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|  | ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections – COVID-19 | http://prognosis.org/isaric/images/WHO_logo.jpg |

## Background and rationale for the study

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

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

The proposed work may require sampling and analysis of the host genome, which may reveal other information about disease susceptibility, or other aspects of health status.

## Purpose of the study

Patients with acute illness suspected to be caused by COVID-19 will be enrolled. This protocol has been designed to enable data, and biological samples, to be prospectively collected, and shared rapidly in a globally-harmonised sampling schedule.

## Primary Objectives

The primary objectives for this study are to:

* Describe the clinical features of the illness or syndrome;
* Describe, where appropriate, the response to treatment, including supportive care and novel therapeutics;
* Observe, where appropriate and feasible, pathogen replication, excretion and evolution, within the host, and identify determinants of severity and transmission using high-throughput sequencing of pathogen genomes obtained from respiratory tract, blood, urine, stool, CSF and other samples;
* Characterise, where appropriate and feasible, the host responses to infection and therapy over time, including innate and acquired immune responses, circulating levels of immune signalling molecules and gene expression profiling in peripheral blood;
* Identify host genetic variants associated with disease progression or severity;
* Understand transmissibility and the probabilities of different clinical outcomes following exposure and infection.

## Secondary Objectives

Secondary objectives are to collect evidence in order to:

* Facilitate effective triage and clinical management of patients with infections relevant to this protocol;
* Determine infectivity and appropriate infection control measures of the various pathogens;
* Develop clinical guidance documents and offer clinical recommendations to policy makers on the basis of evidence obtained;
* Understand the broader epidemiology of an emerging infection through studying potential contacts and asymptomatic individuals.

## Structure of the study

Research settings will vary in terms of clinical infrastructure, resources and capacity. In order to allow for a resource-appropriate implementation of the protocol, 4 tiers have been created. Each Site Investigator is able to choose which tier they can operate at e.g. data and/or specimen collection may not be possible in certain settings.

In all cases, a proportionate case report form (paper CRF or web-based electronic “eCRF”) must be completed.

The tiers are:

* Tier 0 (Clinical data collection only):

**Clinical data** will be collected, but **no** **biological samples** will be obtained for research purposes. The minimum clinical data set will summarise the illness episode and outcome, with the option to collect additional detailed clinical data at frequent intervals, according to local resources/needs.

* Tier 1 (Single biological sample):

**Clinical samples** will be collected on enrolment day (**Day 1**; ideally at initial presentation to a health care facility). Clinical information will be collected at enrolment and discharge.

* Tier 2 (Serial biological sampling):

**Clinical samples** and data will be collected on enrolment day (**Day 1**; ideally at initial presentation to a health care facility), and then **alternate days** for the first **2 weeks**, then weekly until resolution of illness or discharge from hospital, and again at 3 and 6 months after enrolment.

* Tier 3 (Population pharmacokinetics of antimicrobial/immunomodulatory drugs).

## Further information

For further information on how to implement this research study in your setting, please contact: [ncov@isaric.org](mailto:ncov@isaric.org)

The proposed research is the product of several years of discussion within a group of international experts who were brought together following the 2009 influenza pandemic to plan the global research response to future severe and emerging infections: the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC). ISARIC working group 3 (genomics, pathogenesis and pharmacology) comprised senior clinical scientists from 5 continents working together to promote and harmonise observational research during outbreaks of severe infectious disease (Lancet ID 14(1):8; <https://doi.org/10.1016/S1473-3099(13)70327-X)>.

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## Study flow diagram:

**Inclusion criteria**

* Children and adults with **suspected** or **confirmed** Coronavirus Disease 2019 infection as **main reason for admission** to hospital;
* Written **informed consent** has been obtained from the participant, or parent, or appropriate representative.

**Exclusion criteria**

* Confirmed diagnosis of a pathogen unrelated to the objectives of this study, and no indication, or likelihood of co-infection with a relevant pathogen e.g. COVID-19;
* Refusal by participant, parent or appropriate representative.

**NO**

**Data Collection (Tier 0)**

Proportionate case report form (paper CRF or web-based electronic “eCRF”) to be completed.

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| Section of **CRFs** to be completed at:  • Day 1: **Core form**  • Alternate subsequent days: **Daily form**  • Death/discharge: **Outcome form** | On the day of recruitment, and preferably every 2 days whilst in hospital: CRF data ideally entered using the **REDCap platform** |

**Depending on local resources, additional participation in any of the following activities:**

**OR**

**OR**

Tier 1:

Single/Limited Biological Sampling

Tier 2:

Serial Biological Sampling

Tier 3:

Population Pharmacokinetics of antimicrobials & immune modulators

Day 5; Plus weekly (until 100 days); Plus Day 7; Plus Day 11: \*Serial biological samples, including additional pathogen samples on days 7 & 11)

Day 1: Early recruitment samples

Days 3 and 9: \*Serial biological samples, including pathogen samples **AND** blood sample at 3 and 6 months post recruitment

\*Serial sampling will stop when acute illness resolves, or a patient is discharged from hospital.