required</td></tr>
<tr><td></td><td></td><td>Epinephrine / Adrenaline</td><td>> 0.3 µg/kg/min</td></tr>
<tr><td></td><td></td><td>Norepinephrine / Noradrenaline</td><td>> 0.3 µg/kg/min</td></tr>
<tr><td>Renal Replacement Therapy</td><td colspan="3"><ul><li>Select YES if the patient received RRT at any time during this hospital admission prior to randomization.</li><li>The patient does not have to be receiving RRT at the time of randomization.</li><li>RRT is defined in Section 5. General definitions.</li><li>Check NO if the patient usually receives chronic RRT but did not receive RRT during this hospital admission prior to randomization.</li></ul></td></tr>
<tr><td>Extracorporeal gas exchange</td><td colspan="3"><ul><li>Extracorporeal gas exchange is defined as extracorporeal provision of oxygen and/or removal of carbon dioxide.</li><li>Select YES if the patient received extracorporeal gas exchange at any time during this hospital admission prior to randomization.</li><li>The patient does not have to be receiving extracorporeal gas exchange at the time of randomization.</li></ul></td></tr>
<tr><td rowspan="2">Type of extracorporeal gas exchange received</td><td colspan="3"><ul><li>This question only applies if you have indicated that the patient received extracorporeal gas exchange</li><li>Check all that apply.</li></ul></td></tr>
<tr><td>ECMO (Extracorporeal Membrane Oxygenation)</td><td colspan="2"><ul><li>Includes all forms of ECMO (e.g. veno-venous, veno-arterial and other combinations), irrespective of site of cannulation or location where the ECMO was instituted.</li><li>Includes patients already on ECMO at admission to ICU.</li></ul></td></tr>
</table>

| | | |
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| | $ECCO_2R$ (Extracorporeal Carbon Dioxide Removal) | • Includes all forms of $ECCO_2R$, irrespective of site of cannulation or location where the $ECCO_2R$ was instituted.<br>• Includes patients already on $ECCO_2R$ at admission to ICU. |
| Was etomidate administered between hospital admission and randomization | • This question is not required in Australia.<br>• For example, etomidate used for induction of anesthesia or emergency intubation. | |
| Treatment limitation | • At the time of randomization<br>• Includes any form of documented treatment limitation, such as not for intubation, not for CPR, not for vasopressor, etc. | |
| 7. Interventions & Physiology at Baseline | | |
| This section is not required for pediatric participants. | | |
| Ferritin | • Enter the value from the sample collected closest to randomization, up to 8 hours prior to randomization<br>• If no samples were collected up to 8 hours prior to time of randomization, utilize samples collected closest to the time of randomization up to 2 hours after randomization | |
| D-dimer | • Enter the value from the sample collected closest to randomization, up to 8 hours prior to randomization<br>• If no samples were collected up to 8 hours prior to time of randomization, utilize samples collected closest to the time of randomization up to 2 hours after randomization | |
| C-reactive protein | • Enter the value from the sample collected closest to randomization, up to 8 hours prior to randomization | |

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| | • If no samples were collected up to 8 hours prior to time of randomization, utilize samples collected closest to the time of randomization up to 2 hours after randomization |
| Neutrophil count | • Enter the value from the sample collected closest to randomization, up to 8 hours prior to randomization<br>• If no samples were collected up to 8 hours prior to time of randomization, utilize samples collected closest to the time of randomization up to 2 hours after randomization |
| Lymphocyte count | • Enter the value from the sample collected closest to randomization, up to 8 hours prior to randomization<br>• If no samples were collected up to 8 hours prior to time of randomization, utilize samples collected closest to the time of randomization up to 2 hours after randomization |
| Troponin | • Enter the value from the sample collected closest to randomization, up to 8 hours prior to randomization<br>• If no samples were collected up to 8 hours prior to time of randomization, utilize samples collected closest to the time of randomization up to 2 hours after randomization<br>• Enter:<br>○ The test utilized (high-sensitivity Troponin T, high-sensitivity Troponin I, Troponin T, or Troponin I)<br>○ Test result<br>○ The 99$^{th}$ percentile upper reference limit for the test |
| INR or Prothrombin ratio | • Enter the value from the sample collected closest to randomization, up to 8 hours prior to randomization<br>• If no samples were collected up to 8 hours prior to time of randomization, utilize samples collected closest to the time of randomization up to 2 hours after randomization |

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| | • INR is preferred, however prothrombin ratio is accepted if no INR is available |
| Fibrinogen | • Enter the value from the sample collected closest to randomization, up to 8 hours prior to randomization<br>• If no samples were collected up to 8 hours prior to time of randomization, utilize samples collected closest to the time of randomization up to 2 hours after randomization |
| Temperature | • Enter temperature recorded closest to and prior to randomization<br>• Only use temperatures recorded during this hospital admission. |
| Heart rate | • Enter heart rate recorded closest to and prior to randomization<br>• Only use heart rate measurements recorded during this hospital admission |
| Systolic blood pressure | • Enter systolic blood pressure recorded closest to and prior to randomization<br>• Only use systolic blood pressure measurements recorded during this hospital admission<br>• Invasive measurements are preferred. If no invasive blood pressure has been recorded, use non-invasive measurements. |
| Respiratory rate | • Enter respiratory rate recorded closest to and prior to randomization<br>• Only use respiratory rate measurements recorded during this hospital admission |
| Bicarbonate | • Enter serum bicarbonate recorded closest to randomization, up to 8 hours prior to randomization<br>• Only use bicarbonate measurements recorded during this hospital admission<br>• Enter values obtained from ABG or laboratory sample |
| Albumin | • Enter serum albumin recorded closest to randomization, up to 8 hours prior to randomization |

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| | • Only use albumin measurements recorded during this hospital admission |
| ALT | • Enter alanine transaminase recorded closest to randomization, up to 72 hours prior to randomization.<br>• If no samples were collected within 72 hours prior to randomization, utilize samples collected closest to the time of randomization up to 8 hours after randomization.<br>• Also known as alanine aminotransferase or (serum) glutamate-pyruvate transaminase (GPT or SGPT) |
| AST | • Enter aspartate transaminase recorded closest to randomization, up to 72 hours prior to randomization.<br>• If no samples were collected within 72 hours prior to randomization, utilize samples collected closest to the time of randomization up to 8 hours after randomization.<br>• Also known as aspartate aminotransferase or (serum) glutamic-oxaloacetic transaminase (GOT or SGOT) |
| Potassium | • Enter potassium recorded closest to randomization, up to 24 hours prior to randomization. |
| *8.* Ethnicity | |
| Ethnicity Australia (AU sites only) | • Check <u>one</u> option.<br>• An ethnic group is made up of people who have some or all of the following:<br>  ○ A shared culture, such as traditions, customs, beliefs, or language<br>  ○ A common ancestry or history.<br>  ○ A similar geographic, tribal, or clan origin.<br>• Check the appropriate box from the list provided based on the information obtained from the medical record, the patient directly, or other sources, if easily accessible. |

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| Ethnicity New Zealand<br>(NZ sites only) | • Check up to two options.<br>• Never guess or decide ethnicity for the patient.<br>• An ethnic group is made up of people who have some or all of the following:<br>  ○ A shared culture, such as traditions, customs, beliefs, or language<br>  ○ A common ancestry or history<br>  ○ A similar geographic, tribal, or clan origin.<br>• Check the appropriate box from the list provided based on the information obtained from the medical record, the patient directly, family, or other sources, if easily accessible.<br>• If the patient identifies with more than one ethnic group check up to two ethnicities from the list provided. |

# FORM 3: MICROBIOLOGY

## General Guidance

- Complete this form for all ***Platform*** patients.
- This CRF collects information about the causative organism for CAP where an organism has been identified.
- The eCRF is designed to stop asking questions as soon as the causative organism(s) have been identified. Due to this complexity, **it is recommended that only the eCRF is used**.
- A resistance matrix is provided in Appendix 2.
- Specimen Collection:
    - The date and time a specimen was collected is usually reported with the microbiology lab report. Sometimes this may be referred to as the time the specimen was received in the lab.
    - Most questions pertain to specimens collected within 72 hours of hospital admission, except where specified.
    - If a time of specimen collection is not shown on the lab report but the date is available, use calendar days to determine the time window.
    - It is suggested to write down the hour/time at which 72 hours has elapsed, use this date and time, in conjunction with the patient hospital admission time (recorded on the Eligibility CRF) to determine is the specimen fits within the time window.
    - Tests performed at external laboratories prior to admission to this hospital (e.g. due to transfer from another hospital) may be included if available. This may also include specimens collected in the ED.

| Question | Definition or Explanation of Question |
|---|---|
| ***Platform*** | |
| 1. Causative Organism | |
| Upper or lower respiratory tract PCR test result | • Check all PCR tests performed.<br>• A PCR test is also known as:<br>  ○ Nucleic acid test (NAT)<br>  ○ GeneXpert<br>• An upper respiratory tract specimen is defined as:<br>  ○ Oropharyngeal swab |

| | | |
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| | | ○ Nasopharyngeal swab, wash or aspirate.<br>○ Nasal swab or wash<br>• A lower respiratory tract specimen is defined as:<br>○ Sputum<br>○ ETT aspirate<br>○ Bronchial Alveolar Lavage (BAL) samples or any specimen collected by bronchoscopy. |
| | Influenza A | • **Only include specimens collected <u>within 72 hours</u> of hospital admission**.<br>• If reported as isolated or detected check POSITIVE.<br>• On pathology reports, influenza A can be documented as:<br>○ Influenza A (InfA or fluA)<br>○ A(H1N1)pdm09<br>○ A(H1N1)<br>○ A(H3N2)<br>○ A(H5N1)<br>○ A(H7N9)<br>• If Influenza A was not reported as isolated or detected check NEGATIVE<br>• If no PCR test on an upper or lower respiratory tract specimen was performed check NOT TESTED. |
| | Influenza B | • **Only include specimens collected <u>within 72 hours</u> of hospital admission**.<br>• If reported as isolated or detected check POSITIVE.<br>• On pathology reports, influenza B can be documented as: |

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| | | ○ Influenza B (InfB or fluB)<br>○ B/Yamagata/16/88 (can be recorded as – B-like virus)<br>○ B/Victoria/2/87<br>• If Influenza B was not reported as isolated or detected check NEGATIVE<br>• If no PCR on an upper or lower respiratory tract specimen was performed check NOT TESTED. |
| | Legionella spp | • **Only include specimens collected <u>within 72 hours</u> of hospital admission**.<br>• If reported as isolated or detected check POSITIVE.<br>• On pathology reports, Legionella can be documented as:<br>○ Legionella species (spp)<br>○ Legionellosis<br>○ Legionella pneumophila<br>○ Legionella longbeachae<br>○ Legionella (another species name)<br>• If no Legionella is detected or isolated, check NEGATIVE<br>• If no PCR test on an upper or lower respiratory tract specimen was performed check NOT TESTED. |
| | SARS-CoV-2 | • **Only include specimens collected during this acute respiratory illness, up until 72 hours after completion of the eligibility assessment.**<br>• If reported as isolated or detected check POSITIVE<br>• On pathology reports, SARS-CoV-2 may be documented as: |

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| | | ○ SARS-CoV-2<br>○ COVID-19<br>○ Novel Coronavirus<br>○ 2019-nCoV |
| Other upper or lower respiratory tract PCR detected organisms | • **Only include specimens collected <u>within 72 hours</u> of hospital admission**<br>• Check the organism box if it was reported as <u>isolated or detected</u>. | |
| | Chlamydophila pneumoniae | • On pathology reports, Chlamydophila pneumoniae can be documented as, including:<br>○ C. pneumoniae<br>○ Chlamydophila (previously Chlamydia) pneumoniae.<br>• Do not check if other species of Chlamydia (e.g. Chlamydia trachomatis and Chlamydia psittaci are reported. |
| | Coronavirus | • On pathology reports, a coronavirus can be documented as:<br>○ Coronavirus<br>○ Alpha Coronavirus (229E and NL63)<br>○ Beta Coronavirus (OC43, HKU1, SARS-CoV and MERS-CoV)<br>○ Severe Acute Respiratory Syndrome related coronavirus (SARS-CoV)<br>○ Middle East Respiratory Syndrome Coronavirus (MERS-CoV).<br>• Do not select Coronavirus for COVID-19 / SARS CoV-2<br>• Do not check if Rhinoviruses or picornaviruses are reported. |
| | Mycoplasma pneumoniae | • On pathology reports Mycoplasma pneumonia can be documented as: |

| | | |
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| | | ○ Mycoplasma pneumoniae<br>○ *M. pneumonia.* |
| | Respiratory Syncytial Virus | • On pathology reports Respiratory Syncytial Virus (RSV) can be documented as:<br>○ RSV<br>○ RSV type A or type B<br>○ Human RSV (hRSV). |
| | Not tested/ None of the above | • Select this option if:<br>○ No upper or lower respiratory tract specimen was tested by PCR.<br>○ An organism was <u>detected</u>, but it is <u>not</u> listed on the CRF. |
| Tuberculosis detected on PCR or culture | • **Include specimens collected <u>at any time</u> during this hospital admission**.<br>• Only include samples taken from:<br>○ Lower respiratory tract<br>○ Pleural aspirate/biopsy.<br>• On pathology reports tuberculosis can be documented as:<br>○ Mycobacterium tuberculosis<br>○ TB<br>○ MTB<br>○ Mycobacterium tuberculosis<br>○ M tuberculosis complex.<br>• <u>Only check if it was</u> detected by PCR or culture.<br>• If there is a report stating "positive acid-fast bacilli suggestive of tuberculosis" in the absence of the above criteria, check NO.<br>• NOTE: blood tests for TB, including Interferon gamma release assay (IGRA) also known as Quantiferon Gold or EliSpot tests do not confirm TB. In the absence of the above criteria, check NO. | |

<table>
<tr><td>Urinary antigen test performed</td><td colspan="2"><ul><li>Check YES if urinary antigen testing was performed <u>at any time</u> during this hospital admission.</li><li>These tests may be referred to as:<ul><li>Urinary legionella antigen</li><li>Urinary pneumococcal antigen</li><li>Streptococcus pneumoniae antigen card.</li></ul></li></ul></td></tr>
<tr><td rowspan="4">Which organisms were detected</td><td colspan="2"><ul><li>Check <u>all</u> that apply.</li><li>Include specimens collected <u>at any time</u> during this hospital admission.</li></ul></td></tr>
<tr><td>Legionella pneumophila serogroup 1</td><td>Legionella pneumophila serogroup 1, can be documented as:<ul><li>L. pneumophila serogroup 1</li><li>L. pneumophila.</li></ul></td></tr>
<tr><td>Streptococcus pneumoniae</td><td>Streptococcus pneumoniae, also known as<ul><li>S. pneumoniae</li><li>Pneumococcus.</li></ul></td></tr>
<tr><td>None of the above</td><td>If an organism was <u>detected</u> and it is <u>not</u> provided in the list.</td></tr>
<tr><td>Was Aspergillus isolated from the lower respiratory tract</td><td colspan="2"><ul><li>Select YES if Aspergillus was isolated from the lower respiratory tract from specimens collected at any time during this hospital admission.</li></ul></td></tr>
<tr><td>Date and time first positive sample collected</td><td colspan="2"><ul><li>Enter the date and time that the first sample from the patient’s lower respiratory tract was collected that was positive for Aspergillus</li><li>Use only samples collected during this hospital admission.</li></ul></td></tr>
<tr><td>Invasive pulmonary aspergillosis diagnosed and treated with one or more systemic antifungal agents</td><td colspan="2"><ul><li>If the patient was treated with antifungal agents for pulmonary Aspergillus during this hospital admission, check YES</li><li>Select YES only if invasive pulmonary Aspergillus infection was diagnosed and treated by the treating clinician.</li></ul></td></tr>
</table>

## 2. Positive blood culture

| | | |
|---|---|---|
| Positive blood culture result | • **Only include specimens collected <u>within 72 hours</u> of hospital admission**.<br>• If no blood cultures were taken within 72 hours, check NOT TESTED.<br>• If any of the blood culture sets collected in the first 72 hours of hospital admission were positive, check YES.<br>• If all blood culture sets collected in the first 72 hours of hospital admission were negative, check NO. | |
| Which organisms were detected | • This question is only required if a positive blood culture was collected in the first 72 hours of hospital admission.<br>• **Only include specimens collected <u>within 72 hours</u> of hospital admission**.<br>• Check <u>all</u> positive blood culture results.<br>• NOTE:<br>○ Different organisms may be detected on different blood cultures, review the results of all blood culture specimens collected within 72 hours of hospital admission.<br>○ Multiple organisms may be detected in the same blood culture, check all detected organisms<br>○ The same organism may be detected in multiple blood culture samples, check the detected organism once. | |
| | *Acinetobacter spp* | On pathology reports this may be documented as<br>• Acinetobacter species (e.g. A. baumannii)<br>• Acinetobacter baumannii complex. |
| | *Burkholderia pseudomallei* | On pathology reports this may be documented as:<br>• B. pseudomallei<br>• Melioidosis. |
| | *Escherichia coli* | On pathology reports this may be documented as E. coli. |

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| | *Haemophilus influenzae* | On pathology reports this may be documented as:<br>• H. influenzae<br>• H. influenzae type b (Hib)<br>• H. influenzae not typeable. |
| | *Klebsiella* spp | On pathology reports this may be documented as:<br>• Klebsiella pneumoniae<br>• K. pneumoniae<br>• Klebsiella oxytoca. |
| | *Moraxella catarrhalis* | On pathology reports this may be documented as M. catarrhalis. |
| | *Pseudomonas aeruginosa* | • On pathology reports this may be documented as P. aeruginosa<br>• Do not check if any other species of Pseudomonas (e.g. fluorescens) is reported. |
| | *Staphylococcus aureus* | On pathology reports this may be documented as:<br>• S. aureus<br>• MRSA<br>• ca-MRSA<br>• ha-MRSA<br>• nm-MRSA<br>• m-MRSA (multiresistant MRSA). |
| | Streptococcus pneumoniae | On pathology reports Streptococcus pneumoniae may be documented as:<br>• S. pneumoniae<br>• Pneumococci or pneumococcus. |
| | *Streptococcus pyogenes* | On pathology reports this may be documented as:<br>• Group A streptococcus<br>• Group A β-hemolytic streptococcus |

| | | |
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| | | • GAS<br>• S. pyogenes. |
| | *Streptococcus agalactiae* | On pathology reports this may be documented as:<br>• *Group B streptococcus*<br>• Group B Streptococcus<br>• GBS<br>• Streptococcus agalactiae. |
| | Coagulase negative staphylococci | On pathology reports this may be documented as:<br>• Coagulase-Negative Staphylococci<br>• CoNS or CNS<br>• Any staphylococci other than S. aureus<br>• Includes many species of staphylococci such as Staphylococcus epidermidis. |
| | Corynebacterium, Bacillus spp, Micrococcus, Propionibacterium | Check this option if ANY of the organisms are reported:<br>• Corynebacterium (may be documented as C. followed by the subtype e.g. C. pseudotuberculosis, coryneforms or diphtheroids).<br>• Bacillus spp can be documented as B. followed by the subtype (e.g. B. thermophilus).<br>• Bacillus species does not include:<br>  ○ Gram-negative bacillus<br>  ○ Gram-positive bacillus<br>• Micrococcus<br>• Propionibacterium<br>• The report refers to skin contaminant, likely contaminant, skin flora or mixed skin flora. |
| | Other, specify | • Before entering anything in this field, check that no other option is applicable. |

| | | |
|---|---|---|
| | | • Please write the full organism name, as it appears in the pathology report.<br>• If uncertain, discuss with clinical staff or contact the project manager. |
| *If Acinetobacter spp*<br>Reported as resistant to ceftazidime and/or piperacillin-tazobactam | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. | |
| *If Acinetobacter spp*<br>Reported as resistant to meropenem and/or imipenem | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. | |
| *If Escherichia coli*<br>Reported as resistant to ceftriaxone and/or ceftazidime | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant.<br>• If there is a note that this organism is an Extended Spectrum Beta-Lactamases (ESBL) check YES. | |
| *If Escherichia coli*<br>Reported as resistant to meropenem and/or imipenem | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant.<br>• If there is a note that this organism is a Carbapenemase-producing Enterobacteriaceae (CPE) or a Carbapenem-resistant Enterobacteriaceae (CRE) check YES. | |
| *If Klebsiella spp*<br>Reported as resistant to ceftriaxone and/or ceftazidime | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant.<br>• If there is a note that this organism is an ESBL check YES. | |
| *If Klebsiella spp* | • If resistant to one or both check YES. | |

