**ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections COVID-19 Research Response Trial**

ISARIC CCP Version 3.2 (SMHS Version 6.2 02 SEPTEMBER 2020)

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Updates include from ISARIC Covid-19 Follow Up Protocol Version 1.0 (03 AUGUST 2020)

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# Background and Objectives

## Purpose of the Study

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

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

## Background Information

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

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

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

## Target Audience of this Document

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

## Source of this Protocol

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

## Primary Objectives

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

* + - Describe the clinical features of the illness or syndrome.
    - 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 this document: stratified recruitment according to local resource.

The study will be conducted at across Western Australia with the coordinating site being South Metropolitan Health Service (SMHS). It is appreciated that settings will vary in terms of clinical infrastructure, resources and capacity. Distinction is made to allow for a resource-appropriate implementation of the protocol, and it is understood that data and/or specimen collection may be limited in certain settings. Observational analyses will be stratified according to available samples and data.

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

Tiers included in this protocol 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 (Audit, Cohort, Observational and Randomised Controlled Trials)

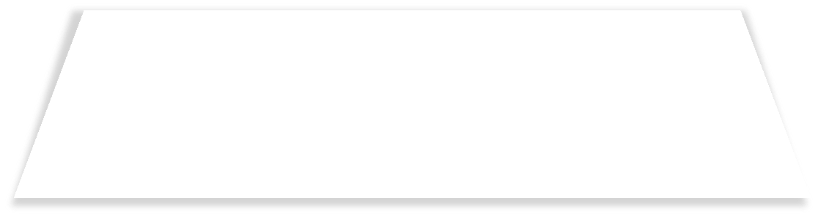
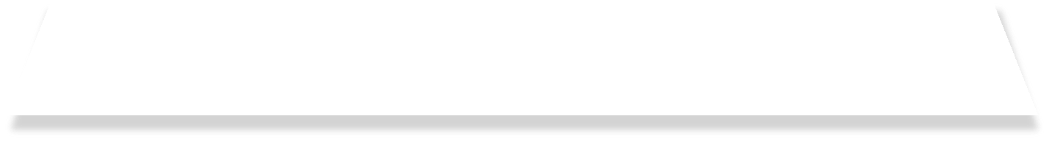
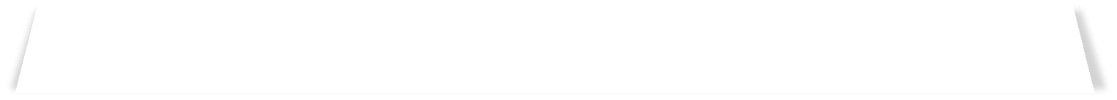
This tier will enable and facilitate the introduction of sister studies. This may include, but not exclusively; audit, cohort and observational studies, and also clinical trials of medication or treatment regimes, either in the pre-hospital setting, emergency department, wards, within the Intensive Care Unit (ICU) environment and after patient discharge.

Eligibility to this tier will be determined by the treating clinical team and study team. Consent to any clinical trial(s) within this tier will be via distinct consent forms/information sheets. However, the objective to incorporate this tier is to ensure a unified, coordinated approach to this pandemic with harmonisation of data and protocols. This will minimise duplication and maximise efficiency of the research response. These trials may be operationally incorporated into a single consent discussion by the study/clinical team.

A list of currently active sister studies within Tier 3 is provided at Appendix A.

Availability of Local Resources

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



Tier 3 Population Pharmacokinetics of antimicrobials & immune modulators

Tier 2 Serial Biological Sampling

Tier 1 Single/Limited Biological Sampling

Tier 0 - Data Collection Only

Number of cases included

## Entry Criteria

This study will enrol eligible adults, pregnant women, and paediatric (newborn to 17 years) patients with confirmed or suspected infection with a pathogen relevant to the study objectives. Confirmed cases and their close contacts are included in order to understand the broader epidemiology of, and variety of host responses to SARS-CoV-2. Close contacts are being included in this study because it is highly likely they were exposed to the virus and they may have had asymptomatic disease. By analysing samples of both confirmed cases and their contacts, it may help us better understand COVID-19 and its variability in symptoms. Recruitment of patients with Day 1 (enrolment) data is the priority. The local study team will dictate whether laboratory confirmation of infection is required prior to enrolment.