| | |
|---|---|
| Reported as resistant to meropenem and/or imipenem | • Check YES if reported as:<br>  ○ Intermediate or<br>  ○ Resistant.<br>• If there is a note that this organism is a CPE or a CRE check YES. |
| *If Pseudomonas aeruginosa*<br>Reported as resistant to ceftazidime and/or piperacillin-tazobactam | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>  ○ Intermediate or<br>  ○ Resistant. |
| *If Pseudomonas aeruginosa*<br>Reported as resistant to meropenem and/or imipenem | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>  ○ Intermediate or<br>  ○ Resistant. |
| *If Staphylococcus aureus*<br>Reported as methicillin-resistant staphylococcus aureus | If reported as <u>intermediate or resistant</u> to any of the following check YES:<br>  ○ methicillin<br>  ○ oxacillin<br>  ○ dicloxacillin<br>  ○ flucloxacillin<br>  ○ nafcillin.<br>If reported as any of the following organisms check YES:<br>  ○ MRSA<br>  ○ ca-MRSA<br>  ○ ha-MRSA<br>  ○ nm-MRSA<br>  ○ m-MRSA (multiresistant MRSA). |
| *If Streptococcus pneumoniae*<br>Reported as resistant to erythromycin and/or azithromycin | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>  ○ Intermediate or<br>  ○ Resistant. |

| | |
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| *If Streptococcus pneumoniae* Reported as resistant to Penicillin | • Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. |
| *If Streptococcus pneumoniae* Reported as resistant to moxifloxacin, norfloxacin and/or levofloxacin | • If resistant to one or more of these agents check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. |
| 3. Late positive blood culture | |
| Positive blood culture result | • **Only include specimens collected <u>between 72 hours</u> after hospital admission and hospital discharge**.<br>• If no blood cultures were taken between 72 hours after hospital admission and hospital discharge, check NOT TESTED.<br>• If any of the blood culture sets collected between 72 hours after hospital admission and hospital discharge were positive, check YES.<br>• If all blood culture sets collected between 72 hours after hospital admission and hospital discharge were negative, check NO. |
| Which organisms were detected | • This question is only required if a positive blood culture was collected between 72 hours after hospital admission and hospital discharge.<br>• **Only include specimens collected <u>between 72 hours</u> after hospital admission and prior to hospital discharge**.<br>• Check <u>all</u> positive blood culture results.<br>• NOTE:<br>○ Different organisms may be detected on different blood cultures, review the results of all blood culture specimens collected within 72 hours of hospital admission.<br>○ Multiple organisms may be detected in the same blood culture, check all detected organisms |

| | | |
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| | ○ The same organism may be detected in multiple blood culture samples, check the detected organism once. | |
| | *Acinetobacter spp* | On pathology reports this may be documented as<br>• Acinetobacter species (e.g. A. baumannii)<br>• Acinetobacter baumannii complex. |
| | *Burkholderia pseudomallei* | On pathology reports this may be documented as:<br>• B. pseudomallei<br>• Melioidosis. |
| | *Escherichia coli* | • On pathology reports this may be documented as E. coli. |
| | *Haemophilus influenzae* | On pathology reports this may be documented as:<br>• H. influenzae<br>• H. influenzae type b (Hib)<br>• H. influenzae not typeable. |
| | *Klebsiella* spp | On pathology reports this may be documented as:<br>• Klebsiella pneumoniae<br>• K. pneumoniae<br>• Klebsiella oxytoca. |
| | *Moraxella catarrhalis* | • On pathology reports this may be documented as M. catarrhalis. |
| | *Pseudomonas aeruginosa* | • On pathology reports this may be documented as P. aeruginosa<br>• Do not check if any other species of Pseudomonas (e.g. fluorescens) is reported. |
| | *Staphylococcus aureus* | On pathology reports this may be documented as:<br>• S. aureus<br>• MRSA<br>• ca-MRSA<br>• ha-MRSA |

| | | |
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| | | • nm-MRSA<br>• m-MRSA (multiresistant MRSA). |
| | *Streptococcus pneumoniae* | On pathology reports Streptococcus pneumoniae may be documented as:<br>• S. pneumoniae<br>• Pneumococci or pneumococcus. |
| | *Streptococcus pyogenes* | On pathology reports this may be documented as:<br>• Group A streptococcus<br>• Group A β-hemolytic streptococcus<br>• GAS<br>• S. pyogenes. |
| | *Streptococcus agalactiae* | On pathology reports this may be documented as:<br>• *Group B streptococcus*<br>• Group B Streptococcus<br>• GBS<br>• Streptococcus agalactiae. |
| | *Coagulase negative staphylococci* | On pathology reports this may be documented as:<br>• Coagulase-Negative Staphylococci<br>• CoNS or CNS<br>• Any staphylococci other than S. aureus<br>• Includes many species of staphylococci such as Staphylococcus epidermidis. |
| | *Corynebacterium, Bacillus spp, Micrococcus, Propionibacterium* | Check this option if ANY of the organisms are reported:<br>• Corynebacterium (may be documented as C. followed by the subtype e.g. C. pseudotuberculosis, coryneforms or diphtheroids). |

| | | |
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| | | • Bacillus spp can be documented as B. followed by the subtype (e.g. B. thermophilus).<br>• Bacillus species does not include:<br>  ○ Gram-negative bacillus<br>  ○ Gram-positive bacillus<br>• Micrococcus<br>• Propionibacterium<br>• The report refers to skin contaminant, likely contaminant, skin flora or mixed skin flora. |
| | Other, specify | • Before entering anything in this field, check that no other option is applicable.<br>• Please write the full organism name, as it appears in the pathology report.<br>• If uncertain, discuss with clinical staff or contact the project manager. |
| Date and time first positive sample collected | • For any organism that was identified between 72 hours after hospital admission and hospital discharge, enter the date and time that the first positive sample was collected. | |
| 4. Pleural aspirate | | |
| Microbiological tests performed on pleural fluid | • **Include specimens collected within the first 7 calendar days of this hospital admission, including specimens collected prior to ICU admission.**<br>• Pleural fluid can be collected by needle aspiration, from a drain or intercostal drain tubes or at the time of surgery (thoracotomy, video-assisted thoroscopy (VATS) or decortication).<br>• If a culture or PCR was performed on pleural fluid check YES. | |
| Positive pleural aspirate culture result | • **Include specimens collected within the first 7 calendar days of this hospital admission**.<br>• If any pleural fluid cultures are positive check YES. | |

<table>
<tr><td></td><td colspan="2">

- If no pleural cultures are positive, check NO

</td></tr>
<tr><td>Which organisms were detected</td><td colspan="2">

- This question is only required if a positive pleural fluid specimen is collected within 7 days of hospital admission
- Check <u>all</u> organisms detected in positive pleural aspirate results.
- Different organisms may be detected in different pleural fluid cultures, and multiple organisms may be detected in the same pleural fluid culture.

</td></tr>
<tr><td></td><td>Acinetobacter spp</td><td>On pathology reports it can be documented as<br>• Acinetobacter species (e.g. A. baumannii)<br>• Acinetobacter complex.</td></tr>
<tr><td></td><td>Burkholderia pseudomallei</td><td>On pathology reports it can be documented as:<br>• B. pseudomallei<br>• Melioidosis.</td></tr>
<tr><td></td><td>Escherichia coli</td><td>On pathology reports it can be documented as E. coli.</td></tr>
<tr><td></td><td>Haemophilus influenzae</td><td>On pathology reports it can be documented as:<br>• H. influenzae<br>• H. influenzae type b (Hib)<br>• H. influenzae not typeable.</td></tr>
<tr><td></td><td>Klebsiella spp</td><td>On pathology reports it can be documented as:<br>• Klebsiella pneumoniae<br>• K. pneumoniae<br>• Klebsiella oxytoca.</td></tr>
<tr><td></td><td>Moraxella catarrhalis</td><td>On pathology reports it can be documented as M. catarrhalis.</td></tr>
<tr><td></td><td>Pseudomonas aeruginosa</td><td>• On pathology reports it can be documented as P. aeruginosa.<br>• Do not check if any other species of pseudomonas (e.g. fluorescans) is reported.</td></tr>
</table>

| | | |
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| | *Staphylococcus aureus* | On pathology reports it can be documented as:<br>• S. aureus<br>• MRSA<br>• ca-MRSA<br>• ha-MRSA<br>• nm-MRSA<br>• m-MRSA (multiresistant MRSA). |
| | Streptococcus pneumoniae | On pathology reports Streptococcus pneumoniae can be documented as:<br>• S. pneumoniae<br>• Pneumococci or pneumococcus. |
| | *Streptococcus pyogenes* | On pathology reports it can be documented as:<br>• Group A streptococcus<br>• Group A β-hemolytic streptococcus<br>• GAS<br>• S. pyogenes. |
| | *Streptococcus agalactiae* | On pathology reports it can be documented as:<br>• *Group B streptococcus*<br>• Group B Streptococcus (GBS)<br>• Streptococcus agalactiae. |
| | Coagulase negative staphylococci | On pathology reports it can be documented as:<br>• Coagulase-Negative Staphylococci<br>• CoNS or CNS<br>• Any staphylococci other than S. aureus<br>• Includes many species of staphylococci such as S. epidermidis. |
| | Corynebacterium, Bacillus spp, | • Check this option if ANY of the organisms are reported: either not platform eligible, or are |

| | | |
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| | Micrococcus, Propionibacterium | platform eligible but not assigned treatment within a Domain Corynebacterium (can be documented as C. followed by the subtype e.g. C. pseudotuberculosis).<br>• Can be documented as coryneforms or diphtheroids.<br>• Bacillus spp can be documented as B. followed by the subtype (e.g. B. thermophilus)<br>• Bacillus species does not include:<br>  ○ Gram-negative bacillus<br>  ○ Gram-positive bacillus<br>• Micrococcus<br>• Propionibacterium<br>• The report refers to skin contaminant, likely contaminant, skin flora or mixed skin flora. |
| | Other, specify | • Before entering anything in this field, check that no other options are applicable.<br>• If uncertain, discuss with clinical staff or contact the project manager. |
| *If Acinetobacter spp*<br>Reported as resistant to ceftazidime and/or piperacillin-tazobactam | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>  ○ Intermediate or<br>  ○ Resistant. | |
| *If Acinetobacter spp*<br>Reported as resistant to meropenem and/or imipenem | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>  ○ Intermediate or<br>  ○ Resistant. | |
| *If Escherichia coli*<br>Reported as resistant to ceftriaxone and/or ceftazidime | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>  ○ Intermediate or<br>  ○ Resistant. | |

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| | • If there is a note that this organism is an ESBL check YES. |
| *If Escherichia coli*<br>Reported as resistant to meropenem and/or imipenem | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant.<br>• If there is a note that this organism is a CPE or a CRE check YES. |
| *If Klebsiella spp*<br>Reported as resistant to ceftriaxone and/or ceftazidime | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant.<br>• If there is a note that this organism is an ESBL check YES. |
| *If Klebsiella spp*<br>Reported as resistant to meropenem and/or imipenem | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant.<br>• If there is a note that this organism is a CPE or a CRE check YES. |
| *If Pseudomonas aeruginosa* Reported as resistant to ceftazidime and/or piperacillin-tazobactam | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. |
| *If Pseudomonas aeruginosa*<br>Reported as resistant to meropenem and/or imipenem | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. |
| *If Staphylococcus aureus*<br>Reported as methicillin-resistant staphylococcus aureus | If reported as <u>intermediate or resistant</u> to any of the following check YES:<br>○ methicillin<br>○ oxacillin<br>○ dicloxacillin<br>○ flucloxacillin |

| | |
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| | ○ nafcillin.<br>If reported as any of the following organisms check YES:<br>○ MRSA<br>○ ca-MRSA<br>○ ha-MRSA<br>○ nm-MRSA<br>○ m-MRSA (multiresistant MRSA). |
| *If Streptococcus pneumoniae*<br>Reported as resistant to erythromycin and/or azithromycin | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. |
| *If Streptococcus pneumoniae*<br>Reported as resistant to Penicillin | • Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. |
| *If Streptococcus pneumoniae*<br>Reported as resistant to moxifloxacin, norfloxacin and/or levofloxacin | • If resistant to one or more of these agents check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. |
| PCR performed on pleural fluid | • **Only include specimens collected within 7 calendar days of hospital admission.**<br>• Check YES if a PCR test was performed on pleural fluid within 7 days of hospital admission.<br>• A PCR test is also known as a NAT or GeneXpert.<br>• Pleural fluid can be collected by needle aspiration, from a drain or intercostal drain tubes or at the time of surgery (thoracotomy, video-assisted thoroscopy (VATS) or decortication). |
| Positive for Streptococcus pneumoniae | • This question is only required if a PCR test is performed on pleural fluid. |

<table>
<tr><td></td><td colspan="2">• Streptococcus pneumoniae is also known as pneumococcus.</td></tr>
<tr><td colspan="3">5. Positive lower respiratory tract specimen culture</td></tr>
<tr><td>Positive lower respiratory tract specimen culture</td><td colspan="2">• Only include specimens collected <u>within 72 hours</u> of hospital admission.<br>• This question is only required if no positive microbiological tests on blood cultures within 72 hours or pleural fluid within 7 days of hospital admission.<br>• Select NOT TESTED if no lower respiratory tract culture was collected.<br>• A lower respiratory tract specimen is defined as:<br>○ Sputum<br>○ ETT aspirate<br>○ BAL samples or any specimen collected by bronchoscopy.</td></tr>
<tr><td rowspan="4">Which organisms were detected</td><td colspan="2">• This question is only required if a positive lower respiratory tract culture was collected within 72 hours of hospital admission.<br>• Only include specimens collected <u>within</u> <u>72 hours of hospital admission</u>.<br>• Check <u>all</u> positive lower respiratory tract culture results.<br>• Different organisms may be detected in different lower respiratory tract cultures, and multiple organisms may be detected in the same lower respiratory tract culture.</td></tr>
<tr><td>Acinetobacter spp</td><td>On pathology reports this may be documented as<br>• Acinetobacter species (e.g. A. baumannii)<br>• Acinetobacter complex.</td></tr>
<tr><td>Burkholderia pseudomallei</td><td>On pathology reports this may be documented as:<br>• B. pseudomallei<br>• Melioidosis.</td></tr>
<tr><td>Escherichia coli</td><td>On pathology reports this may be documented as E. coli.</td></tr>
</table>

| | | |
|---|---|---|
| | *Haemophilus influenzae* | On pathology reports this may be documented as:<br>• H. influenzae<br>• H. influenzae type b (Hib)<br>• H. influenzae not typeable. |
| | *Klebsiella* spp | On pathology reports this may be documented as:<br>• Klebsiella pneumoniae<br>• K. pneumoniae<br>• Klebsiella oxytoca. |
| | *Moraxella catarrhalis* | On pathology reports this may be documented as M. catarrhalis. |
| | *Pseudomonas aeruginosa* | • On pathology reports this may be documented as P. aeruginosa.<br>• Do not check if any other species of pseudomonas (e.g. fluorescans) is reported. |
| | *Staphylococcus aureus* | On pathology reports this may be documented as:<br>• S. aureus<br>• MRSA<br>• ca-MRSA<br>• ha-MRSA<br>• nm-MRSA<br>• m-MRSA (multiresistant MRSA). |
| | Streptococcus pneumoniae | On pathology reports Streptococcus pneumoniae may be documented as:<br>• S. pneumoniae<br>• Pneumococci or pneumococcus. |
| | *Streptococcus pyogenes* | On pathology reports may be documented as:<br>• Group A streptococcus<br>• Group A β-hemolytic streptococcus |

| | | |
|---|---|---|
| | | • GAS<br>• S. pyogenes. |
| | *Streptococcus agalactiae* | On pathology reports it may be documented as:<br>• *Group B streptococcus*<br>• Group B Streptococcus (GBS)<br>• Streptococcus agalactiae. |
| | None of the above | If an organism was detected and it is not provided in the list. |
| *If Acinetobacter spp*<br>Reported as resistant to ceftazidime and/or piperacillin-tazobactam | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. | |
| *If Acinetobacter spp*<br>Reported as resistant to meropenem and/or imipenem | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. | |
| *If Escherichia coli*<br>Reported as resistant to ceftriaxone and/or ceftazidime | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant.<br>• If there is a note that this organism is an ESBL check YES. | |
| *If Escherichia coli*<br>Reported as resistant to meropenem and/or imipenem | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant.<br>• If there is a note that this organism is a CPE or a CRE check YES. | |
| *If Klebsiella spp*<br>Reported as resistant to ceftriaxone and/or ceftazidime | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. | |

| | |
|---|---|
| | • If there is a note that this organism is an ESBL check YES. |
| *If Klebsiella spp*<br>Reported as resistant to meropenem and/or imipenem | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant.<br>• If there is a note that this organism is a CPE or a CRE check YES. |
| *If Pseudomonas aeruginosa*<br>Reported as resistant to ceftazidime and/or piperacillin-tazobactam | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. |
| *If Pseudomonas aeruginosa* Reported as resistant to meropenem and/or imipenem | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. |
| *If Staphylococcus aureus*<br>Reported as methicillin-resistant staphylococcus aureus | If reported as <u>intermediate or resistant</u> to any of the following check YES:<br>○ methicillin<br>○ oxacillin<br>○ dicloxacillin<br>○ flucloxacillin<br>○ nafcillin.<br>If reported as any of the following organisms check YES:<br>○ MRSA<br>○ ca-MRSA<br>○ ha-MRSA<br>○ nm-MRSA<br>○ m-MRSA (multiresistant MRSA). |
| *If Streptococcus pneumoniae* | • If resistant to one or both check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. |

| | |
|---|---|
| Reported as resistant to erythromycin and/or azithromycin | |
| *If Streptococcus pneumoniae*<br>Reported as resistant to Penicillin | • Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. |
| *If Streptococcus pneumoniae*<br>Reported as resistant to moxifloxacin, norfloxacin and/or levofloxacin | • If resistant to one or more of these agents check YES.<br>• Check YES if reported as:<br>○ Intermediate or<br>○ Resistant. |
| 6. Immunocompromised Patients | |
| Positive lower respiratory tract or lung tissue specimen | • Only answer this question if prompted to by the eCRF.<br>• This question will appear if the patient was identified as having evidence of immunosuppression or an immunocompromised state at Baseline.<br>• **All specimens must have been collected within 7 days of hospital admission.**<br>• The lung tissue specimen must have been collected by bronchoscopy or other type of lung biopsy (e.g. open, VATS, bronchoscopy, transbronchial).<br>• A lower respiratory tract specimen is defined as:<br>○ Sputum<br>○ ETT aspirate<br>○ BAL samples or any specimen collected by bronchoscopy.<br>• The tests by which these organisms may be detected is outlined below. |
| Which organisms were detected | • This question is only required if a positive lower respiratory tract of lung tissue specimen was collected within 7 days of hospital admission. |

- Check <u>all</u> that apply.
- **Only include** lung tissue and lower respiratory tract **specimens collected <u>within 7 days of</u> hospital admission**.
- Only check YES, if the organism was identified by the microbiological test indicated below.

| Organism name | Also reported as | Type of test performed |
|---|---|---|
| Aspergillus | Aspergillus species (e.g. A. fumigatus) | • A galactomannan test if reported as positive<br>• Culture<br>• Histopathology<br>• PCR, NAT or GeneXpert |
| Cryptococcus species | Cryptococcus species (e.g. C. gattii) | • Culture<br>• Histopathology<br>• Microscopy<br>• PCR, NAT or GeneXpert |
| Mucormycosis species | Mucor OR Rhizopuses | • Culture<br>• Histopathology<br>• Microscopy<br>• PCR, NAT or GeneXpert |
| Nocardia species | Nocardia species (e.g. N. asteroids) | • Culture<br>• Histopathology<br>• PCR, NAT or GeneXpert |
| Non--TB mycobacteria | • Mycobacterium avium complex (MAC)<br>• Mycobacterium species other than tuberculosis e.g.<br>  ○ M abscessus OR | • Culture<br>• PCR, NAT or GeneXpert |

| | | | |
|---|---|---|---|
| | | ○ Mycobacteria other than tuberculosis (MOTT) | |
| | Pneumocystis | • Pneumocystis jiroveci pneumonia (PJP)<br>• Pneumocystis carinii pneumonia (PCP) | • Histopathology<br>• PCR, NAT or GeneXpert |
| | Tuberculosis | • Mycobacterium tuberculosis<br>• TB<br>• MTB<br>• Mycobacterium tuberculosis<br>• M tuberculosis complex | • Culture<br>• MPT-64 antigen<br>• PCR, NAT or GeneXpert |
| | Varicella zoster virus | • VZV<br>• Chickenpox<br>• Shingles | • PCR, NAT or GeneXpert |

# FORM 4: DAILY

## General Guidance

- Complete this form for all ***Platform*** patients.
- A study day is defined in Section 4.4.
- Daily data should not be collected prior to randomization.
- Data collection:
  - Complete the daily CRF for any day that the patient was in ICU, up to 28 days after last randomization
  - Study day 1 commences at the time of first randomization. The start and end of each subsequent study day is defined by the ICU chart day
  - If a patient dies in ICU collect data until the time of death
  - On the day of discharge from ICU, collect daily data until ICU discharge (ICU discharge is defined in Section 5. General definitions)

| Question | Definition or Explanation of Question |
|---|---|
| ***Platform*** | |
| 1. Study Day | |
| Study Day | • The study day will be auto-filled by the database. Check the auto-fill.<br>• Study days are numbered from the first randomization for each patient. If using the paper CRF enter study day. |
| Date | • The calendar date relating to the beginning of the study day will be auto-filled by the database. Check the auto-fill.<br>• If using the paper CRF enter calendar date. |
| Patient in ICU during this day | • If the patient was in ICU at any time on this study day check YES.<br>• During a pandemic if the patient is located in an area that is capable of providing ICU-level care (NIV with sealed mask, IMV, or vasopressors via continuous infusion), select YES |
| 2. Daily Treatments | |
| Airway | Select the highest level of airway support received on that study day. |

| | | |
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| | Maintaining own | The patient did not require ventilatory support via ETT or TT as defined below.<br>Includes:<br>• No oxygen therapy received at any time, or<br>• Oxygen received only via a mask or nasal prongs, including:<br>  ○ HFNP (e.g. defined below)<br>  ○ NIV (e.g. defined in Section 5. General Definitions). |
| | Endotracheal Tube | • The patient had an ETT at any time on this study day and did not have a TT.<br>• If the patient had an ETT placed solely for a procedure do not check the box (e.g. they are intubated for a procedure and then extubated immediately afterwards). |
| | Tracheostomy | • The patient had ventilatory support delivered via tracheostomy at any time on this study day.<br>• Includes tracheostomy irrespective of the type of ventilation (e.g. CPAP via a TT).<br>• If the patient has an end stoma, with no TT (for example after laryngectomy) do not check the box. |
| Low-flow oxygen therapy | • This question only applies if you have indicated that the patient is maintaining their own airway.<br>• Select YES if the patient was treated with low-flow oxygen for at least one continuous hour<br>• Low-intensity supplemental oxygen is defined as: | |

| | |
|---|---|
| | ○ A FiO2 of > 0.21 delivered at a flow rate of < 30 liters per minute (or < 2 L/min/kg of bodyweight in children less than 15 kilograms); OR<br>○ delivered at a flow rate of ≥ 30 liters per minute or more (or ≥2 L/min/kg of bodyweight in children less than 15 kilograms) with a FiO2 of > 0.21 and < 0.4 |
| High flow nasal prong oxygen therapy | • This question only applies if you have indicated that the patient is maintaining their own airway.<br>• Select YES if the patient was treated with HFNP for at least one continuous hour.<br>• If gas flow rate is less than 20 liters per minute, check NO.<br>• If $FiO_2$ is 0.21 check NO.<br>• If HFNP was provided only for humidification (e.g. $FIO_2$ was equal to or less than 0.21), check NO. |
| Non-invasive ventilation | • This question only applies if you have indicated that the patient is maintaining their own airway.<br>• Select YES if the patient was being treated with NIV for at least one continuous hour.<br>• NIV is defined in Section 5. General definitions. |
| Hours of invasive mechanical ventilation | • This question only applies if you have indicated that the patient has an ETT or TT.<br>• Enter the total number of hours of IMV received during the study day.<br>• If the patient received less than 1 hour enter 00.<br>• If the patient has multiple episodes of ventilation round part hours to the closest hour.<br>• IMV defined in Section 5. General definitions. |
| $FiO_2$ associated with lowest P:F ratio | • If the patient has had one or more ABGs record the $FiO_2$ associated with the lowest P:F ratio while the patient is receiving IMV. |

| | | |
|---|---|---|
| | • If a $PaO_2$ is not available or no ABG was taken, enter the highest $FiO_2$ recorded on that study day while the patient received IMV.<br>• Short periods of high $FiO_2$ for suctioning or a transient desaturation should not be entered. | |
| Corresponding $PaO_2$ | • The $PaO_2$ associated with the lowest P:F ratio and the $FiO_2$ entered above.<br>• Record the result and select the unit of measurement (mmHg or kPa).<br>• Only utilize ABGs collected while the patient is in ICU<br>• If the patient has not had an ABG performed check the NOT RECORDED. | |
| Corresponding PEEP | • The PEEP the patient received at the time of the ABG associated with the lowest P:F ratio.<br>• If no ABG was taken enter the PEEP the patient was receiving at the time of the HIGHEST $FiO_2$ recorded above was taken.<br>• If the patient did not receive any PEEP (e.g. T-piece) enter zero (00).<br>• If the patient was receiving invasive mechanical ventilation using APRV mode at the time that the ABG was obtained, select 'patient receiving APRV'. | |
| Extended Cardiovascular SOFA score | • Check the highest (most deranged) extended cardiovascular (CVS) SOFA score.<br>• The patient must have received that level of support for at least one hour.<br>• If the ICU Chart only records hourly interventions and observations, the intervention must have been recorded for two consecutive hours.<br>• If the patient received multiple inotrope or vasopressor infusions check the highest score. | |
| | Score 0 | Both of the following criteria are met:<br>1. MAP equal to or higher than (≥) 70 mm Hg or 9.33 kPa for all recordings<br>**AND**<br>2. No inotrope/vasopressor support received. |

<table>
<tr><td></td><td>Score 1</td><td colspan="2">Both of the following criteria are met:<br><br>1. Patient’s MAP is less than (<) 70 mmHg or 9.33 kPa<br><br>AND<br><br>2. No inotrope/vasopressor support received.</td></tr>
<tr><td></td><td>Score 2</td><td colspan="2">Any of the following inotrope/vasopressor(s) were administered as an infusion for at least one hour at the indicated dose:</td></tr>
<tr><td></td><td></td><td>Inotrope/ Vasopressor</td><td>Dose required</td></tr>
<tr><td></td><td></td><td>Dopamine</td><td>Equal to or Less than (≤) 5 µg/kg/min</td></tr>
<tr><td></td><td></td><td>Dobutamine</td><td>any dose</td></tr>
<tr><td></td><td></td><td>Levosimendan (Simdax)</td><td>any dose</td></tr>
<tr><td></td><td></td><td>Milrinone (Primacor)</td><td>any dose</td></tr>
<tr><td></td><td>Score 3</td><td colspan="2">Any of the following inotrope/vasopressors were administered as an infusion for at least one hour at the indicated dose:</td></tr>
<tr><td></td><td></td><td>Inotrope/ Vasopressor</td><td>Dose required</td></tr>
<tr><td></td><td></td><td>Epinephrine / Adrenaline</td><td>Equal to or Less than (≤) 0.1 µg/kg/min</td></tr>
<tr><td></td><td></td><td>Dopamine</td><td>Greater than (>) 5 µg/kg/min<br>AND<br>Equal to or less than (≤) 15 µg/kg/min</td></tr>
<tr><td></td><td></td><td>Norepinephrine / Noradrenaline</td><td>Equal to or Less than (≤) 0.1 µg/kg/min</td></tr>
<tr><td></td><td></td><td>Metaraminol</td><td>any dose</td></tr>
</table>

| | | | |
|---|---|---|---|
| | | (Aramine, Metaradrine, Metaramin, Pressonex) | |
| | | Phenylephrine | any dose |
| | | Vasopressin (Pitressin) | any dose |
| | Score 4 | Any of the following inotrope/vasopressors were administered as an infusion for at least one hour at the indicated dose: | |
| | | Inotrope/ Vasopressor | Dose required |
| | | Epinephrine / Adrenaline | Greater than (>) 0.1 µg/kg/min **AND** Equal to or less than (≤) 0.3 µg/kg/min |
| | | Dopamine | Greater than (>) 15 µg/kg/min |
| | | Norepinephrine / Noradrenaline | Greater than (>) 0.1 µg/kg/min **AND** Equal to or less than (≤) 0.3 µg/kg/min |
| | Score 4+ | Any of the following inotrope/vasopressors were administered as an infusion for at least one hour at the indicated dose: | |
| | | Inotrope/ Vasopressor | Dose required |
| | | Epinephrine / Adrenaline | Greater than (>) 0.3 µg/kg/min |
| | | Norepinephrine / Noradrenaline | Greater than (>) 0.3 µg/kg/min |

<table>
<tr><td rowspan="20">Extended Cardiovascular Pediatric SOFA score</td><td colspan="3"><ul><li>Use MAP value and corresponding dose of inotropes and/or vasopressors documented during this hospital admission prior to randomization (closest to randomization).</li><li>Only required for pediatric patients.</li></ul></td></tr>
<tr><td rowspan="8">Score 0</td><td>Age</td><td>MAP</td></tr>
<tr><td>< 1 Month</td><td>≥ 46 mmHg</td></tr>
<tr><td>1 – 11 months</td><td>≥ 55 mmHg</td></tr>
<tr><td>12 – 23 months</td><td>≥ 60 mmHg</td></tr>
<tr><td>24 – 59 months</td><td>≥ 62 mmHg</td></tr>
<tr><td>60 – 143 months</td><td>≥ 65 mmHg</td></tr>
<tr><td>144 – 216 months</td><td>≥ 67 mmHg</td></tr>
<tr><td>> 216 months</td><td>≥ 70 mmHg</td></tr>
<tr><td rowspan="8">Score 1</td><td>Age</td><td>MAP</td></tr>
<tr><td>< 1 Month</td><td>< 46 mmHg</td></tr>
<tr><td>1 – 11 months</td><td>< 55 mmHg</td></tr>
<tr><td>12 – 23 months</td><td>< 60 mmHg</td></tr>
<tr><td>24 – 59 months</td><td>< 62 mmHg</td></tr>
<tr><td>60 – 143 months</td><td>< 65 mmHg</td></tr>
<tr><td>144 – 216 months</td><td>< 67 mmHg</td></tr>
<tr><td>> 216 months</td><td>< 70 mmHg</td></tr>
<tr><td rowspan="3">Score 2</td><td colspan="2">Any of the following vasopressors were administered as an infusion for at least one hour at the indicated dose:</td></tr>
<tr><td>Inotrope / Vasopressor</td><td>Dose required</td></tr>
<tr><td>Dopamine hydrochloride</td><td>≤ 5 µg/kg/min</td></tr>
<tr><td>Dobutamine hydrochloride</td><td>Any</td></tr>
<tr><td rowspan="3">Score 3</td><td colspan="2">Any of the following vasopressors were administered as an infusion for at least one hour at the indicated dose:</td></tr>
<tr><td>Inotrope / Vasopressor</td><td>Dose required</td></tr>
<tr><td>Dopamine hydrochloride</td><td>> 5 µg/kg/min and ≤ 15 µg/kg/min</td></tr>
</table>

| | | | |
|---|---|---|---|
| | | Epinephrine / Adrenaline | ≤ 0.1 µg/kg/min |
| | | Norepinephrine / Noradrenaline | ≤ 0.1 µg/kg/min |
| | Score 4 | Any of the following vasopressors were administered as an infusion for at least one hour at the indicated dose: | |
| | | Inotrope / Vasopressor | Dose required |
| | | Dopamine hydrochloride | > 15 µg/kg/min |
| | | Epinephrine / Adrenaline | > 0.1 µg/kg/min and ≤ 0.3 µg/kg/min |
| | | Norepinephrine / Noradrenaline | > 0.1 µg/kg/min and ≤ 0.3 µg/kg/min |
| | Score 4+ | Any of the following vasopressors were administered as an infusion for at least one hour at the indicated dose: | |
| | | Inotrope / Vasopressor | Dose required |
| | | Epinephrine / Adrenaline | > 0.3 µg/kg/min |
| | | Norepinephrine / Noradrenaline | > 0.3 µg/kg/min |
| RRT | • Select YES if the patient received RRT at any time.<br>• Includes RRT administered outside the ICU while they were an ICU patient (e.g. RRT given in dialysis unit).<br>• RRT is defined in Section 5. General definitions. | | |
| Extracorporeal gas exchange | • Select YES if the patient received extracorporeal gas exchange support at any time on that study day. | | |
| Extracorporeal gas exchange received | • This question is only required if you have indicated that the patient received extracorporeal gas exchange support.<br>• Check all that were received at any time on this study day. | | |
| | ECMO | All forms of ECMO (e.g. veno-venous, veno-arterial and other combinations) should be included, irrespective of | |

| | | |
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| | | site of cannulation or location where the ECMO was instituted. |
| | $ECCO_2R$ | All forms of $ECCO_2R$ should be included, irrespective of site of cannulation or location where the $ECCO_2R$ was instituted. |

## *Corticosteroid Domain*

### General Guidance

- Complete this Section for all patients randomized to the ***Corticosteroid Domain***.
- Corticosteroid daily data is collected up to and including on study day 28 while patients remain in ICU.
- For patients discharged from ICU before the end of study day 9, who are assigned to the fixed-duration Hydrocortisone intervention, it is necessary to collect daily data regarding corticosteroid administration between ICU discharge and until the end of study day 9, or hospital discharge, whichever occurs first.
- For further guidance refer to ICU daily data collection instructions in Form 4: Daily, Section 4 General Guidance.

### 3. Corticosteroid Administration

| | |
|---|---|
| Was a corticosteroid administered on this study day | • Select YES if a systemic corticosteroid (including hydrocortisone) was administered to the patient on this study day.<br>• The following questions only apply if the patient was administered a systemic corticosteroid on this study day. |
| Which corticosteroid was administered | • Select the corticosteroid that was administered on this study day.<br>• Only one corticosteroid can be selected. Enter the details of each corticosteroid administered on that study day separately.<br>• Only include corticosteroids administered systemically (e.g. IV, intramuscular, oral, NG, NJ, PEG and PEJ administration).<br>• Do not enter corticosteroid administered non-systemically (e.g. topically, inhaled, intraventricular or intra-articular).<br>• Include the following corticosteroids:<br>  ○ Any systemic administration (IV or oral) of:<br>  ▪ Hydrocortisone (IV)<br>  ▪ Hydrocortisone (oral) |

| | |
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| | ▪ Betamethasone<br>▪ Dexamethasone<br>▪ Methylprednisolone<br>▪ Prednisolone<br>▪ Prednisone<br>▪ Triamcinolone. |
| Total daily dose | • Sum (add up) all doses of the selected corticosteroid given on that study day.<br>• Enter the total dose given that day in mg. |
| Was this dose administered for the patient's initial episode of CAP or its complications | • This question is only required if a corticosteroid was administered on this study day.<br>• Select YES if the dose of hydrocortisone was administered for the patient's initial episode of CAP or its complications (e.g. septic shock, respiratory failure, acute kidney injury, multiorgan failure from CAP). |
| What was the corticosteroid administered for | • This question is only required if the corticosteroid was not administered for CAP or its complications.<br>• Provide the indication for the systemic corticosteroid, as succinctly as possible. Where possible, enter diagnoses, not symptoms. |
| Was another corticosteroid administered | • If the patient received any amount of another corticosteroid check YES. |
| Space for additional corticosteroid administration is provided in Form S: Supplementary in the paper CRFs.<br>Space for additional corticosteroid administration is provided on the eCRF. | |

# FORM 5: MEDICATION ADMINISTRATION

## General Guidance

Complete this form for all ***Platform*** patients.

- Obtain from medication administration record (e.g. drug chart).
- The completed CRF should be similar to the patient's medication administration record (e.g. drug chart).
- Enter all listed medications administered systemically.
- Do not enter medications administered non-systemically (e.g. topically, inhaled, intraventricular or intra-articular). Note that inhaled Zanamivir should still be entered. Anticoagulants administered into the hemofilter circuit are recorded.

Medication administration time period

- Pre-hospital medications:
  - Enter selected medications administered for the treatment of this acute illness prior to admission to the randomizing hospital.
- Medications administered at the randomizing hospital:
  - Enter all courses of specified medications administered between arrival at the randomizing hospital and the end of study day 14.
  - Enter all courses of statins and RAS modulators administered between arrival at the randomizing hospital and the end of study day 28.
  - Include medications administered prior to randomization (e.g. medications administered in ED or on a ward) even if not continued in ICU.
  - If the patient is randomized on a ward and later admitted to ICU collect 14 days of administration while in ICU
  - Where a STAT dose of the same medication is received prior to the administration of a regular course, record as one entry.
  - Administration of corticosteroids within the Corticosteroid Domain should be entered on the daily form.

Medication course definition

- Enter all administration including STAT or single doses.

- Where a STAT dose of the same medication is received prior to the administration of a regular course, record as one entry.
- Enter a new course if:
    - the same agent was switched from IV to enteral administration (and vice versa).
    - the medication was ceased for more than 36 hours and then recommenced.
- Do not enter a new course if:
    - the initial prescribed frequency was changed, with the exception of non-warfarin anticoagulant or antiplatelet agents
    - the initial prescribed dose was changed, with the exception of non-warfarin anticoagulant or antiplatelet agents.
    - the medication was ceased and recommenced within 36 hours, or for anticoagulants administered as continuous infusions, if any infusion is ceased and recommenced within 12 hours

| | Platform – non-pandemic | Platform – pandemic suspected /confirmed | Domain specific only | Duration of data collection |
|---|---|---|---|---|
| Pre-hospital medications | | ✓ | | This acute illness prior to admission to randomizing hospital |
| Antibiotic Administration | ✓ | ✓ | | Hospital admission to study day 14 |
| Antiviral Administration | ✓ | ✓ | | |
| Immune modulation Administration | | ✓ | | |
| Immunomodulatory and antibody administration | | | ✓ | |

| | | | | |
|---|---|---|---|---|
| Corticosteroid Administration | | ✓ | | |
| Monoclonal Antibody Administration | | ✓ | | |

| Question | Definition or Explanation of Question |
|---|---|
| 1. Pre-hospital Medications | |
| Molnupiravir | • Select "Yes" If the patient is known to have received molnupiravir for the treatment of this acute illness prior to admission to the hospital in which randomization to REMAP-CAP occurred.<br>• It is not necessary to contact clinicians involved in the care of the patient prior to hospital admission or while admitted to a hospital prior to admission to the randomizing hospital to obtain this information. |
| Remdesivir | • Select "Yes" If the patient is known to have received remdesivir for the treatment of this acute illness prior to admission to the hospital in which randomization to REMAP-CAP occurred.<br>• It is not necessary to contact clinicians involved in the care of the patient prior to hospital admission or while admitted to a hospital prior to admission to the randomizing hospital to obtain this information. |
| Inhaled budesonide | • Select "Yes" If the patient is known to have received inhaled budesonide for the treatment of this acute illness prior to admission to the hospital in which randomization to REMAP-CAP occurred.<br>• It is not necessary to contact clinicians involved in the care of the patient prior to hospital admission or while admitted to a hospital prior to admission to the randomizing hospital to obtain this information. |

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| Nirmatrelvir / ritonavir (Paxlovid) | • Select "Yes" If the patient is known to have received paxlovid (nirmatrelvir/ritonavir) for the treatment of this acute illness prior to admission to the hospital in which randomization to REMAP-CAP occurred.<br>• It is not necessary to contact clinicians involved in the care of the patient prior to hospital admission or while admitted to a hospital prior to admission to the randomizing hospital to obtain this information. |
| Monoclonal antibody directed against SARS-CoV-2 | • Select "Yes" If the patient is known to have received a monoclonal antibody directed against SARS-CoV-2 prior to admission to the hospital in which randomization to REMAP-CAP occurred, including at another acute hospital prior to transfer to the randomizing hospital, or out of hospital but within 30 days before admission to hospital for this acute illness.<br>• Includes monoclonal antibody therapy administered either for treatment of this acute illness or prophylaxis<br>• It is not necessary to contact clinicians involved in the care of the patient prior to hospital admission or while admitted to a hospital prior to admission to the randomizing hospital to obtain this information. |
| Monoclonal antibody name | • This question is only required if the patient has received a monoclonal antibody directed against SARS-CoV-2 prior to admission to the randomizing hospital.<br>• Specify the name of the monoclonal antibody directed against SARS-CoV-2 |
| 2. Antibiotic Administration | |
| Antibiotic name | • Generic antibiotic names only.<br>• To ensure study antibiotics are included enter study antibiotics prior to entering all other antibiotics. Study antibiotics are:<br>  ○ Amoxicillin-clavulanate (also known as co-amoxiclav, Augmentin)<br>  ○ Azithromycin<br>  ○ Ceftaroline<br>  ○ Ceftriaxone<br>  ○ Clarithromycin |

| | |
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| | ○ Erythromycin * (not macrolide duration domain study antibiotic)<br>○ Levofloxacin<br>○ Moxifloxacin<br>○ Piperacillin-tazobactam (Tazocin)<br>○ Roxithromycin (Rulide).<br>• Do not enter long-term prophylactic antimicrobials, for example, Trimethoprim with Sulfamethoxazole given on non-consecutive days to patients who are immune suppressed, or long-term antibiotics to prevent urinary tract infection.<br>• Do not enter short-term prophylactic antibiotics, such as administered after surgical procedures |
| Date & time first dose administered | • Date and time the patient received that antibiotic during this hospital admission.<br>• If you are unsure what time of the day the first dose was administered, please enter 1 am on the day you know it was administered e.g. 01:00hrs.<br>• Where a STAT dose of the same medication is received prior to the administration of a regular course record as one antibiotic entry, use the date & time of first dose (STAT) as the time first dose administered.<br>• Include doses given <u>prior to randomization and prior to ICU admission.</u> Do not include antibiotics given in the community (e.g. in a general practice or ambulance). Include doses given <u>prior</u> to <u>randomization and prior to ICU admission.</u> |
| Prescribed dose | • Enter the initial prescribed dose (e.g. the dose of antibiotic when it was first administered during this hospital admission).<br>• <u>Do not enter</u> a new course if only the initial prescribed dose was changed.<br>• Where a STAT dose is received prior to the administration of a regular course record the initial dose associated with the regular course.<br>• Where the antibiotic is intermittent dosing and the dose may be variable, enter the dose of the first administration. |