Daily follow-up and convalescent visits of patients (Table 1 - Tier 2) should proceed according to local resources.

##### Inclusion criteria

1. Suspected or proven novel Coronavirus (nCoV) infection or Serious Acute Respiratory Infection (SARI) as main reason for presentation to hospital.
2. Individuals in a high-risk category for exposure to nCoV (e.g. health care workers, household and close contacts). Close contact can happen in many ways, but examples include:
   1. living in the same household or household-like setting (for example, a boarding school or hostel)
   2. direct contact with the body fluids or laboratory specimens of a confirmed case
   3. being in the same room or office for two hours or more
   4. face-to-face contact for more than 15 minutes in some other setting such as in a car or a lift or sitting next to them on public transport

##### Exclusion criteria:

1. Confirmed diagnosis of a pathogen unrelated to the objectives of this study and no indication or likelihood of co-infection with a relevant pathogen.
2. Refusal by participant, parent or appropriate representative.
3. Any other reason, as determined by the Lead Investigator or treating clinician, that the patient should not be included in the study, in-line with ICH GCP (E6 R2) requirements and the Australian Code for Responsible Conduct of Research (2018).

# 

# Study Design

This protocol is for a prospective observational cohort study. An optional pathway to clinical trials is included within the design (Tier 3). Inclusion in any interventional trials will require a separate consent process with specific study information sheets.

## Sample Size

This is a descriptive study of a syndrome, which may be caused by a number of different known or poorly understood pathogens. Therefore, the sample size is not prospectively determined. Recruitment of participants will depend on the emergence and spread of the various pathogens and the resources available to the recruitment centres. The sample size will vary for each location but should be as large as feasible and preferably without limit in order to capture as much clinical data as possible early in the outbreak.

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

# Methods

## Identification of Potential Patients

Potential participants will be identified by staff and clinicians from presentation to recruiting sites and through notification to public health agencies. These include people with confirmed SARS-CoV-2 infection notified to the Communicable Disease Directorate at WA Health and their close contacts, primary care, hospitals and ‘COVID’ testing clinics. When resources limit the number of patients enrolled to less than the number of patients presenting, sites should establish procedures to minimise bias in the selection of participants.

Research staff from WA health may be used to collect consent/samples from participants in the study and will be in COVID clinical areas. Study specific training will be provided to all staff receiving consent for the study. These staff will be able to answer some questions related to the study and a clinical contact person will be included in the PICF for any additional questions.

## Approach to Potential Participants

The process of consent will comply with the principles of Good Clinical Practice and with the laws regulating clinical research in the recruiting centre. Participants will only be considered for enrolment if appropriate local infection control and prevention measures are in place and can be maintained.

To support inclusion of participant within an infectious disease pandemic, multiple modalities of consent may be used as appropriate to the clinical situation, to minimise risk, appropriately manage resources (including Personal Protective Equipment), and ensure the safety of staff and participants. When it has been decided that biological sampling can be performed safely and appropriate consent has been obtained, samples taken early may be most useful for identification or evaluation of risk factors for disease progression at a clinically-relevant decision point. Therefore, it is desirable to begin sampling as early as possible during a patient's illness.

Individuals recruited to the ISARIC study will be contacted for follow up samples by a member of the study team in line with the PICF. Potential participants initially identified in the recovery phase from hospital & public health records will initially be contacted by contact tracers employed by Sthe Centre for Disease Control Directorate. They will record whether these individuals are happy to be contacted by researchers regarding various research projects. A list of COVID-19 +ve individuals and their close contacts who consented to being contacted will be transferred to the ISARIC study team. A member of the study team who is a WA Health employee will then contact the potential participants utilising the telephone script and invite the participant to come to a hospital site to provide follow up samples and follow up survey (see appendix D for phone script). Those that consider enrolment will be provided with participant information and a follow up clinic appointment.

Staff will explain the details of the study to the participant or parent/guardian/consultee and allow them time to discuss and ask questions. The staff will review the informed consent form with the participant and endeavour to ensure understanding of the contents, including study procedures, risks, benefits, the right to withdraw and alternatives to participation. The consenting party will be asked to sign and date an informed consent form. This may be performed digitally to minimise infection risk. Where it is not possible for the participant to sign a consent form, due to being critically ill, witnessed verbal consent may be obtained. The witnessed episode of verbal consent should be appropriately documented in the patient’s clinical notes. If verbal consent is obtained, the investigator and witness the should sign the consent form. The patient will be given a copy of the consent form and PICF to take home with them, with instruction that they may contact the study’s clinical contact to withdraw at any time if they change their mind.