<table>
<tr><td></td><td colspan="2">For antibiotics which are a combination of agents (an antibiotic plus a β-lactamase inhibitor, or two antibiotics), enter the total dose including both components.</td></tr>
<tr><td></td><td>Example</td><td>Enter</td></tr>
<tr><td></td><td>Levofloxacin 750 mg IV was prescribed on study day 1.<br>On study day 3, the prescribed dose of levofloxacin was changed to 500 mg IV</td><td>750 mg</td></tr>
<tr><td></td><td>Amoxicillin-clavulanate (co-amoxiclav) = amoxicillin 1g + clavulanate 200mg</td><td>1.2 g</td></tr>
<tr><td></td><td>Piperacillin-tazobactam = piperacillin 4g + tazobactam 500mg</td><td>4.5 g</td></tr>
<tr><td></td><td>TMP-SMX (trimethoprim-sulfamethoxazole, co-trimoxazole) = trimethoprim 160mg + sulfamethoxazole 800mg</td><td>960 mg</td></tr>
<tr><td>Prescribed route of administration</td><td colspan="2">• Check <u>one</u> option.<br>• Enter a new antibiotic course if the route of administration is changed.</td></tr>
<tr><td></td><td>IV</td><td>Includes:<br>• Intravenous (IV)<br>• Intramuscular (IM)</td></tr>
<tr><td></td><td>Enteral</td><td>Includes:<br>• Oral or oral gastric (OG)<br>• Nasogastric (NG) or Nasojejunal (NJ)<br>• Percutaneous endoscopic gastrostomy (PEG) or Percutaneous Endoscopic Jejunostomy (PEJ)</td></tr>
<tr><td></td><td>Example</td><td>Enter</td></tr>
<tr><td></td><td>Levofloxacin 750 mg IV was administered on study day 1.<br>On study day 3, levofloxacin was changed to Oral administration.</td><td>Course 1: IV<br>Course 2: Enteral</td></tr>
<tr><td>Prescribed frequency</td><td colspan="2">• Check <u>one</u> option.<br>• Enter the frequency prescribed in the medical administration record (e.g. drug chart).<br>• Check <u>intermittent frequency depending on levels</u> if an antibiotic is given as multiple STAT doses or doses are administered up to every 36 hours (e.g. vancomycin or gentamicin).</td></tr>
</table>

| | |
|---|---|
| | • Do not enter a new course if the initial prescribed frequency was changed. |
| Date last dose administered | • Date the patient last received the antibiotic during this hospital admission.<br>• If a patient is still receiving the antibiotic at time of discharge from hospital, enter the date of hospital discharge. |
| Space for additional antibiotic courses is provided on the eCRF.<br><br>Space for additional antibiotic courses is provided in Form S: Supplementary in the paper CRFs. | |
| 3. Antiviral Administration | |
| Antiviral name | • Record only **selected** antiviral medications.<br>• Generic antiviral names only.<br>• Selected **antiviral medications** include:<br>○ Oseltamivir<br>○ Amantadine<br>○ Baloxavir<br>○ Laninamivir octanoate<br>○ Peramivir<br>○ Ribavirin<br>○ Rimantadine<br>○ Zanamivir.<br>○ Lopinavir / Ritonavir (Kaletra)<br>○ Remdisivir<br>○ Umifenovir (arbidol)<br>○ Darunavir/cobicistat<br>○ Favipiravir<br>○ Chloroquine<br>○ Hydroxychloroquine<br>○ Nafamostat<br>○ Camostat<br>○ Ivermectin |

<table>
<tr><td>Date & time first dose administered</td><td colspan="2"><ul><li>Date and time the patient received that antiviral during this hospital admission.</li><li>If you are unsure what time of the day the first dose was administered, please enter 1 am on the day you know it was administered e.g. 01:00hrs.</li><li>Where a STAT dose of the same medication is received prior to the administration of a regular course record as one antiviral entry, use the date & time of first dose (STAT) as time first dose administered.</li><li>Includes doses given <u>prior to randomization and prior to ICU admission.</u></li><li>Do not include antivirals given in the community (e.g. in a general practice or ambulance).</li></ul></td></tr>
<tr><td>Prescribed dose</td><td colspan="2"><ul><li>Enter the initial prescribed dose (e.g. the dose of antiviral agent when it was first administered during this hospital admission).</li><li><u>Do not enter</u> a new course if only the initial prescribed dose was changed.</li><li>Where a STAT dose is received prior to the administration of a regular course record the dose associated with the regular course.</li><li>For antivirals which are a combination of agents (for example lopinavir + ritonavir), enter the total dose including both components.</li></ul></td></tr>
<tr><td rowspan="4">Prescribed route of administration</td><td colspan="2"><ul><li>Check <u>one</u> option.</li><li>Enter a new antiviral course if the route of administration is changed.</li></ul></td></tr>
<tr><td>IV</td><td>Intravenous (IV)</td></tr>
<tr><td>Inhaled</td><td>Inhaled</td></tr>
<tr><td>Enteral</td><td>Includes:<ul><li>Oral or oral gastric (OG)</li><li>Nasogastric (NG) or Nasojejunal (NJ)</li><li>Percutaneous endoscopic gastrostomy (PEG) or Percutaneous Endoscopic Jejunostomy (PEJ).</li></ul></td></tr>
<tr><td>Prescribed frequency</td><td colspan="2"><ul><li>Check <u>one</u> option.</li></ul></td></tr>
</table>

| | |
|---|---|
| | • Enter the frequency prescribed in the medical administration record (e.g. drug chart).<br>• Do not enter a new course if the initial prescribed frequency was changed. |
| Date last dose administered | • Date the patient last received the antiviral during this hospital admission.<br>• If a patient is still receiving the antiviral at time of discharge from hospital, enter the date of hospital discharge. |
| Space for additional antiviral courses is provided on the eCRF.<br>Space for additional antiviral courses is provided in Form S: Supplementary in the paper CRFs. | |
| 4. Immune Modulation Administration | |
| Agent name | • Record immunomodulatory agents administered<br>• Generic names only.<br>• Examples include:<br>○ Interferon-β 1a<br>○ Interferon-β 1b<br>○ Interferon-α<br>○ Interferon-γ<br>○ Anakinra (IL1-Ra)<br>○ Tocilizumab<br>○ Sarilumab<br>○ Baricitinib<br>○ Imatinib<br>○ Dasatinib<br>○ Nilotinib<br>○ Ponatinib |
| Date & time first dose administered | • Date and time the patient received that immunomodulatory agent during this hospital admission.<br>• If you are unsure what time of the day the first dose was administered, please enter 1 am on the day you know it was administered e.g. 01:00hrs. |

<table>
<tr><td></td><td colspan="2"><ul><li>Where a STAT dose of the same medication is received prior to the administration of a regular course record as one immunomodulatory agent entry, use the date & time of first dose (STAT) as time first dose administered.</li><li>Includes doses given <u>prior to randomization and prior to ICU admission.</u></li><li>Do not include immunomodulators given in the community (e.g. in a general practice or ambulance).</li></ul></td></tr>
<tr><td>Prescribed dose</td><td colspan="2"><ul><li>Enter the initial prescribed dose (e.g. the dose of immunomodulatory agent when it was first administered during this hospital admission).</li><li><u>Do not enter</u> a new course if only the initial prescribed dose was changed.</li><li>Where a STAT dose is received prior to the administration of a regular course record the dose associated with the regular course.</li></ul></td></tr>
<tr><td rowspan="4">Prescribed route of administration</td><td colspan="2"><ul><li>Check <u>one</u> option.</li><li>Enter a new course if the route of administration is changed.</li></ul></td></tr>
<tr><td>IV</td><td>Intravenous (IV)</td></tr>
<tr><td>Inhaled<br><br>Enteral</td><td>Inhaled<br><br>Includes:<ul><li>Oral or oral gastric (OG)</li><li>Nasogastric (NG) or Nasojejunal (NJ)</li><li>Percutaneous endoscopic gastrostomy (PEG) or Percutaneous Endoscopic Jejunostomy (PEJ).</li></ul></td></tr>
<tr><td>Sub-cutaneous or Intra-muscular</td><td>Includes:<ul><li>Subcutaneous</li><li>Intra-muscular</li></ul></td></tr>
<tr><td>Prescribed frequency</td><td colspan="2"><ul><li>Select <u>one</u> option.</li><li>Enter the frequency prescribed in the medical administration record (e.g. drug chart).</li></ul></td></tr>
</table>

| | |
|---|---|
| | • Do not enter a new course if the initial prescribed frequency was changed. |
| Date last dose administered | • Date the patient last received the immunomodulator during this hospital admission.<br>• If a patient is still receiving the immunomodulator at time of discharge from hospital, enter the date of hospital discharge. |
| Space for additional immunomodulatory agent courses is provided on the eCRF.<br>Space for additional immunomodulatory agent courses is provided in Form S: Supplementary in the paper CRFs. | |
| 4a. Daily imatinib administration | |
| This section only appears when a course of imatinib is entered into Immune Modulation Administration.<br>For each study day in this course, enter the total dose of imatinib administered as swallowed tablets, or as crushed tablets via gastric tube. | |
| Total daily dose | Swallowed whole tablets, dissolved tablets via gastric tube, or via gastric tube: • Enter total dose of imatinib administered on study day as swallowed whole tablets, or dissolved tablets via gastric tube<br>• If no imatinib was administered on this study day as swallowed whole tablets, or dissolved tablets enter 0 (zero) |
| | Crushed tablets via gastric tube: • Enter total dose of imatinib administered on study day as crushed tablets via gastric tube<br>• If no imatinib was administered on this study day as crushed tablets via gastric tube, enter 0 (zero) |
| 5. Immunomodulatory and Antibody Administration | |
| Agent name | • Intravenous immunoglobulin (non-pandemic specific)<br>• Pandemic hyperimmune globulin |

| | |
|---|---|
| | • Pandemic convalescent plasma |
| Date & time infusion commenced | • Date and time the infusion was first commenced.<br>• If you are unsure what time of the day the first dose was administered, please enter 1 am on the day you know it was administered e.g. 01:00hrs.<br>• Includes doses given prior to randomization and prior to ICU admission.<br>• Do not include immunomodulators given in the community (e.g. in a general practice or ambulance).<br>• Enter each unit of intravenous immunoglobulin or convalescent plasma separately |
| Volume transfused | • Enter the volume of the antibody therapy transfused |
| Donation number | • Enter the donation number of the unit of intravenous immunoglobulin or convalescent plasma administered. |
| Date infusion ceased | • Date that the infusion was completed. |
| 6. Corticosteroid Administration | |
| Medication name | • This section only applies to patients with suspected or confirmed pandemic infection who are not randomized to the Corticosteroid Domain<br>• Enter all **systemic** corticosteroids administered from the beginning of this acute hospital admission until the end of study day 14<br>• An interruption of more than 36 hours should be entered as a new course<br>• Generic names only.<br>• Selected **corticosteroid medications** include:<br>  ○ Hydrocortisone<br>  ○ Betamethasone<br>  ○ Dexamethasone<br>  ○ Methylprednisolone<br>  ○ Prednisolone |

<table>
<tr><td></td><td colspan="2">
<ul>
<li>Prednisone</li>
<li>Triamcinolone</li>
</ul>
</td></tr>
<tr><td>Date & time first dose administered</td><td colspan="2">
<ul>
<li>Date and time the patient received that medication during this hospital admission.</li>
<li>If you are unsure what time of the day the first dose was administered, please enter 1 am on the day you know it was administered e.g. 01:00hrs.</li>
<li>Includes doses given <u>prior to randomization and prior to ICU admission.</u></li>
</ul>
</td></tr>
<tr><td>Prescribed dose</td><td colspan="2">
<ul>
<li>Enter the initial prescribed dose (e.g. the dose of medication when it was first administered during this hospital admission).</li>
</ul>
</td></tr>
<tr><td rowspan="3">Prescribed route of administration</td><td colspan="2">
<ul>
<li>Select one option</li>
<li>Enter a new course if the route of administration is changed</li>
</ul>
</td></tr>
<tr><td>IV</td><td>
<ul>
<li>Intravenous (IV)</li>
</ul>
</td></tr>
<tr><td>Enteral</td><td>Includes:
<ul>
<li>Oral or orogastric (OG)</li>
<li>Nasogastric (NG) or Nasojejunal (NJ)</li>
<li>Percutaneous Endoscopic gastrostomy (PEG) or Percutaneous Endoscopic Jejunostomy (PEJ)</li>
</ul>
</td></tr>
<tr><td>Prescribed frequency</td><td colspan="2">
<ul>
<li>Check <u>one</u> option.</li>
<li>Enter the frequency prescribed in the medical administration record (e.g. drug chart).</li>
<li><u>Do not enter</u> a new course if the initial prescribed frequency was changed.</li>
</ul>
</td></tr>
<tr><td>Date last dose administered</td><td colspan="2">
<ul>
<li>Date the patient <u>last received</u> the medication during this hospital admission.</li>
<li>If a patient is still receiving the medication at time of discharge from hospital, <u>enter the date of hospital discharge</u>.</li>
</ul>
</td></tr>
<tr><td colspan="3">7. Monoclonal Antibody administration</td></tr>
</table>

| | | |
|---|---|---|
| Agent name | • Select the name of the monoclonal antibody therapy directed against SARS-CoV-2 | |
| Specify | • If “other” monoclonal antibody therapy directed against SARS-CoV-2, enter the name of the agent<br>• Enter generic medication names only | |
| Date and time infusion commenced | • Enter the date and time that the monoclonal antibody infusion was commenced.<br>• For patients enrolled in the Monoclonal Antibody Domain, it is vital that the date and time that the infusion was commenced is accurate to the precise minute of commencement | |
| Prescribed dose | • Enter the prescribed dose of the monoclonal antibody | |
| Prescribed route of administration | Select one option<br>• IV<br>• Sub-cutaneous | • Intravenous (IV)<br>Includes:<br>• Subcutaneous<br>• Intra-muscular |

# FORM 6: DISCHARGE

## General Guidance

- Complete this form for all ***Platform*** patients.
- If the patient is transferred to another hospital prior to hospital discharge refer to Section 3.2 Patient Transfers.

| Question | Definition or Explanation of Question | |
|---|---|---|
| ***Platform*** | | |
| 1. ICU Discharge | | |
| ICU discharge date & time | • Enter the date and time that the patient was first discharged from ICU following randomization.<br>• ICU discharge is defined in Section 5. General definitions.<br>  ○ If the patient remains in the ICU because of ward bed block the patient is still an ICU patient and Form 4, Daily Data, should be completed.<br>  ○ If the patient is transferred to an intensivist-supervised HDU this is not ICU discharge. The date of ICU discharge, in this case, is when the patient is discharged to the general ward from the HDU.<br>• If the patient died in ICU enter the date and time of death.<br>• If, during a pandemic, ICU care is being provided in an area not usually designated as an ICU, discharge is defined as the time at which a patient leaves an area in which ICU-level care (NIV with sealed mask, IMV, or vasopressor via continuous infusion) can be provided. | |
| Status | Check one option. | |
| | Alive | • If the patient was alive at the time of ICU discharge check alive.<br>• Includes patients discharged for palliation who are not expected to survive. |
| | Deceased | • If the patient died in ICU.<br>• If the patient is deemed brain dead the date of death is recorded as the date of the 2nd confirmation of this diagnosis. |

| | | |
|---|---|---|
| | | • If the patient has died and they remain in the ICU for organ donation workup the date of death is the date of the 2nd confirmation of brain death (or physician determined date of death) even though the patient has not physically left the ICU.<br>• All efforts must be made to collect the death certificate for source data and inspection at monitoring. |
| Date and time of first organ support in ICU | • This question is only required for patients who were not receiving organ support at the time of randomization.<br>• Enter the date and time during this ICU admission at which the first of the following organ supports was documented as being provided<br>○ Invasive mechanical ventilation<br>○ Non-invasive ventilation via sealed mask<br>○ Continuous infusion of vasopressor or inotrope medication<br>○ High-flow nasal prong oxygen with an FiO2 ≥ 0.4 and at a flow-rate of at least 30 L/min (or at least 2 L/min/kg in children less than 15 kilograms) | |
| Date and time of last organ support in ICU | • Enter the date and time during this ICU admission at which the last of the following organ supports was documented as being provided:<br>○ Invasive mechanical ventilation<br>○ Non-invasive ventilation via sealed mask<br>○ Continuous infusion of vasopressor or inotrope medication<br>○ High-flow nasal prong oxygen with an FiO2 ≥ 0.4 and at a flow-rate of at least 30 L/min (or at least 2 L/min/kg in children less than 15 kilograms)<br>• If a patient is enrolled with HFNP as the qualifying organ support and never received any of the above, select NEVER RECEIVED. | |

## 2. Add ICU admission

| | |
|---|---|
| Add ICU admission | • Check YES if the patient was discharged and readmitted to ICU during the same hospital admission, or if the patient was first randomized outside of ICU and later admitted to ICU<br>• Readmission can occur on the same chart day as ICU discharge. |
| ICU admission date & time | • Enter the date and time that the patient was admitted to ICU.<br>• The time and date at which a patient physically arrives in the ICU.<br>• During a pandemic, for a patient admitted to a location that is not usually designated as an ICU, the time of ICU admission is the time of first administration of qualifying organ support (do not commence the eligibility process until patient has a qualifying organ failure support). |
| ICU discharge date & time | • Enter the date and time that the patient was discharged from ICU.<br>• ICU discharge is defined in Section 5. General definitions.<br>• If the patient died in ICU enter the date and time of death.<br>• If, during a pandemic, ICU care is being provided in an area not usually designated as an ICU, discharge is defined as the time at which a patient leaves an area in which ICU-level care (NIV with sealed mask, IMV, or vasopressor via continuous infusion) can be provided.<br>• If the time of ICU discharge is unknown, enter 12:00 on the date of discharge. |
| Did the patient receive organ support during this ICU admission | • Select YES if the patient received any of the following during this hospital admission:<br>○ Invasive mechanical ventilation<br>○ Non-invasive ventilation via sealed mask<br>○ Continuous infusion of vasopressor or inotrope medication<br>○ High-flow nasal prong oxygen with an FiO2 ≥ 0.4 and at a flow rate of at least 30 L/min (or at least 2 L/min/kg in children less than 15 kilograms) |
| Date and time of first organ support in ICU | • This question is only required for patients who received organ support during this ICU admission. |

| | |
|---|---|
| | • Enter the date and time during this ICU readmission at which the first of the following organ supports was documented as being provided<br>○ Invasive mechanical ventilation<br>○ Non-invasive ventilation via sealed mask<br>○ Continuous infusion of vasopressor or inotrope medication<br>○ High-flow nasal prong oxygen with an FiO2 ≥ 0.4 and at a flow rate of at least 30 L/min (or at least 2 L/min/kg in children less than 15 kilograms) |
| Date and time of last organ support in ICU | • This question is only required for patients who received organ support during this ICU admission<br>• Enter the date and time during this ICU readmission at which the last of the following organ supports was documented as being provided:<br>○ Invasive mechanical ventilation<br>○ Non-invasive ventilation via sealed mask<br>○ Continuous infusion of vasopressor or inotrope medication<br>○ High-flow nasal prong oxygen with an FiO2 ≥ 0.4 and at a flow rate of at least 30 L/min (or at least 2 L/min/kg in children less than 15 kilograms)<br>• If a patient is enrolled with HFNP as the qualifying organ support and never received any of the above, select NEVER RECEIVED. |
| Add another ICU readmission | Multiple readmissions to ICU during the index hospitalization can be recorded. Refer to the definitions provided above. |
| Space for additional ICU readmissions is provided in Form S: Supplementary in the paper CRFs.<br>Space for additional ICU readmissions is provided on the eCRF. | |
| 3. Hospital Discharge | |
| Dialysis at hospital discharge | • If RRT was received within 4 days of hospital discharge and there is a plan to continue it after hospital discharge check YES.<br>• Includes RRT received outside of the hospital ward they are admitted to (e.g. received in a dialysis unit). |

| | | |
|---|---|---|
| | • RRT is defined in Section 5. General definitions. | |
| Last creatinine | • This question only applies if the patient is not receiving dialysis at hospital discharge.<br>• Enter the last creatinine recorded during this hospital admission.<br>• Taken from serum or plasma samples.<br>• Record the result and select the unit of measurement (umol/L or mg/dL). | |
| Hospital discharge date & time | • Enter the date and time that the patient physically leaves the hospital.<br>• If the patient died in hospital enter the date and time of death.<br>• If the time of hospital discharge is unknown, enter 12:00 on the date of discharge. | |
| Status | Check one option. | |
| | Alive | • The patient was alive at the time of hospital discharge.<br>• Includes patients discharged for palliation who are expected not to survive. |
| | Deceased | • The patient died during this hospital admission.<br>• If the patient is deemed brain dead the date of death is recorded as the date of the 2nd confirmation of this diagnosis.<br>• All efforts must be made to collect the death certificate for source data and inspection at monitoring. |
| Destination | This question only applies if the patient is alive at hospital discharge.<br>Check one option that best describes the place (or facility) the patient was discharged from hospital to. | |
| | Home | • Home is defined in Section 5. General Definitions.<br>• Includes patients who are discharged to a private dwelling for palliative care. |

| | | |
|---|---|---|
| | Nursing home or long-term care facility | • Nursing home is defined in Section 5. General Definitions.<br>• If a patient is discharged to a hospice or palliative long-term care facility, select nursing home. |
| | Rehabilitation Hospital | Rehabilitation hospital includes:<br>• A separate rehabilitation hospital<br>• A transitional living facility<br>• Includes patients sent from an acute hospital to a chronic care facility (or unit) that is geographically separate from the acute wards (but still on the same hospital campus) and managed by a different team. |
| | Transfer to another acute hospital | • The patient was transferred to another acute hospital (not participating in REMAP-CAP).<br>• If the patient is transferred to another REMAP-CAP participating hospital refer to Section 3.2 Patient Transfers. |
| Ultimate hospital discharge date | • This question only applies if the patient was transferred to another acute hospital.<br>• Date the patient was ultimately discharged from hospital for this illness (final hospital discharge).<br>• Contact the receiving hospital to obtain this date.<br>• Includes any hospital, irrespective of the hospital's REMAP-CAP participation status.<br>• Check still in hospital on study day 90 only if the patient has not been discharged from the acute hospital at any time since randomization.<br>• Select UNABLE TO ASCERTAIN if the patient's ultimate hospital discharge date is unknown and unable to be obtained. | |

<table>
<tr><td></td><td colspan="2">

- If the time of ultimate hospital discharge is unknown, enter 12:00 on the date of discharge.

</td></tr>
<tr><td rowspan="4">Status at ultimate hospital discharge</td><td colspan="2">

- This question only applies if the patient was transferred to another acute hospital.
- Select one option:

</td></tr>
<tr><td>Alive</td><td>

- The patient was alive at the time of hospital discharge.
- Includes patients discharged for palliation who are expected not to survive.

</td></tr>
<tr><td>Deceased</td><td>

- The patient died during this hospital admission.
- If the patient is deemed brain dead the date of death is recorded as the date of the 2nd confirmation of this diagnosis.
- All efforts must be made to collect the death certificate for source data and inspection at monitoring.

</td></tr>
<tr><td>Unable to ascertain</td><td>

- Select unable to ascertain if unable to determine the patient’s vital status at the time of ultimate hospital discharge

</td></tr>
<tr><td>Was patient admitted to ICU during this hospital admission</td><td colspan="2">

- This question is only required for patients with suspected or proven pandemic infection.
- This question only applies if the patient was discharged to another acute hospital
- If the patient was admitted to ICU in the acute hospital that they were discharged to, select YES

</td></tr>
</table>

| | |
|---|---|
| ICU admission date and time | • This question only applies if the patient was discharged to another acute hospital and patient was admitted to ICU.<br>• Enter the date and time that the patient was admitted to ICU at the other acute hospital. |
| ICU discharge date and time | • This question is only required for patients with suspected or proven pandemic infection.<br>• This question only applies if the patient was discharged to another acute hospital and patient was admitted to ICU.<br>• Enter the date and time that the patient was discharged from ICU at the other acute hospital.<br>• ICU discharge is defined in Section 5. General definitions.<br>• If the patient died in ICU enter the date and time of death.<br>• If, during a pandemic, ICU care is being provided in an area not usually designated as an ICU, discharge is defined as the time at which a patient leaves an area in which ICU-level care (NIV with sealed mask, IMV, or vasopressor via continuous infusion) can be provided.<br>• If the date of ICU discharge at the other acute hospital is unknown and is not able to be determined, select UNABLE TO ASCERTAIN<br>• If the time of ICU discharge is unknown, enter 12:00 on the date of discharge. |
| Did the patient receive organ support during this ICU admission | • This question is only required for patients with suspected or proven pandemic infection.<br>• This question only applies if the patient was discharged to another acute hospital and patient was admitted to ICU<br>• Select YES if the patient received any of the following during this hospital admission:<br>  ○ Invasive mechanical ventilation<br>  ○ Non-invasive ventilation via sealed mask<br>  ○ Continuous infusion of vasopressor or inotrope medication |

| | |
|---|---|
| | ○ High-flow nasal prong oxygen with an FiO2 ≥ 0.4 and at a flow rate of at least 30 L/min (or at least 2 L/min/kg in children less than 15 kilograms) |
| Date and time of first organ support in ICU | • This question is only required for patients with suspected or proven pandemic infection.<br>• This question only applies if the patient was discharged to another acute hospital and patient was admitted to ICU and patient received organ support during ICU admission<br>• Enter the date and time during this ICU admission at which the first of the following organ supports was documented as being provided<br>○ Invasive mechanical ventilation<br>○ Non-invasive ventilation via sealed mask<br>○ Continuous infusion of vasopressor or inotrope medication<br>○ High-flow nasal prong oxygen with an FiO2 ≥ 0.4 and at a flow rate of at least 30 L/min (or at least 2 L/min/kg in children less than 15 kilograms) |
| Date and time of last organ support in ICU | • This question is only required for patients with suspected or proven pandemic infection.<br>• This question only applies if the patient was discharged to another acute hospital and patient was admitted to ICU and patient received organ support during ICU admission<br>• Enter the date and time during this ICU admission at which the last of the following organ supports was documented as being provided:<br>○ Invasive mechanical ventilation<br>○ Non-invasive ventilation via sealed mask<br>○ Continuous infusion of vasopressor or inotrope medication<br>○ High-flow nasal prong oxygen with an FiO2 ≥ 0.4 and at a flow rate of at least 30 L/min (or at least 2 L/min/kg in children less than 15 kilograms) |

| | |
|---|---|
| | • If a patient is enrolled with HFNP as the qualifying organ support and never received any of the above, select NEVER RECEIVED |
| Co-enrolled in another study | • Answer YES if the patient is co-enrolled in another study.<br>• Only include multi-center observational studies or interventional clinical trials<br>• Include all studies the patient is enrolled in during this hospitalization. |
| Co-enrolment study name | • This question is only required if the patient is co-enrolled in another study<br>• Enter the study name. |
| Co-enrolment study ID | • This question is only required if the patient is co-enrolled in another study.<br>• Enter the patient's participant ID from this study.<br>• In regions where date of birth and initials are not collected for REMAP-CAP, do not enter any identifier for another study that contains personal information (such as initials or date of birth). |
| ***Platform secondary endpoints*** | |
| Select the highest level of organ support on day 14 after randomization | • This question is only required for patients with suspected or confirmed pandemic infection who are located on the ward<br>• Select the highest level of organ support the patient received on study day 14<br>• Patients who have more than one randomization will be asked to select the highest level of organ support on the study day that is 14 days after each randomization<br>• It is <u>not</u> necessary to follow up patients who have been discharged from hospital prior to Day 14 to ascertain their status. |
| ***Domain-specific Secondary Outcomes*** | |
| ***Antibiotic Domain*** | |
| **General Guidance**<br>Complete Section 4 for all patients randomized to the ***Antibiotic Domain.*** | |
| 4. Multi-Resistant Organisms | |
| **General Guidance** | |

| | |
|---|---|
| Include all specimens collected at any time during this hospital admission. Specimens can include:<br>○ Antigen tests<br>○ Blood cultures<br>○ BAL samples or any specimen collected by bronchoscopy<br>○ Enzyme linked immunoassay (EIA)<br>○ ETT or TT aspirate<br>○ Immunofluorescence<br>○ Nasal swabs or wash<br>○ Nasopharyngeal swabs, wash or aspirate.<br>○ Oropharyngeal swabs<br>○ PCR (also known as a NAT or GeneXpert<br>○ Serology<br>○ Sputum<br>○ Urine<br>○ Wound cultures<br>○ Wound swabs. | |
| Clostridium difficile toxin detected on a fecal specimen | • Check YES if Clostridium difficile toxin is detected on a fecal specimen collected at any time during this hospital admission.<br>• Clostridium difficile has recently been re-named as Clostridioides difficile, and is also known as C. difficile or C diff.<br>• If Clostridium difficile is isolated in the absence of toxin positive check NO.<br>• Fecal specimens include the PCR (NAT or GeneXpert) tests for toxin genes and EIA for toxin A and/or toxin B. |
| Date first positive specimen collected | • Enter the date that the first toxin positive specimen was collected.<br>• If multiple specimens are positive, enter the date the first positive specimen was collected. |
| Methicillin-resistant | • Methicillin-resistant Staphylococcus aureus is also known as<br>○ MRSA |

<table>
<tr><td>Staphylococcus aureus isolated or detected:</td><td>
<ul>
<li>ca-MRSA</li>
<li>m-MRSA</li>
<li>ha-MRSA</li>
<li>nm-MRSA</li>
<li>m-MRSA (multi-resistant MRSA).</li>
</ul>
<ul>
<li>If reported as <u>intermediate or resistant</u> to any of the following check YES:
<ul>
<li>Methicillin</li>
<li>Oxacillin</li>
<li>Dicloxacillin</li>
<li>Flucloxacillin</li>
<li>Nafcillin.</li>
</ul>
</li>
</ul>
</td></tr>
<tr><td>Date first positive specimen collected</td><td>
<ul>
<li>Date the first positive <u>specimen was collected</u> during this hospital admission.</li>
<li>Only include specimens that <u>reported MRSA as isolated or detected</u>.</li>
<li>If multiple specimen types report MRSA, enter the date the <u>first positive specimen</u> was collected.</li>
</ul>
<table>
<tr><th>Example</th><th>Enter</th></tr>
<tr><td>A nasal swab collected at ICU admission (12 October 2018) reported MRSA and a blood culture collected on 15 October 2018 reported MRSA.</td><td>12 October 2018</td></tr>
</table>
</td></tr>
<tr><td>History of this organism during previous hospital admissions</td><td>
<ul>
<li>If the patient’s medical record has a history of this MRO being detected during a <u>previous hospital admission</u> check YES.</li>
<li>This may include alerts placed at other hospitals prior to this hospital admissions (if known).</li>
<li>It is not necessary to examine microbiology results prior to this hospital admission.</li>
<li>For many MROs, alerts or flags are placed in the patient notes for infection control purposes, indicating that the patient has had a history of infection or colonization in a prior admission.</li>
<li>If the alert has been placed because of the detection of an MRO in the current admission (without the alert being present previously), check NO.</li>
</ul>
</td></tr>
</table>

<table>
<tr><td>Vancomycin-resistant Enterococci isolated or detected</td><td>
<ul>
<li>Check YES if Vancomycin-resistant Enterococci was isolated or detected.</li>
<li>Vancomycin-resistant Enterococci is also known as
<ul>
<li>VRE</li>
<li>Van-A</li>
<li>Van-B</li>
<li>Van-D.</li>
</ul></li>
<li>Vancomycin-resistant Enterococci is defined as an Enterococcus faecalis or E faecium that is resistant to vancomycin and/or teicoplanin, or has vanA or vanB or vanD, genes detected.</li>
</ul>
</td></tr>
<tr><td>Date first positive specimen collected</td><td>
<ul>
<li>Enter the date that the specimen was collected during this hospital admission.</li>
<li>Only include specimens that reported VRE as isolated or detected.</li>
<li>If multiple specimen types report VRE, enter the date the first positive specimen was collected.</li>
</ul>
</td></tr>
<tr><td>History of this organism during previous hospital admissions</td><td>Refer to definition above.</td></tr>
<tr><td>Extended-Spectrum Beta-Lactamases producing Escherichia coli and/ or Klebsiella spp isolated or detected:</td><td>
<ul>
<li>Check YES if Extended Spectrum Beta-Lactamases were isolated or detected</li>
<li>Extended Spectrum Beta-Lactamases are also known as ESBL.</li>
<li>ESBL is also indicated if either organism is reported as resistant or intermediate to ceftriaxone or ceftazidime.</li>
<li>On pathology reports Klebsiella spp it can be documented as:
<ul>
<li>Klebsiella pneumoniae</li>
<li>K. pneumoniae</li>
<li>Klebsiella oxytoca.</li>
</ul></li>
<li>On pathology reports as Escherichia coli it can be documented as E coli.</li>
</ul>
Guide
<table>
<tr><th>Organism</th><th>Reported as resistant to</th><th>Check</th></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>Escherichia coli</td><td>Ceftriaxone and/or ceftazidime</td><td>Yes</td></tr>
<tr><td></td><td>Klebsiella spp</td><td>Ceftriaxone and/or ceftazidime</td><td>Yes</td></tr>
<tr><td>Date first positive specimen collected</td><td colspan="3"><ul><li>Date the specimen was collected during this hospital admission.</li><li>Only include specimens that reported ESBL as isolated or detected.</li><li>If multiple specimen types report ESBL, enter the date the first positive specimen was collected. If multiple specimen types report ESBL, enter the date the first positive specimen was collected.</li></ul></td></tr>
<tr><td>History of this organism during previous hospital admissions</td><td colspan="3">Refer to definition above.</td></tr>
<tr><td>Carbapenem-resistant gram-negative organism isolated or detected</td><td colspan="3"><ul><li>Check YES if Carbapenem-resistant gram-negative organism was isolated or detected.</li><li>CRE is also known as a CPE.</li><li>It is defined as a gram-negative organism that is resistant to carbapenem antibiotics (e.g. meropenem or imipenem).</li><li>Carbapenem resistance can be defined by<ul><li>Demonstration of resistance on antibiotic susceptibility testing (see guide below) and/or</li><li>Detection of carbapenemase genes (including NDM, IMP, KPC, VIM).</li></ul></li><li>Refer to guide below for list of gram-negative organisms and resistance.</li></ul></td></tr>
<tr><td></td><td>Organism</td><td>Reported as resistant to</td><td>Check</td></tr>
<tr><td></td><td>Acinetobacter</td><td>Ceftazidime AND either meropenem or imipenem</td><td>Yes</td></tr>
<tr><td></td><td>Citrobacter</td><td>Meropenem or imipenem</td><td>Yes</td></tr>
<tr><td></td><td>E coli</td><td>Meropenem or imipenem</td><td>Yes</td></tr>
<tr><td></td><td>Enterobacter</td><td>Meropenem or imipenem</td><td>Yes</td></tr>
</table>

| | | | |
|---|---|---|---|
| | Klebsiella | Meropenem or imipenem | Yes |
| | Proteus | Meropenem or imipenem | Yes |
| | Pseudomonas aeruginosa | Ceftazidime **AND** either meropenem or imipenem | Yes |
| | Serratia | Meropenem or imipenem | Yes |

| | |
|---|---|
| Date first positive specimen was collected | • Date the specimen was collected during this hospital admission.<br>• Only include specimens that reported a CRE organism as isolated or detected.<br>• If multiple specimen types report a CRE organism, enter the date the first positive specimen was collected. |
| History of this organism during previous hospital admissions | Refer to definition above. |

## ***Macrolide Duration Domain***

**General Guidance**

- Complete Section 5 for all patients randomized to the ***Macrolide Duration Domain***

### 5. Macrolide Duration Domain Secondary Outcomes

| | |
|---|---|
| Documented serious ventricular arrhythmia | • Includes any serious ventricular arrhythmia occurring after randomization and prior to hospital discharge.<br>• A serious ventricular arrhythmia is defined as a suspected or proven sustained ventricular tachycardia requiring intervention.<br>• A serious ventricular arrhythmia includes:<br>  ○ Torsades de pointes (TdP)<br>  ○ Ventricular fibrillation<br>• Only include the following interventions:<br>  ○ Cardioversion (electrical or pacing cardioversion) OR<br>  ○ Infusion of an antiarrhythmic agent |

| | |
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| | • If the ventricular arrhythmia does not require intervention (e.g. 10 beats of self-limiting VT) check NO. |
| Date and time of first documented serious ventricular arrhythmia | • Enter the date and time that serious ventricular arrhythmia is documented in the patient's clinical record, between first randomization and hospital discharge. |
| Patient died while not receiving continuous cardiac monitoring | • This question only applies if the patient did not have a documented serious ventricular arrhythmia.<br>• Continuous cardiac monitoring records the electrical activity of the heart as an electrocardiogram (ECG).<br>• If the patient did not have continuous cardiac monitoring at the time of death check YES. |
| Death was unexpected and sudden | • This question only applies if the patient died while not receiving continuous cardiac monitoring.<br>• Death is sudden and unexpected if:<br>  ○ Cardiac arrest triggered activation of a medical emergency team, or<br>  ○ If the patient was found dead <u>without</u> a treatment limitation being in place<br>• A treatment limitation is defined as documentation within the medical record that the <u>patient is not to receive</u>:<br>  ○ Cardiopulmonary resuscitation<br>  ○ Readmission to an ICU or higher dependency area or both that was active at the time of death.<br>  ○ In many hospitals a treatment limitation is documented on a separate form. This form should be considered the definitive source. In hospitals that do not have such a form, a treatment limitation must be identified in the medical record. |

## *Corticosteroid Domain*

**General Guidance**

- Complete Section 6 for all patients randomized to the ***Corticosteroid Domain.***

### 6. Etomidate Administration

| | |
|---|---|
| Was Etomidate administered between randomization in the Corticosteroid Domain and the end of study day 8 | • Select YES if the patient was administered Etomidate at any time between the time of randomization in the Corticosteroid Domain and the end of study day 8.<br>• Question not required for sites in Australia and New Zealand |

## *Immunoglobulin and Endothelial Domains*

**General Guidance**

Complete Section 7 for all patients randomized to the ***Immunoglobulin and/or Endothelial Domains.***

### 7. Immunoglobulin and Endothelial Domain-specific outcomes

| | |
|---|---|
| Major bleeding | • Between first randomization to the Endothelial Domains and end of study day 15<br>• Enter YES if there are one or more bleeding events that are any of the following:<br>  ○ fatal bleeding, symptomatic or clinically manifest bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome),<br>  ○ Bleeding causing a fall in hemoglobin of ≥2 g/dL, or leading to the transfusion of 2 or more whole blood or red cell units within a 24 hour period. |