In the instance that participants are too unwell to engage with the PICF. For example, within the Emergency Department (ED) and for patients on the ward a verbal consent will assist. On the ward currently, many medical consultations are by telephone or video conferencing. Therefore, consent in this setting by verbal consent would be appropriate. Documentation that verbal consent was obtained will be recorded in the patient notes and the trial site file. A script to support this process is provided at Appendix C. Subsequently, the participant will be contacted at the first available opportunity to discuss the study in detail, full PICF with contact details will be provided and confirm their choice to participate. This process is established and previously approved for previous ED studies within WA.

The children’s recruitment in the study is led by a team of experienced paediatrics researchers and paediatric clinicians who have experience in making this assessment. Furthermore, the capacity of children under 18 years to consent will be assessed by the research team in consultation with the child’s parents/guardians and the child’s treating paediatric teams.

Those children under 18 yrs who have been deemed to have sufficient capacity to consent, will co-sign the‘Paediatrics Parent/Guardian Consent Form’

Children participating in the study are required to re-consent when they become 18 years old. The samples of this cohort will be destroyed if there is no re-consenting

In view of the importance of early samples, participants will be permitted to consent and begin to participate in the study immediately if they wish to do so. Those who prefer more time to consider participation will be approached again after an agreed time, normally one day, to discuss further. As part of Tier 3 patients may be offered details of relevant trials for which they may or may not become eligible and offered potential enrolment to these trials should the inclusion criteria be met.

For patients eligible for any of the clinical trials within Tier 3, specific trial participant information sheets will be provided and discussed, and consent received alongside enrolment in this study. Patients will be encouraged to take as much time as required to make informed decisions regarding participation in any part of the study and any clinical trials.

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

**Waiver of Consent**

*The National Statement on Ethical Conduct in Human Research (2007)* (National Statement (2007) series of guidelines made in accordance with the *National Health and Medical Research Council Act 1992* has been used to satisfy the lead reviewing HREC to waive the requirement for consent.

The waiver of consent requests access to all available deidentified study data, and leftover (surplus) stored biological samples to the central ISARIC/WHO pooled dataset, and to answer additional research questions regarding the epidemiological features of COVID19 patients in WA.

Western Australia (WA) set up the study in the context of a pandemic disease and due to the nature of establishing and conducting the ISARIC/WHO study realised that the early suspected and proven COVID19 patient data is crucial to understanding the full extent of the pandemic and the COVID19 patient journey in WA.

Patients who have been assessed at COVID-19 clinics and ED in addition to the COVID-19 positive patients who were admitted prior to the necessary site approvals are the patients where a *Waiver of Consent* will be applicable to access and include any clinical data (Tier 0 within the CRR protocol) available from the medical and laboratory records. In addition, if available, include any surplus sputum, blood or urine samples if they are likely to be comparable to the prospectively collected samples (i.e. if these were stored appropriately and remain viable).

## Standard of Care

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

## Data Collection and Sampling for Patients

Samples and data will be collected according to the protocol tier approach, available resources and the weight of the patient, to prevent excessive volume sampling for small or elderly adults.

Samples required for clinical management will at all times have priority over samples taken for research tests. Additional blood tests may be required for some participants (those who don’t have clinically indicated need for blood samples). Aliquots or samples for research purposes should never compromise the quality or quantity of samples required for medical management. Wherever practical, taking research samples should be timed to coincide with clinical sampling. The research team will be responsible for sharing the sampling protocol with health care workers supporting patient management in order to minimise disruption to routine care and avoid unnecessary procedures.

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

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

PANDA (paediatrics) subgroup will also be recruiting mildly symptomatic (runny noses) children 5-year of age and under (classified under suspected COVID-19 category as this could be the only symptom in this age group). These will be recruited from the familes (children or siblings) of the adults/children patients presenting at the hospital or outpatients identified from Day care centres. These participants will serve as ‘controls’ for the hospitalized patients. Parental consent will be obtained and only one-time respiratory swabs and rectal swabs will be collected from these participants. No bloods collected.