<table>
<tr><td></td><td colspan="2">• Occurrence of major bleeding after study day 15 should be recorded as an SAE, irrespective of treatment assignment.<br>• More than one major bleeding event may be entered, if major bleeding occurs more than once between randomization to Endothelial Domains and end of study day 15 days.</td></tr>
<tr><td>Date and time of major bleeding event</td><td colspan="2">• This question only applies if the patient had a major bleeding event<br>• Enter the date and time of major bleeding event</td></tr>
<tr><td>Major bleeding description of events</td><td colspan="2">• Enter description of bleeding event and evidence for meeting definition of Major Bleeding</td></tr>
<tr><td rowspan="5">Which major bleeding criteria were met</td><td colspan="2">Note that if none of the criteria below are met, the bleeding event does not meet the definition of a major bleeding event.</td></tr>
<tr><td>• Fatal bleeding</td><td>• Select this option if the major bleeding event directly contributed to the patient’s death</td></tr>
<tr><td>• Symptomatic or clinically manifest bleeding in a critical area or organ</td><td>• Select this option if there was symptomatic or clinically manifest bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome)</td></tr>
<tr><td>• Blood loss causing a fall in hemoglobin of 2g/dL or more</td><td>• Select this option if the major bleeding resulted in a fall in hemoglobin of 2 g/dL or more within a 24-hour period</td></tr>
<tr><td>• Blood loss leading to a transfusion of two or more units of red cells or whole blood</td><td>• Select this option if the patient required transfusion of two or more units of red blood cells or whole blood within a single transfusion episode within a 24-hour period</td></tr>
</table>

| | |
|---|---|
| Clinically diagnosed acute myocardial infarction: | • Between first randomization to Immunoglobulin, or Endothelial Domain and hospital discharge<br>• Select YES if the patient was diagnosed with an Acute Myocardial Infarction (AMI). It is not necessary to evaluate all ECGs, echocardiograms, or recorded symptoms, this question should be answered on the basis of whether there was consideration of a clinical diagnosis of AMI.<br>• Select NO if the diagnosis of AMI was considered but the definition of AMI was not met.<br>• Among patients in whom a diagnosis of AMI was considered, the definition of an AMI requires detection of rise and fall or just a fall of cardiac biomarkers, such as any form of troponin assay, with at least one value above the upper reference limit (URL) PLUS evidence of myocardial ischemia with at least one of the following:<br>o Symptoms of cardiac ischemia<br>o ECG changes indicative of new ischemia (new ST-T changes or new LBBB)*<br>o Development of pathological Q waves in the ECG**<br>o Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality<br>• *ECG manifestation of acute myocardial ischemia (in the absence of LVH and LBBB):<br>o ST Elevation - New ST elevation at the J-point in two contiguous leads with the cut-off points of ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.<br>o ST depression and T-wave changes – New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R waves or R/S ratio >1.<br>• **Pathological Q waves: |

| | |
|---|---|
| | ○ Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3<br>○ Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 an any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, aVF; V7-V9).<br>○ R-wave ≥ 0.04 s in V1–V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect |
| Date and time of myocardial infarction | • Enter the date and time of acute myocardial infarction between first randomization into the Immunoglobulin or Endothelial Domain and hospital discharge. |
| Confirmed deep vein thrombosis | • Confirmed on ultrasound or CT between first randomization to the Immunoglobulin or Endothelial Domain and hospital discharge<br>• Select YES if the patient has a proximal deep vein thrombosis. Proximal is a thrombus located in axillary vein or more proximal, including the internal jugular vein, and a thrombus located in popliteal vein or more proximal. Confirmation requires imaging with techniques that include ultrasound or CT scan. |
| Date and time of deep vein thrombosis | • Enter the date and time that deep vein thrombosis was confirmed between first randomization into the Immunoglobulin or Endothelial Domain and hospital discharge. |
| Confirmed pulmonary emboli | • Between first randomization to the Immunoglobulin or Endothelial Domain and hospital discharge<br>• Select YES if the patient has segmental or multi-sub-segmental pulmonary emboli that is confirmed using CT pulmonary angiography or has a high probability ventilation: perfusion lung scan |
| Date and time of pulmonary emboli | • Enter the date and time that pulmonary embolism was confirmed between first randomization into the Immunoglobulin or Endothelial Domain and hospital discharge. |
| Confirmed ischemic stroke | • Between first randomization to Immunoglobulin or Endothelial Domain and hospital discharge |

| | |
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| | • Select YES if the patient was diagnosed with an acute ischemic stroke i.e. central nervous system infarction defined as brain, spinal cord, or retinal cell death attributable to ischemia, based on:<br>  ○ Pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; OR<br>  ○ Clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded. (Note: CNS infarction includes types I and II hemorrhagic infarctions) OR<br>  ○ Infarction or hemorrhage in the brain, spinal cord, or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible edema without infarction or hemorrhage do not qualify as stroke. |
| Other confirmed thrombotic event | • Between first randomization to the Immunoglobulin or Endothelial Domain and hospital discharge<br>• Select **Mesenteric Ischemia** for arterial or venous mesenteric ischemia diagnosed on contrast imaging by CT or angiography or diagnosed at laparotomy or via laparoscopy.<br>• Select **limb ischemia** if evidence of acute limb ischemia sufficient to require surgical revascularization including bypass procedure, intraarterial thrombolysis, or embolectomy; amputation of a limb due to acute ischemia; or decision to withdraw of limit treatment because of acute limb ischemia. It is not sufficient for there to be evidence of limb ischemia that does not result in surgical intervention or determine a decision to institute palliative care. Ischemia attributed to vasopressor medication is insufficient unless also meets the above definition.<br>• Select **Other** for any thrombotic event other than ischemic stroke, acute myocardial infarction, mesenteric ischemia, and critical limb ischemia, then describe event. |

| | |
|---|---|
| Date and time of other thrombotic event | • Enter the date and time that another thrombotic event was confirmed between first randomization into the Immunoglobulin or Endothelial Domain and hospital discharge. |
| ***Endothelial Domain*** | |
| Peak ALT in the first 14 days after randomization | • Enter the highest alanine transaminase measured between randomization to the Endothelial Domain and 14 calendar days (i.e. 336 hours) after randomization.<br>• Also known as alanine aminotransferase, or (serum) glutamate-pyruvate transaminase (GTP or SGPT) |
| Peak AST in the first 14 days after randomization | • Enter the highest aspartate transaminase measured between randomization to the Endothelial Domain and 14 calendar days (i.e. 336 hours) after randomization.<br>• Also known as aspartate aminotransferase or (serum) or (serum) glutamin-oxaloacetic transaminase (GOT or SGOT) |
| Peak Bilirubin in the first 14 days after randomization | • Enter the highest bilirubin measured between randomization to the Endothelial Domain and 14 calendar days (i.e. 336 hours) after randomization. |
| Lowest platelet count in first 14 days after randomization | • Enter the lowest platelet count measured between randomization to the Endothelial Domain and 14 calendar days (i.e. 336 hours) after randomization. |
| Lowest neutrophil count in first 14 days after randomization | • Enter the lowest neutrophil count measured between randomization to the Endothelial Domain and 14 calendar days (i.e. 336 hours) after randomization. |
| ***COVID-19 Antiviral (II) Domain*** | |

| | | |
|---|---|---|
| Did the patient develop any of the following during the treatment course acute kidney injury | • Acute kidney injury | • Defined as KDIGO stage 2 or above, occurring within 14 days from randomization to this domain<br>• If the participant has experienced acute kidney injury, please indicate whether, in the opinion of the treating clinician, this event is possibly, probably, or definitely related to study participation |
| | • Acute liver injury | • Defined as an increase in AST or ALT to > 5 times upper limit of normal (40 IU/L) within 14 days after randomization to this domain<br>• If the participant has experienced acute liver injury, please indicate whether, in the opinion of the treating clinician, this event is possibly, probably, or definitely related to study participation |
| | • Any adverse event attributable to an interaction between the allocated intervention and any concurrent non-assigned medication | • If the participant has experienced an adverse event that is attributable to an interaction between the allocated intervention and any co-administered medication, please indicate whether, in the opinion of the treating clinician, this event is possibly, probably, or definitely related to study participation |

# FORM 7: CONSENT

## General Guidance

- Complete this form for all ***Platform*** patients.
- Refer to your Human Research Ethics Committee (HREC)/Institution Review Board (IRB) approval to determine the consent practices you should follow.
- For the purposes of this CRF the term AGREEMENT has been used to cover multiple terms to allow the CRF to be used in multiple jurisdictions, including:
    - Consent
    - Approval
    - Assent
    - Agreement
    - Another term where a proxy cannot provide legal consent for a patient to participate but where the proxy should be consulted to ascertain whether, in their opinion, the patient would want to participate in the trial. Subsequent patient agreement to continue in the trial should be obtained once they can provide consent for themselves.

In most jurisdictions to participate in the Macrolide Duration Domain, agreement must be obtained and entered in the eCRF before the end of Study Day 5. If agreement is not obtained complete the Macrolide Duration Domain Protocol Deviation Form.

Note that the Consent Form was updated in July 2024. The following applies to participants enrolled prior to this time.

| Question | Definition or Explanation of Question |
|---|---|
| ***Platform*** | |
| 1. Discussion | |

## General Guidance

- To be completed by ***New Zealand sites*** only.
- Other sites can complete this section on the paper CRF for reporting purposes.
- Enter all discussions/provision of information with patient, relative, whanau, friend.

| | | |
|---|---|---|
| Was there a discussion / information provided to the patient or proxy (NZ only) | • Select YES, if the patient's wishes were discussed (and documented) with the patient, relative, whanau or friend.<br>• Select NO, if no family or friends are available or the patient dies before this discussion takes place.<br>• NOTE: If discussion with the patient is not possible every effort should be made to ascertain the patient's wishes by asking the family or friend, regarding participation in this study. This is an ethical and legal obligation for all New Zealand patients. | |
| Discussion/information provided to<br>(NZ only) | • Select the people who participated in the discussion.<br>• Multiple selections allowed. | |
| | • Patient | • If the patient participated in the discussion. |
| | • Relative/whanau/ friend | • If a relative/whanau/friend participated in the discussion. |
| Date & time of discussion<br>(NZ only) | • Date and time of the discussion. | |
| Domain(s)<br>(NZ only) | • Check <u>all</u> that apply.<br>• Check each domain a member of the research team discussed with the patient. | |
| Space for additional Discussions with a proxy is provided in the eCRF. | | |
| Has the patient or proxy agreed or declined in writing. | • If YES, complete section 2, Agreement/Declined/Revoked event.<br>• If NO, complete section 3, Written agreement not obtained. | |
| 2. Agreement/Declined/Revoked event | | |
| Provided by | Check <u>one</u> option. | |
| | Patient | • If the patient provided agreement to participate in REMAP-CAP. |

| | | |
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| | Proxy | • If the patient was not able to provide agreement for themselves and<br>  ○ a proxy provided agreement on the patient's behalf for them to participate in REMAP-CAP<br>  ○ a proxy considered that the patient would want to participate in REMAP-CAP.<br>• For the purposes of this CRF the term PROXY has been used to cover multiple terms to allow the CRF to be used in multiple jurisdictions, including:<br>  ○ Next of Kin<br>  ○ Legal surrogate<br>  ○ Relative<br>  ○ Whanau<br>  ○ Friend<br>  ○ Personal Consultee<br>  ○ Person responsible (aka Medical Treatment Decision Maker)<br>  ○ Substitute decision maker. |
| | Other | If another person or group with HREC/IRB approval provided agreement on the patient's behalf for them to participate in REMAP-CAP. Includes agreements provided by: |

| | | |
|---|---|---|
| | | • An independent clinician at your site.<br>• A Public Guardian/Advocate. |
| Date & time | • Date and time agreement were provided.<br>• If unknown, provide best estimate of time of agreement. | |
| Domain outcome | Select <u>one</u> option for each domain in which the patient has received an allocation. | |
| | Agreement obtained | • The patient/proxy or other provided agreement to participate in this domain. |
| | Declined/Revoked | • The patient/proxy or other declined agreement to participate in this domain.<br>• Since agreement the patient/proxy or other has revoked agreement to participate in this domain. |
| | No outcome | • The patient/proxy or other has not decided at this time.<br>• The patient/proxy decided if they would participate in this domain during a previous agreement event and it has not changed. |
| | Not applicable | Check this option if:<br>• Your hospital is not participating in the domain.<br>• The domain was not discussed with the patient or proxy because the |

| | | |
|---|---|---|
| | | patient is not eligible for the domain. |
| Declined/Revoked in all domains | • NOTE: a patient and/or proxy can revoke consent from one domain and remain a participant in other domains, depending on HREC approvals.<br>• The following questions need to be answered for all patients where participation is declined/revoked from all eligible domains. | |
| | Can data already collected be used | • This relates to data collected before the time the patient/proxy withdrew from the study.<br>• If the patient doesn't allow REMAP-CAP to use data already collected check NO.<br>• If NO is selected the data will be deleted from the database and the patient will not be included in any analysis.<br>• If NO is selected no further questions are required. |
| | Can we use the patient's medical record to collect vital status at ICU and/or hospital discharge | • This question only applies if the previous question is answered as YES.<br>• Answer YES if you have permission to access the patient's medical record to collect vital status at ICU and hospital discharge. |
| | Can we use the patient's medical record to collect vital status on day 90 & 180 | • This question only applies if the previous question is answered as YES.<br>• Answer YES if you have permission to access the patient's medical record to collect vital status in subsequent follow-ups. |

| | | |
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| | Can we contact the patient to collect vital status on day 90 & 180 | • This question only applies if the previous question is answered as YES.<br>• Answer YES if you have permission to contact the patient or proxy directly to collect vital status in subsequent follow ups. |
| Space for additional Agreement/Declined/Revoked Events is provided in the eCRF. | | |
| 3. Written agreement not obtained | | |
| What is the reason written agreement was not obtained | • This question is required for all patients where written consent was not obtained.<br>• Select the primary reason why consent was not obtained:<br>○ Patient lost to follow-up<br>○ Patient not competent to give consent and no proxy available<br>○ Patient deceased<br>○ Other (please specify). | |
| Has the reviewing ethics committee approved the use of patient data | • Select YES if the reviewing HREC has approved use of patient data in a circumstance where consent was not able to be obtained. HREC approval may depend on the reason listed in the previous question.<br>• Select NO if the reviewing HREC has not approved use of data. | |
| What has the reviewing ethics committee approved | • Question only applies if HREC has approved use of patient data.<br>• Select the data option that the HREC has approved<br>○ All data collection<br>○ Vital status only<br>○ Other (please specify). | |
| Date of ethics committee approval | • Question only applies if HREC has approved use of patient data.<br>• Enter the date the HREC granted approval to use patient data.<br>• May be before randomization. | |

| | |
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| Was verbal agreement obtained from the patient or proxy | • Select YES if there was a verbal agreement with the patient/proxy before written consent was able to be obtained.<br>• Select NO if there was no verbal agreement with the patient/proxy before written consent was able to be obtained. |

## FORM 7B: CONSENT

### General Guidance

Enter all consent discussions that occur, even where the discussion does not result in a decision or written outcome. Each discussion should be entered as a separate event.

Note that the Consent Form was updated in July 2024. The following applies to participants enrolled **after** this time.

| Question | Definition or Explanation of Question |
|---|---|
| Randomization that the discussion event is related to | • This question is only required for participants who have received allocations in both the Moderate State and the Severe State.<br>• For such participants, enter all consent discussions as separate events, indicating which of these randomization events the discussion related to.<br>• If both randomization events were discussed at the same time, both may be selected. |
| Date and time of discussion | • Enter the date and time of the discussion |
| Discussion with | • Select whether the discussion event was with:<br>  ○ the patient themselves,<br>  ○ a personal legal representative (e.g. a family member, next-of-kin, or carer), or<br>  ○ In some regions, discussions may involve a professional legal representative (e.g. an independent clinician)<br>• If the discussion involved both the patient and their family, select ‘patient’.<br>• If the discussion was with an individual who does not fall into one of the above categories, select ‘other’ and specify their relationship to the participant |

| | |
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| | ○ **Do not** enter the individual's name into this field. Only enter their relationship to the participant using a succinct description. |
| Outcome | • If the discussion resulted in the patient, their personal legal representative, or a professional legal representative (where applicable) agreeing to participation in at least one domain, select "agreed to participation in one or more domain"<br>• If the discussion resulted in the patient, their personal legal representative, or a professional legal representative (where applicable) declining or withdrawing consent for participation in <u>all</u> domains, select "declined / withdrew consent for participation in all domains".<br>• If no decision was made about participation at the time of the discussion (e.g. the participant or their legal representative wanted more time to consider participation), select "Information provided, no decision made"<br>○ Any subsequent discussions should be entered as separate events<br>• In some jurisdictions, an opt-out consent model may be utilized. In these regions, you may select "opt-out information sheet provided" |
| Was the outcome provided in writing, or verbal only | • If there was a decision to agree to participation or to decline/withdraw participation, please indicate whether this was provided in writing.<br>• A decision in writing means that the decision is documented in writing using an approved informed consent form.<br>• If the outcome was communicated verbally, the following questions will be asked in some jurisdictions, where applicable:<br>○ Did an impartial witness observe the verbal consent process |

| | |
|---|---|
| | ○ If yes, did the impartial witness sign and informed consent form<br>○ Was verbal consent recorded through appropriate alternative means, such as audio or video recording |
| Which domains did they agree to participation in | • If the outcome of the discussion was agreement to participate in one or more domains, select all domains that the patient or their representative agreed to participation in<br>• The eCRF will display a list of all domains in which the participant has received an allocation |
| **Consent for use of data.**<br>If the participant or their authorized representative decline participation in all domains, you will be asked to specify consent for use of data. | |
| Can data collected to the point of withdrawal be used | • Indicate whether the participant or authorized representative has agreed to allow any data collected up to the point of withdrawal to be stored and used.<br>• The default in this trial is to use data collected to the point of withdrawal, unless otherwise specified. Select 'no' only where the participant or their representative has clearly expressed that they do not want *any* of their data to be used. |
| Can data available from medical records be used to continue to collect data, where available | • Indicate whether the participant or their authorized representative agreed to the continued collection of data using routinely-collected hospital records available to research staff (e.g. medical records created as part of the patient's routine care) |
| Can the participant be contacted to collect follow-up information at Day 90 and Day 180 | • Indicate whether the participant of their authorized representative agree to be contacted to participate in follow-up interviews conducted after hospital discharge at day 90 and day 180 |

| | |
|---|---|
| Was the agreement for the storage and use of data for other research studies that are closely related to this research project, or any future research | • These questions will only appear in regions where IRBs have approved the potential storage and use of participant data for future research. |
| **No written consent obtained from participant**<br>This section will appear where all consent discussions have been entered and there is no entry indicating that consent for participation has been obtained in writing from the participant<br>While every attempt will be made to obtain consent in writing from the participant, it is acknowledged that this may not be possible or necessary in every instance. | |
| Indicate why written consent was not obtained from the participant | • Select the reason that best describes why written consent could not be obtained from the participant. This includes situations where:<br>○ the participant was deceased before consent could be obtained<br>○ the participant did not have capacity to provide consent for participation, and is not anticipated to regain capacity to do so<br>○ Verbal agreement was obtained but written consent could not be obtained, for example due to isolation requirements during a pandemic<br>○ Patient lost to follow up, for example patients who leave hospital against medical advice before consent can be obtained<br>○ In some regions, an opt-out consent model may have been used<br>○ Another reason not specified above |
| Can patient data be used without written consent from the participant, according to | • Select 'no' only where applicable regulations and approvals exclude the use of patient data in this context. |

| | |
|---|---|
| local regulations and approvals | • If you are unsure of the answer to this question, contact your regional coordinating center for assistance |
| Date of ethics committee / regulatory approval to use data in the absence of written consent | • Enter the date of approval from the appropriate ethics committee or regulator in your jurisdiction to use patient data in the absence of written consent from the participant<br>• If such approval is not required, select 'not applicable'<br>• If you are unsure about how to answer this question, contact your regional coordinating center for assistance. |

# FORM 8: DAY 90

## General Guidance

- Complete this form for all ***Platform*** patients who were alive at hospital discharge.
- Vital status at Day 90 is the ***PRIMARY OUTCOME***, therefore this data is of the utmost importance. Delays in submission reduce the effectiveness of the Response Adaptive Randomization (RAR).
- All patients who survive to hospital discharge ***MUST*** be followed up at 90 days post-randomization, unless a request has been made by the patient or their proxy to:
    - Cease data collection or
    - Not contact them.
- Complete this form no earlier than on study day 91 and no later than study day 104.
- If vital status cannot be ascertained by Day 104, complete the CRF. Further attempts to follow up the patient should be made, and the CRF updated as new information becomes available (this assists the effectiveness of the RAR).
- Follow up should be completed by the Research Coordinator or other research staff at the site.
- Day 90 and Day 180 follow-up cannot be completed at the same time.
- Before completing this form use all available information to ascertain if the patient has died after hospital discharge but before Study Day 90. Depending on your HREC/ IRB approvals sources could include:
    - Patient administration system or medical record at your hospital (or elsewhere with appropriate approval)
    - The patient's General Practitioner or community health clinic
    - Death records
    - In Australia, we recommend checking on the Ryerson Index (an index of death notices and obituaries published in Australian newspapers.
- NOTE: advice is provided in the MoP on talking to distressed patients. Please refer to this document before contacting a patient and or proxy.

| Question | Definition or Explanation of Question |
|---|---|
| 1. Vital Status | |
| Assessment Date | • Date the follow up was conducted. |

<table>
<tr><td></td><td colspan="2">• The date status was determined not the follow-up due date.</td></tr>
<tr><td>Status</td><td colspan="2">• Check <u>one</u> option.<br>• The patient's status at the end (midnight) on study day 90.</td></tr>
<tr><td></td><td>Alive</td><td>• The patient was alive at midnight on study day 90.</td></tr>
<tr><td></td><td>Deceased</td><td>• The patient was deceased at midnight on study day 90.</td></tr>
<tr><td></td><td>Unable to ascertain</td><td>• Vital status on day 90 is <u>unable to be ascertained by day 104</u>.<br>• Only check if you made 3 - 4 attempts to contact the patient, proxy or collect day 90 status.<br>• If all avenues to ascertain vital status have proven unsuccessful contact the project manager.</td></tr>
<tr><td>Date of death</td><td colspan="2">• This question only applies if the patient is deceased<br>• Enter the patient's date of death.<br>• If not immediately known, attempt to ascertain date of death from all potential sources.<br>• If all possibilities are exhausted and date of death is still unknown, contact the project manager.</td></tr>
<tr><td>Date last known alive</td><td colspan="2">• This question only applies if you are unable to ascertain the patient's survival status at day 90.<br>• Enter the date that the patient was last known to be alive.<br>• If a later date becomes known, update the CRF.</td></tr>
</table>

# FORM 9: DAY 21

## General Guidance

- Complete this form for all patients **with suspected or confirmed pandemic infection**
- Vital status at Day 21 is the ***PRIMARY OUTCOME*** for patients with suspected or confirmed pandemic infection, therefore this data is of the utmost importance. Delays in submission reduce the effectiveness of the Response Adaptive Randomization (RAR).
- Complete this form no earlier than on study day 22 and **no later than study day 28**.
- D21 outcome is censored at hospital discharge. **Do not** contact patients who have been discharged from hospital to ascertain their vital status.
- As much as is possible, enter details of all ICU admissions occurring up to D21 or ultimate hospital discharge for this acute illness. This includes transfers to another acute hospital for the same acute illness.
- If the patient is transferred from the study ICU directly to another non-REMAP-CAP participating ICU in a different acute hospital, record this as a separate ICU admission.

| Question | Definition or Explanation of Question |
|---|---|
| 1. ICU discharge | |
| ICU status | • Select the patient's status at the end of study day 22<br>• If the patient has been DISCHARGED FROM ICU complete the relevant sections of the discharge CRF. |
| Was patient discharged and readmitted to ICU prior to the end of study day 22 | • Select YES if the patient was discharged and readmitted to ICU prior to the end of study day 22<br>• Enter the details of any ICU discharges and readmissions into the discharge CRF. |
| 2. Hospital Discharge | |
| Hospital status | • This question only applies if the patient has been discharged from ICU prior to the end of study day 22.<br>• Select the patient's hospital discharge status at the end of study day 22. |

| | |
|---|---|
| | • If the patient has been discharged from hospital, complete the discharge CRF. |

# FORM 10: DAY 180 VITAL STATUS

## General Guidance

- Day 180 follow-up is competed at all sites in ANZ and some sites in Europe.
- Complete this form for all ***Platform*** patients who were alive on study day 90.
- All patients who are alive at day 90 ***MUST*** be followed up at 180 days post-randomization, unless your site isn't completing day 180 follow-up, or a request has been made by the patient or their proxy to:
    - Cease data collection or
    - Not contact them.
- Complete this form on or after study day 181 (as close to day 181 as possible) not before study day 181.
- If a patient's status was unable to be ascertained on day 90 attempts should be made to contact the patient at day 180.
- Before completing this form use all available information to ascertain if the patient has between study day 90 and study day 180. Depending on your HREC/ IRB approvals sources could include:
    - Patient administration system or medical record at your hospital (or elsewhere with appropriate approval)
    - The patient's General Practitioner or community health clinic
    - Death records
    - In Australia, we recommend checking on the Ryerson Index (an index of death notices and obituaries published in Australian newspapers.
- Vital status and the EQ-5D-5L should be prioritized over the WHODAS questionnaire, baseline or EARL questions. If a patient/proxy can only complete one questionnaire, complete the EQ-5D-5L.
- NOTE: advice is provided in the MoP on talking to distressed patients. Please refer to this document before contacting a patient and or proxy.

| Question | Definition or Explanation of Question |
|---|---|
| ***Platform*** | |
| 1. Vital Status | |
| Assessment Date | • Date of follow up. |

| | | |
|---|---|---|
| | • Enter the date that survival status was determined, not the date that follow up was due. | |
| Status | • Check <u>one</u> option.<br>• The patient's status at the end (midnight) on study day 180. | |
| | Alive | The patient was alive at midnight on day 180. |
| | Deceased | The patient was deceased at midnight on day 180. |
| | Unable to ascertain | Only check this option if you are unable to locate or contact the patient or proxy after 3 - 4 telephone contacts and a letter which can be tracked (registered or express post). |
| Location on study day 180 | • Check <u>one</u> option.<br>• Only answer this question if the patient is alive at midnight on study day 180.<br>• The patient's location at midnight on study day 180. | |
| | Home | Home is defined in Section 5. General Definitions. |
| | Nursing home or long-term care facility | • Nursing home is defined in Section 5. General Definitions. |
| | Rehabilitation hospital | Rehabilitation hospital includes:<br>• A separate rehabilitation hospital<br>• A transitional living facility<br>• A patient is sent from an acute hospital to a chronic care facility (or unit) that is geographically separate from the acute wards (but still on the same hospital campus) and managed by a different team. |
| | Acute care hospital | • If at the end of study day 180, the patient is an inpatient in an acute hospital. |

| | | |
|---|---|---|
| | | • If the patient is in a patient in acute care rehabilitation services at your hospital. |
| | Hospital ICU | If at the end of study day 180, the patient is an inpatient in an ICU. |
| | Other, specify | Any other discharge destination not listed e.g. Jail. |
| Date of death | • This question only applies if the patient is deceased at day 180<br>• Enter the patient's date of death.<br>• If date of death is not immediately known, attempt to ascertain date of death from all potential sources.<br>• If all possibilities are exhausted and date of death is still unknown, contact the project manager. | |
| Date last known alive | • This question only applies if you are unable to ascertain the patient's survival status at day 180<br>• Enter the date the patient was last known to be alive. | |
| Additional information | • Provide any additional information regarding why the patient's vital status is not known. | |

# FORM 10: DAY 180 FOLLOW-UP QUESTIONNAIRES

## General Guidance

- The EQ-5D-5L should be prioritized over the WHODAS questionnaire, baseline or EARL questions. If a patient/proxy can only complete one questionnaire, complete the EQ-5D-5L.
- Use appropriate sensitivity in conducting the interview e.g. establish rapport, acknowledge the challenges of recovery from critical illness, be aware of the capacity of the patient to cope with the interview, and be aware that questions may trigger a range of emotional responses.

## 2. D180 Surveys

| | |
|---|---|
| Were any of the survey tools completed | • Select YES if one or more of the survey tools were completed.<br>• Select NO if none of the survey tools were completed. |
| Reason unable to proceed | • This question only applies if NO is selected above.<br>• Select one option that best describes why the surveys were not completed.<br>  ○ Unable to contact patient or suitable proxy<br>  ○ Language or competence barrier<br>  ○ Declined to answer subsequent questions<br>  ○ Other, specify. |
| Date completed | • The following questions only apply if one or more of the survey tools were completed.<br>• Date the Patient or Proxy was interviewed.<br>• If the date is the same as when Day 180 vital status was ascertained, check SAME AS ASSESSMENT DATE. |
| Person interviewed | • Select who completed the follow-up |

| | |
|---|---|
| | • A patient interview is preferred.<br>• A proxy (family member, person responsible, carer, etc.) can complete the questionnaire if the patient is unable to be interviewed.<br>• If a proxy is being interviewed, please use the Proxy version of the tools (if available).<br><br>The proxy must answer the questions (to the best of their ability) about how the patient would feel, not how they view the patient's life. Therefore, it is important to find the best person to answer the questions for the patient and that may take some investigation to establish this. |
| Do they live with the patient | • This question only applies if the survey tools were completed by a proxy<br>• Check YES if the proxy is living in the same residence as the patient. |

### 3. EQ5D-5L

**General Guidance**

- EuroQol EQ5D-5L 5 Level (EQ-5D-5L) is a validated instrument, developed by EuroQol,
- ONLY use relevant country-specific version(s) as appropriate for each patient.
- **The following Country-specific versions are available**:

| | |
|---|---|
| ○ English (Australia)<br>○ Dutch (Belgium)<br>○ French (Belgium)<br>○ German (Belgium)<br>○ English (Canada)<br>○ Croatian (Croatia)<br>○ Czech (Czech Republic)<br>○ Danish (Denmark)<br>○ German (Germany) | ○ Greek (Greece)<br>○ Hungarian (Hungary)<br>○ English (Ireland)<br>○ Dutch (Netherlands)<br>○ Portuguese (Portugal)<br>○ Spanish (Spain)<br>○ English (United Kingdom)<br>○ English (New Zealand)<br>○ Romanian (Romania) |

- Contact your local project manager (Section 2: Contact Details) to request any of these version(s).
- To request additional versions (not listed above) email Info@remapcap.org with the subject line "EQ5D-5L Request".
- This quality of life questionnaire may be conducted over the phone or via post (depending on local HREC/IRB approvals).
- There is no right or wrong answer to the quality of life questions.
- The data should reflect how the patient views their life even if it seems implausible to others.
- For more information and tools to help you administer the questionnaire, refer to the EuroQol website here.
- Tools available on this website include:
  - User Guide
  - FAQs.

| | |
|---|---|
| Was the EQ5D-5L completed | • Check YES if the patient or proxy completed all or some of the EQ-5D-5L questionnaire. |
| EQ-5D-5L | • The appropriate Country-specific instrument(s) is provided in a Follow-up pack.<br>• Use the questionnaire associated with your country.<br>• If a version for your country isn't provided contact your local project manager.<br>• The questions and instruction are self-explanatory.<br>• Do not use the paper CRF or eCRF version while conducting the EQ-5D-5L interview. It is unlikely that this version will be appropriate for participants or their proxy in your country. Please use the appropriate follow-up instruments provided in your Follow-up pack.<br>• It is recommended that you read the EuroQol User Guide before using the survey for the first time. This guide is provided in the Follow-up pack. |

## 4. WHODAS 2.0

**General Guidance**

- World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) 12 item questionnaire

<table>
<tr><td colspan="2">
<ul>
<li>ONLY use relevant language version(s) as appropriate for each patient.</li>
<li>The following language versions are available:</li>
</ul>
</td></tr>
<tr><td>
<ul>
<li>Bangla</li>
<li>Chinese</li>
<li>Danish</li>
<li>English</li>
</ul>
</td><td>
<ul>
<li>French</li>
<li>German</li>
<li>Serbian</li>
<li>Spanish</li>
</ul>
</td></tr>
<tr><td colspan="2">
<ul>
<li>Contact your local project manager (Section 2: Contact Details) to request version(s).</li>
<li>To request additional versions (not listed above) email Info@remapcap.org with the subject line “WHODAS 2.0 Request”.</li>
<li>It is recommended interviewers read and are familiar with the manual Measuring Health and Disability: Manual for WHO Disability Assessment Schedule – WHODAS 2.0 (WHO, 2010), particularly the sections from page 35 onwards, including the interview guide and training material. The manual is provided in the Follow-up pack.</li>
<li>This quality of life questionnaire may be conducted over the phone or via post (depending on local HREC/IRB approvals).</li>
<li>A number of the questions at the beginning of the questionnaire have been removed. This is because this data has already been collected in REMAP-CAP (e.g. patient age and sex).</li>
</ul>
</td></tr>
<tr><td>Was the WHODAS 2.0 completed</td><td>
<ul>
<li>Check YES if the patient or proxy completed all or some of the WHODAS questionnaire.</li>
</ul>
</td></tr>
<tr><td>How many years in all did you spend studying in school, college or university</td><td>
<ul>
<li>If the respondent dropped out of school or university, do not give credit for a partial year.</li>
<li>If an individual has been in school both full and part-time, note the number of years in full time education.</li>
<li>Count any repeated grades as two years.</li>
</ul>
</td></tr>
<tr><td>What is your current marital status</td><td>
<ul>
<li>Check one option.</li>
<li>Allow the respondent to answer this question without reading the choices in advance.</li>
</ul>
</td></tr>
</table>

| | |
|---|---|
| | • If the response does not correspond exactly with one of the provided responses, clarify by reading the choices that could correspond with the response.<br>• Check the option that best reflects current marital status. For example, if the respondent is currently married but was divorced in the past, score only currently married. |
| Which describes your main work status best | • Check the option that best reflects the respondent's current main work status. If doubtful about how to code a respondent (e.g. as homemaker or unemployed), rely on the respondent's judgement of their work status.<br>• There is no minimum number of hours per week that a respondent must work to qualify for the paid work category. Similarly, students need not be full time in order to be classed as such. |
| WHODAS 2.0 | • The questions and instruction are self-explanatory.<br>• The manual to train the person performing the WHODAS interview is provided in the Follow-up pack.<br>• Everyone administering the WHODAS is expected to complete pre-interview training provided in the WHODAS 2.0 manual.<br>• The appropriate instrument(s) are provided in a Follow-up pack<br>• Use the most appropriate instrument for the patient or proxy.<br>• Do not use the paper CRF or eCRF version while conducting the WHODAS interview. It is unlikely that this version will be appropriate for participants or their proxy in your country. Please use the appropriate follow-up instruments provided in your Follow-up pack. |
| 5. Premorbid Baseline | |
| Were the baseline questions completed | • Check YES if the patient or proxy completed all or some of the baseline questions. |
| Before your ICU admission which | • Check <u>one</u> option. |

| | |
|---|---|
| describes your main work status best | • This question relates to the patient's usual work status immediately prior to their hospital admission for CAP.<br>• If in doubt about the respondent's answer (e.g. as homemaker or unemployed), rely on the respondent's judgement of their work status.<br>• There is no minimum number of hours per week that a respondent must work to qualify for the paid work category. Similarly, students need not be full time in order to be classed as such. |
| In the month before your ICU admission were you receiving any treatment for anxiety or depression | • This question relates to the month prior to the hospital admission for CAP.<br>• It includes medications prescribed for anxiety or depression OR any other medical treatment, including:<br>  ○ Psychology or<br>  ○ Psychiatry |

## 6. Ethics

**General Guidance**

- This section is only required in some countries. Check on the eCRF before asking these questions.
- Before asking these questions take note of what type(s) of agreement was obtained for the patient (Form 7: Consent).
- A proxy (family member, person responsible, carer, etc.) cannot complete this questionnaire if the patient is unable to be interviewed.
- These questions are asked as part of the Ethical, Administrative, Regulatory and Logistical (EARL) Study. The EARL Study aims to identify and implement solutions to key structural (ethical, administrative, regulatory and logistical) bottlenecks as well as behavioral and cultural barriers to the rapid implementation of large multi-site clinical studies in response to severe infectious disease outbreak.

| | |
|---|---|
| Person interviewed. | • Check one option that best describes the person being interviewed at the start of this section.<br>• Due to the nature of the questions, it is important that **only the patient is interviewed.** |

| | |
|---|---|
| | • If only the proxy is available, do not ask the following questions. Follow-up is complete. |
| **Interview introduction. Please read the following to the patient:**<br>When you were admitted to the ICU, you were signed up to take part in REMAP-CAP. The following questions will help us understand your views on the way we signed you up to the REMAP-CAP study. As you were unable to make a decision yourself about taking part, a relative or someone similar made that decision for you | |
| If you had been able to give consent yourself before we signed you up to the study, would you have agreed to participate in the trial. | • Check <u>one</u> option.<br>• This question relates to patient who were randomized into REMAP-CAP with <u>proxy agreement</u>.<br>• Review the patients Form 7 Consent CRF, if the patient provided prospective agreement to participate in REMAP-CAP, check NOT APPLICABLE.<br>  ○ To determine if prior agreement was obtained by the patient:<br>  **Step 1:** Review the patient's eCRF summary page take note of the randomization date and time.<br>  **Step 2:** Review form 7 Consent, Section 2. Agreement Event date and time<br>  **Step 3**: If the patient provided agreement before the randomization date and time, then the patient provided prior agreement and this question is not relevant.<br>• The question is aimed at understanding whether the patient would have made the same decision as the proxy decision maker if they had had capacity to do so at the time of randomization. |
| Prior to the hospital admission had you ever discussed your participation in research with the person who made the | • Check <u>one</u> option<br>• This question relates to whether the patient had ever discussed their wishes regarding participating in research with their relative prior to this hospital admission, e.g. how the relative/ proxy decision maker knew the patient's wishes. |

| | |
|---|---|
| decision for you to participate in the trial. | |
| **New topic introduction. Please read the following:**<br>Imagine this study had happened during a public health emergency, such as a severe flu outbreak. | |
| How acceptable would it be to you if a doctor not involved in the study gave consent for you to be included in the trial instead of a family member. | • Check <u>one</u> option<br>• This question relates to when a patient is not able to make a choice for themselves due to severe illness. |

# FORM 11: ADVERSE EVENT

## General Guidance

- Complete this form for all ***Platform*** patients who experience an adverse event (AE).
- AEs are collected for events occurring between randomization and ICU discharge.
- Please ensure the principal investigator (PI) at your site is made aware of any adverse event.
- If the patient did not experience an AE leave this form blank.
- List one AE per line.
- There are no pre-specified adverse events. Events that are part of the natural history of the primary disease process or expected compilations of critical illness will not be reported.
- AEs which are considered to be potentially causally related to the study intervention or are otherwise of concern in the investigator's judgement should be reported.
- AEs include any unexpected or untoward medical events experienced by the patient which are not anticipated and in the opinion of the investigator are related to participation in REMAP-CAP.

| Question | Definition or Explanation of Question |
|---|---|
| ***Platform*** | |
| 1. Adverse Event | |
| Event | • Provide the diagnostic term for the AE (e.g. contraindication, hypoglycemia).<br>• Do not list the symptoms.<br>• If any of these events are determined to be life threatening or medically important then report as an SAE (Form 10: SAE), do not report the events twice. |
| Participation | • Check all that apply.<br>• Check the domain(s) of REMAP-CAP participation in which the investigator believes is linked to the AE.<br>• Check GENERAL PARTICIPATION if the AE is suspected to be linked to REMAP-CAP but the link to a specific domain/intervention is not known. |
| AE onset date | Date the AE first developed. |
| Action taken | Action taken by clinicians to treat the AE. |

| | |
|---|---|
| | **None:** The patient continues to be given the REMAP-CAP intervention or at the time of the event the REMAP-CAP intervention is ceased.<br>**Treatment modified or temporarily discontinued**: The REMAP-CAP intervention is stopped temporarily with the expectation of recommencing when the AE is resolved.<br>**Treatment permanently discontinued**: The REMAP-CAP intervention is permanently ceased because of the AE. |
| Outcome | Check one option.<br>**Unknown/ lost to follow-up:** The event could not be follow-up to hospital discharge and it is not known if the event resolved.<br>**Unresolved:** In the investigator's opinion, the event is unresolved.<br>**Resolved:** In the investigator's opinion, the event is resolved.<br>**Resolved with sequelae**: In the investigator's opinion, the event is resolved but the patient continues to have sequelae from the event. |
| Relationship to treatment | Check one option.<br>The definitions are provided for the investigator to determine causality of the event.<br>**Not related**: The investigator determines that the REMAP-CAP intervention / participation had no effect on this event.<br>**Unlikely**: it is possible but unlikely that the REMAP-CAP intervention / participation made some contribution to the event. There is another far more likely cause.<br>**Possibly**: The investigator determines that the REMAP-CAP intervention / participation contributed to the event but may not be the prime cause. There is another contributing factor such as a co-morbid condition which has more likely caused the event.<br>**Probably**: The investigator determines that the REMAP-CAP intervention / participation has more likely caused the event than another factor.<br>**Definitely**: The investigator determines that the REMAP-CAP intervention / participation caused the event and there are no other factors which could have contributed. This would ordinarily include a strong temporal relationship. |

| | |
|---|---|
| AE resolution date | • Answer this question If AE Outcome was answered with either Resolved or Resolved with sequelae.<br>• Enter the date the AE resolved.<br>• If any other option is checked from the Outcome section leave blank in the paper CRF. The date of resolution will be disabled in the eCRF. |

# FORM 12: SERIOUS ADVERSE EVENT

- **ANZ and Ca sites**
  - Report the event online via eCRF up to 3 working day (72 hours) of the event becoming known to research staff.
  - Refer to the Database User Guide for instructions on how to report an SAE using the eCRF.
- **EU sites**
  - Report the event **within 24 hours** of the event becoming known to research staff.
  - Notify the EU Sponsor by completing the SAE eCRF
  - If you have any questions **Tel**: +31 62 77 44477.

## General Guidance

- Complete this form for all ***Platform*** patients who experience a serious adverse event (SAE).
- Complete one SAE form for each SAE.
- **Report SAEs that occur between randomization and hospital discharge.**
- It is recommended that a copy of the SAE eCRF is filed in the patient's medical record.
- SAEs are defined in accordance with the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) (July 2000) as any untoward medical occurrence which may or may not have a causal relationship with the study treatment that:
  - Results in death
  - Is life-threatening
  - Requires inpatient hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability/incapacity
  - Results in a congenital anomaly/birth defect
  - Results in an important medical event which may require intervention to prevent one of the previously listed outcomes.
- In addition, for an event to be reported as a SAE in REMAP-CAP the event must also meet all the following criteria:
  - Occurs after randomization but before hospital discharge, and
  - The event is believed to be possibly, probably, or definitely related to a study intervention or participation (irrespective of whether the event is a trial primary or secondary endpoint for this participant)

- Events that otherwise meet the GCP SAE definition that are expected as part of the natural course of the critical illness should not be reported unless they also meet the criteria above.
- Deaths are not reportable SAEs unless the investigator believes that the death is directly attributed to a REMAP-CAP intervention or participation (or if in their opinion, the cause of death means that the death should be reported).
- Supporting evidence, such as laboratory results, radiological diagnostic reports (e.g. chest x-ray report), if applicable should be scanned and emailed to the project manager.
- Contact the project manager if you wish to discuss SAE reporting. Project manager contact details are in Section 2.
- **Reporting an SAE:**
    - A confirmation email will be sent to the project manager, the site principal investigator and research coordinator/s that the submission of the SAE Form has been successful.
    - Do not wait for all the information before submitting an initial SAE eCRF report (e.g. answers to all CRF questions aren't known).
    - Additional information can be added at a later date by entering the information and checking Follow-up report or Final report.
    - File the SAE confirmation email.

Note that the Serious Adverse Event form was updated in April 2024. Some of the questions below will not appear for reports submitted for participants enrolled after this date.

| Question | Definition or Explanation of Question |
|---|---|
| ***Platform*** | |
| 1. Serious Adverse Event Details | |
| Report type | Check the stage of the report from the following list:<br>• **Initial report**: The first report will always be labelled Initial.<br>• **Follow-up report:** If one or more subsequent reports are required before the final report then check Follow-up report.<br>• **Final report**: The final report for this event and no further information is required. |

<table>
<tr><td>Diagnosis</td><td colspan="2"><ul><li>Provide the diagnostic term for the SAE. Do not list the symptoms.<ul><li>For example, anaphylaxis, rather than hypotension and bronchospasm.</li></ul></li><li>Death is not a diagnosis it is an outcome. Do not record Death as an SAE diagnosis.</li></ul></td></tr>
<tr><td>SAE diagnosis</td><td colspan="2"><ul><li>Select the most appropriate diagnosis to describe the event.</li><li>You will be asked to select a high-level diagnosis category, which will reveal a list of sub-categories.</li><li>A full list of diagnostic categories is provided in Appendix 3</li></ul></td></tr>
<tr><td rowspan="5">SAE severity</td><td colspan="2"><ul><li>Select the appropriate grading from the Common Terminology Criteria for Adverse Events (CTCAE) categories, in the opinion of the investigator.</li><li>The grades are as follows:</li></ul></td></tr>
<tr><td>Grade 1</td><td><ul><li>Mild, asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated</li></ul></td></tr>
<tr><td>Grade 2</td><td><ul><li>Moderate, minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL</li></ul></td></tr>
<tr><td>Grade 3</td><td><ul><li>Severe or medically-significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL</li></ul></td></tr>
<tr><td>Grade 4</td><td><ul><li>Life-threatening consequences; urgent intervention indicated</li></ul></td></tr>
<tr><td></td><td>Grade 5</td><td><ul><li>Death related to the SAE</li></ul></td></tr>
</table>

| | |
|---|---|
| SAE description | • Describe the event as succinctly as possible.<br>• Be specific so that the medical monitors can assess causality, include any results of relevant supportive laboratory data and other investigations if applicable.<br>• Use standard medical terminology. |
| SAE onset date | • Enter the date and time of the onset of the serious adverse event |
| Suspected intervention | • Select all that apply.<br>• Select the domain(s) of REMAP-CAP participation in which the investigator believes is linked to the SAE.<br>• Select NOT RELATED TO PARTICIPATION IN ANY DOMAIN if the SAE is not suspected as being linked to a specific domain intervention / participation. |
| Is this event a SUSAR | • Select YES only if the event meets both of the following criteria:<br>  ○ The event is severe (CTCAE grade 3 and above), **and**<br>  ○ The event is unexpected, meaning not described in the current approved version of the reference safety information (Summary of Product Characteristics, Investigator Brochure, or Protocol)<br>• This question was replaced in April 2024 and will not appear for participants enrolled after this time. |
| Is the event expected in the context of available reference safety information for the allocated intervention in the domain | • An SAE is considered 'expected' if the nature and severity of the event is consistent with the current approved version of the reference safety information for the intervention (e.g., summary of product characteristics / investigator brochure / protocol documents).<br>• The event should be assessed as expected or unexpected "*from the perspective of previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product*" (ICH E2A, 1994). |

| | |
|---|---|
| | • If you are unsure about whether the event is consistent with current reference safety information, contact your regional coordinating center.<br>• If the event is deemed to be unexpected (i.e., if you answer NO) then the event may meet the definition of a SUSAR. Please contact your regional coordinating center immediately. |
| Suspected relationship | Check <u>one</u> option for each suspected intervention checked above.<br>The definitions are provided for the investigator to determine causality of the event.<br>• **Not related**: The investigator determines that the REMAP-CAP intervention / participation had no effect on this event.<br>• **Unlikely**: it is possible but unlikely that the REMAP-CAP intervention / participation made some contribution to the event. There is another far more likely cause.<br>• **Possibly**: The investigator determines that the REMAP-CAP intervention / participation contributed to the event, but may not be the prime cause. There is another contributing factor such as a co-morbid condition which has more likely caused the event.<br>• **Probably**: The investigator determines that the REMAP-CAP intervention / participation has more likely caused the event than another factor.<br>• **Definitely**: The investigator determines that the REMAP-CAP intervention / participation caused the event and there are no other factors which could have contributed. This would ordinarily include a strong temporal relationship. |
| Date and time intervention started | • Enter the date and time that the allocated intervention was commenced. |
| Date and time intervention last | • Enter the date and time that the intervention was last administered prior to the onset of the SAE. |

| | |
|---|---|
| administered prior to SAE onset | • For interventions administered continuously, enter the date and time that the intervention was ceased prior to SAE onset. If the intervention was being administered at the time on SAE onset, enter the date and time of SAE onset. |
| 2. Action Taken | |
| Action taken | Check <u>one</u> option.<br>• **No action taken:** The patient continues to receive the REMAP-CAP Domain intervention OR at the time of the event the intervention had been completed OR the SAE was not related to an intervention.<br>• **Temporarily discontinued:** the REMAP-CAP Domain intervention was ceased temporarily or is ceased temporarily with the expectation of recommencing.<br>• **Modification to intervention:** the allocated intervention was modified in some way, for example by reducing the dose, or adjusting the intensity or frequency of administration<br>• **Permanently discontinued:** the REMAP-CAP Domain intervention has been permanently ceased. |
| Date & time intervention started | • Date and time when the REMAP-CAP Domain intervention commenced. |
| Date & time intervention stopped | • Date and time when the REMAP-CAP Domain intervention was ceased. |
| Treatment | • Describe the treatment given to treat the SAE.<br>• Do not include all treatment the patient is receiving, just the SAE treatment.<br>• Describe the treatment as succinctly as possible.<br>• Use standard medical terminology. |
| 3. Outcome | |
| Outcome | Check the most appropriate status with respect to the outcome from the SAE. |

| | |
|---|---|
| | • **Unknown / lost to follow-up:** The event could not be followed up to hospital discharge and it is not known if the event resolved.<br>• **Unresolved:** In the investigator's opinion, the outcome of the event has not resolved.<br>  ○ Follow up the SAE at regular intervals until resolved or death and report any changes with a follow up SAE report.<br>  ○ If the status of the SAE is unknown at hospital discharge check UNKNOWN/LOST TO FOLLOW UP.<br>  ○ If the SAE is not resolved at hospital discharge check UNRESOLVED.<br>• **Resolved:** In the investigator's opinion, the outcome of the event has resolved, and the patient does not have sequelae from the event.<br>  ○ Date the SAE was resolved.<br>• **Resolved with sequelae**: In the investigator's opinion, the outcome of the event has resolved but the patient continues to have sequelae from the event.<br>  ○ Date the SAE was resolved.<br>  ○ The nature of the sequelae that remained or developed as a result of the event.<br>• **Death:** Date of death if the outcome from the SAE was death. If the cause of death was not related to the SAE do not check this option. |
| Resolution date | The date the SAE resolved. |
| Specify | The nature of the sequelae that remained or developed as a result of the event. |
| Date of death | • If the patient died as a result of the SAE enter the date of death.<br>• If the cause of death was not related to the SAE leave blank. |
| Cause | Enter the cause of death. |
| Location | Enter the patient's location at the time of death. |
| Autopsy | Indicate if an autopsy was performed.<br>Note that this question was removed in April 2024 and will not be required for patients enrolled after this time. |

| | |
|---|---|
| Report emailed | • If an autopsy was performed indicate if you have emailed the report to the project manager.<br>• If an autopsy report is emailed this should be identified with the REMAP-CAP PSN, remove all other patient identifiers (e.g. full name, initials, date of birth).<br>• Before sending the autopsy report to the project manager check with the project manager to make sure you have ethical approval to send it.<br><br>Note that this question was removed in April 2024 and will not be required for patients enrolled after this time. |

# FORM 13: PROTOCOL DEVIATION

## General Guidance

- Complete this form for all ***Platform*** patients for each protocol deviation that occurs.
- Complete a new form for each protocol deviation.
- Contact the project manager if you wish to discuss protocol deviation reporting, contact details are provided in Section 2.
- Protocol deviations can only be reported via the eCRF.
- For the purposes of this study the term 'protocol deviation' is used consistently throughout the protocol and study materials. Protocol Deviation has the same meaning as protocol violation. We have elected to use one consistent term for deliberate or accidental deviations from the protocol.
- The expected protocol deviations are listed. Do not check other if the deviation is listed. If uncertain discuss with the project manager.
- Only report protocol deviations to the HREC/IRB if this is the requirement of your HREC/IRB and/or site governance.

| Question | Definition or Explanation of Question |
|---|---|
| Platform or domain specific deviation | • Select whether the protocol deviation relates to a specific domain, or to enrolment in the platform.<br>• Platform deviations relate to study procedures and data collection that apply to all patients, regardless of which domains they are randomized into<br>• Domain level protocol deviations refer to study procedures and data collection that is specific to a study domain.<br>• You may only select one domain or general participation that the protocol deviation applies to. |
| 1. Protocol Deviation | |
| Deviation date | • The date the protocol deviation occurred.<br>• If the deviation is ongoing or intermittent, enter the date the deviation first occurred. |

| | |
|---|---|
| Platform eligibility deviation | • Check all that apply.<br>• If the deviation is not listed, check OTHER and summarize it in the free text box. |
| Reason | • Briefly describe the reason for the deviation as succinctly as possible. |
| What were the consequences or action taken | • Briefly describe the consequences and actions taken as a result of the deviation.<br>• There may be no consequences or actions taken due to the protocol deviation, please state this if it applies.<br>• Do not leave blank. |
| 2. Protocol Domain-Specific Deviation | |
| Deviation date | • The date the protocol deviation occurred.<br>• If the deviation is ongoing or intermittent, enter the date the deviation commenced. |
| Deviation type | • Check one option.<br>• Check the type of deviation from the list.<br>• If the deviation is not listed, check OTHER and summarize it in the free text box. |
| Specify | • Check the most appropriate option.<br>• Check one option.<br>• If the deviation is not listed, check OTHER and summarize it in the free text box. |
| Administration of prohibited antibiotic | • This question only applies if the patient received prohibited empiric antibiotic therapy.<br>• Briefly describe the prohibited antibiotic that was administered (e.g. antibiotic name, dose given and route of administration). |
| Reason | • Briefly describe the reason for the deviation as succinctly as possible. |

| | |
|---|---|
| What were the consequences or action taken | • Briefly describe the consequences and actions taken as a result of the deviation.<br>• There may be no consequences or actions taken due to the protocol deviation, please state this if it applies.<br>• Do not leave blank. |

# FORM 14: BIOLOGICAL SAMPLING

## General Guidance

- This form is required only for participants who have received an allocation in specified domains, at sites that have agreed to collect biological samples.

| Question | Definition or Explanation of Question |
|---|---|
| 1. Influenza Antiviral Domain | |
| For the Influenza Antiviral Domain, there are three time points for biological samples to be collected at participating sites:<br>• Baseline: collected on the day of randomization to the Influenza Antiviral Domain<br>• Day 3: collected on calendar day 3 after randomization to the Influenza Antiviral Domain, while the patient is admitted to hospital<br>• Day 7: collected on calendar day 7 after randomization to the Influenza Antiviral Domain, while the patient is admitted to hospital | |
| Was a sample collected at the time point | • Select 'Yes' if a sample was collected during the corresponding time period |
| Date and time sample collected | • Enter the date and time that the sample was collected |
| Sample ID | • Contact your regional coordinating center for instructions on how to label samples. |
| 2. Influenza Immune Modulation Domain | |
| For the Influenza Immune Modulation Domain, there are three time points for biological samples to be collected at participating sites:<br>• Baseline: collected on the day of randomization to the Influenza Immune Modulation Domain<br>• Day 3: collected on calendar day 3 after randomization to the Influenza Immune Modulation Domain, while the patient is admitted to hospital | |

| | |
|---|---|
| • Day 7: collected on calendar day 7 after randomization to the Influenza Immune Modulation Domain, while the patient is admitted to hospital | |
| Was a sample collected at the time point | • Select 'Yes' if a sample was collected during the corresponding time period |
| Date and time sample collected | • Enter the date and time that the sample was collected |
| Sample ID | • Contact your regional coordinating center for instructions on how to label samples. |

## FORM 15: Day 7

### General Guidance

- This form is required only for participants who have received an allocation in the COVID-19 Antiviral (II) Domain who had signs and symptoms of an acute respiratory tract infection at randomisation
- If the participant has been discharged from hospital before day 7 after randomization to the COVID-19 Antiviral (II) Domain, please contact them to ascertain whether the patient still has respiratory symptoms.

| Question | Definition or Explanation of Question |
|---|---|
| Did the patient still have acute respiratory symptoms on Day 7 post-randomization to the COVID-19 Antiviral (II) Domain | • Respiratory symptoms are defined as one or more of: cough, sore throat, runny nose sneezing, shortness of breath or chest pain. “Acute” means the symptom in question is not usually present in that individual, or during the current COVID episode was substantially worse or more frequent than usual.<br>• Resolution of all acute Respiratory symptoms means return to baseline state – not necessarily the absence of all Respiratory symptoms.<br>• Ongoing non-Respiratory symptoms (such as fatigue, anorexia, delirium, diarrhea) are not counted as part of this endpoint. |
| Information obtained by | • Select the source of the information entered into this form. |
| Date information ascertained | • Enter the date that the information was obtained, either by follow-up contact or medical records. |

# APPENDIX 1. FORM 2: BASELINE CLINICAL FRAILTY SCORE

## Clinical Frailty Scale*

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

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

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

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

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

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

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

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

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

**Scoring frailty in people with dementia**

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

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

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

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

# APPENDIX 2. FORM 3: MICROBIOLOGY RESISTANCE MATRIX

| Organism | Reported as intermediate or resistance to | Detected organism | Check |
|---|---|---|---|
| | *(check YES if either is reported)* | | |
| Acinetobacter spp | Either of the following:<br>• ceftazidime<br>• piperacillin-tazobactam | N/A | YES |
| | Either of the following:<br>• meropenem<br>• imipenem | N/A | YES |
| Escherichia coli | Either of the following:<br>• ceftriaxone<br>• ceftazidime | Extended Spectrum Beta-Lactamases (ESBL). | YES |
| | Either of the following:<br>• meropenem<br>• imipenem | Either of the following:<br>• Carbapenemase-producing Enterobacteriaceae (CPE)<br>• Carbapenem-resistant Enterobacteriaceae (CRE) | YES |
| Klebsiella spp | Either of the following:<br>• ceftriaxone<br>• ceftazidime | ESBL | YES |
| | Either of the following:<br>• meropenem<br>• imipenem | Either of the following:<br>• CPE<br>• CRE | YES |
| Pseudomonas aeruginosa | Either of the following:<br>• ceftazidime<br>• piperacillin-tazobactam | N/A | YES |
| | Either of the following:<br>• meropenem<br>• imipenem | N/A | YES |
| Staphylococcus aureus | Any of the following:<br>• methicillin<br>• oxacillin<br>• dicloxacillin<br>• flucloxacillin<br>• nafcillin | Any of the following:<br>• MRSA<br>• ca-MRSA<br>• ha-MRSA<br>• nm-MRSA<br>• m-MRSA (multiresistant MRSA) | YES |
| Streptococcus pneumoniae | Either of the following:<br>• erythromycin<br>• azithromycin | N/A | YES |
| | penicillin | N/A | YES |
| | Either of the following:<br>• moxifloxacin<br>• levofloxacin<br>• norflaxacin | N/A | YES |

# APPENDIX 3. SAE Diagnostic Categories

| High-level Diagnostic Category | Sub-Category |
|---|---|
| Abnormal laboratory results | • Hyperkalaemia<br>• Pancytopenia<br>• Haemolytic anaemia<br>• Thrombocytopaenia<br>• Agranulocytosis<br>• Rhabdomyolysis<br>• Elevated ALT/AST<br>• Elevated creatinine kinase<br>• Serum glucose decreased<br>• Other abnormal laboratory result |
| Bleeding | • Disseminated intravascular coagulation<br>• Eye haemorrhage<br>• Gastrointestinal haemorrhage<br>• Intra-abdominal haemorrhage<br>• Muscle haemorrhage<br>• Intracranial haemorrhage<br>• Spinal cord haemorrhage<br>• Respiratory tract haemorrhage<br>• Hemarthrosis<br>• ENT haemorrhage<br>• Bleeding from surgical site<br>• Other bleeding |
| Cardiac disorders | • Cardiac arrest |

| | |
|---|---|
| | • Ventricular arrythmia<br>• Atrial fibrillation<br>• Electrocardiogram QT prolonged<br>• Acute myocardial infarction<br>• Other cardiac disorder |
| Drug reaction | • Heparin-induced thrombocytopaenia<br>• Allergic reaction (non-anaphylactic)<br>• Anaphylactic reaction<br>• Stevens-Johnson Syndrome / Toxic Epidermal Necrosis<br>• Angioedema<br>• Drug-induced liver injury<br>• Drug-induced hypotension<br>• Other drug reaction |
| Gastrointestinal disorders | • Gastrointestinal obstruction<br>• Gastrointestinal perforation<br>• Mesenteric ischemia<br>• Bowel ischemia<br>• Nausea<br>• Vomiting<br>• Diarrhea<br>• Other gastrointestinal disorder |
| Hepatobiliary disorders | • Cholestasis<br>• Hepatitis<br>• Drug-induced liver injury<br>• Other hepatobiliary disorders |

| | |
|---|---|
| Infection | • Soft tissue infection<br>• Respiratory tract infection<br>• Abdominal infection<br>• Intracranial infection<br>• Meningitis<br>• Bloodstream infection<br>• Sepsis of unknown origin<br>• Febrile neutropenia<br>• Other infection |
| Nervous system disorders | • Neuromyopathy<br>• Seizure<br>• Cerebral ischemia<br>• Irritability<br>• Other nervous system disorder |
| Renal disorders | • Acute kidney injury<br>• Other renal disorder |
| Respiratory disorders | • Pneumothorax<br>• Respiratory distress<br>• Other respiratory disorder |
| Thromboembolic disorders | • Pulmonary embolism<br>• Acute myocardial infarction<br>• Deep vein thrombosis<br>• Cerebral ischemia<br>• Thrombosis<br>• Mesenteric ischemia |

| | |
|---|---|
| | • Bowel ischemia<br>• Other thromboembolic disorders |
| Transfusion reaction | • Acute haemolytic transfusion reaction<br>• Anaphylactic transfusion reaction<br>• Transfusion-related acute lung injury<br>• Transfusion-related circulatory overload<br>• Other transfusion reaction |
| Pregnancy or birth complication | • Foetal loss<br>• Congenital anomaly<br>• Other birth complication |
| Other | • Multi-organ failure<br>• Other not specified elsewhere |