## Sample and Data Collection Schedules - Tables 1, 2 and 3

Table 1. Potential samples to be obtained.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **REQUIREMENTS** | **Samples** | **Processing/ storage** | **Purpose** | | |
| CONSENT FORM |  | Site file |  | | |
| SINGLE SAMPLE SET TAKEN AT RECRUITMENT | Pathogen samples: Urine (up to 10ml) Stool (up to 10ml) or rectal swab; respiratory samples [combined nose and throat swab, sputum, saliva or AND endotracheal aspirate if intubated, AND, where resources permit, nasopharyngeal aspirate (NPA) OR (if NPA impossible) flocked nose and throat swab]; samples from infected sites/sores. For pregnant women, the following at or near delivery: Vaginal swab,rectal swab, placental swab, breast milk (after delivery) (up to 5ml), stool sample. For newborns, paediatric patients or pregnant women, Guthrie card (blood spot) may be collected.  For all patients: Also store any residual from samples taken for clinical care. | Aliquot stored at -80°C\* | Pathogen studies to reveal changes in pathogen during infection and during spread between individuals, detect development of resistance and recovery after illness. | | |
| Blood sample in serum (clotted) tube (patients > 40kg only) | Centrifuge 1500g for 10mins. Serum (3 aliquots -80°C\*) | Test for mediators and potential biomarkers | | |
| Serology to detect antibodies | development | of |
| Blood sample in EDTA/Heparin tube | Centrifuge 1500g for 10mins at 4°C.  Plasma (3 aliquots -80°C\*) | Test for mediators, potential biomarkers Test for drug levels. | metabolites | and |
| Extract RNA/DNA from causative pathogen and other circulating pathogens. | | |
| Cell fraction (1 aliquot -80°C\*) | Extract host DNA for genomic studies | | |
| Extract RNA/DNA from causative pathogen and other circulating pathogens; leftover cellular fractions from research or clinical samples can be used for PBMC isolation if feasible. | | |
| Blood sample in blood RNA tube (e.g. TempusTM or PAXgene®) | Freeze at -20°C; transfer to -80°C after 24h where possible | Microarray and CAGE analysis of host immune cell transcriptome | | |
| Cerebrospinal fluid sample (if suspected CNS disease) | 3 aliquots stored at -80°C\* | Extract RNA/DNA from causative pathogens and other circulating pathogens for | | |
|  |  |  |  | | |
|  | If after recruitment a lumbar puncture is clinically indicated, an additional sample of up to 5mls will be collected in a universal sterile tube, provided it is deemed appropriate by the supervising clinician.  Any residual CSF from samples taken as part of routine clinical care will be collected and stored if available. |  | molecular testing, genomic studies and virus isolation | | |
| Perform serological testing for pathogen- specific antibodies | | |
| Test for mediators, metabolites and potential biomarkers | | |
| CASE REPORT FORM | Complete CORE CRF or WHO NATURAL HISTORY PROTOCOL  (depending on local resources)  For VHFs collect any amount of clinical data e.g. <50 cases. | Site file | Clinical data | | |

|  |  |  |  |
| --- | --- | --- | --- |
| SERIAL SAMPLES THROUGHOUT ACUTE ILLNESS, CONVALESCENT SAMPLES WHERE POSSIBLE | Pathogen samples: Urine (up to 10ml) Stool (up to 10ml) or rectal swab; respiratory samples [combined nose and throat swab, sputum, saliva orendotracheal aspirate if intubated, AND, where resources permit, nasopharyngeal aspirate (NPA) OR (if NPA impossible) flocked nose and throat swab; samples from infected sites/sores. For pregnant women, the following at or near delivery: Vaginal swab,rectal swab, placental swab, breast milk (after delivery) (up to 5ml), stool sample  For all patients: Also store any residual from samples taken for clinical care. | Freeze at -80°C | Pathogen studies to reveal changes in pathogen during infection and during spread between individuals, detect development of resistance and recovery after illness.. |
| Blood sample in serum (clotted) tube (patients > 40kg only) | Centrifuge 1500g for 10mins. Serum (3 aliquots -80°C\*) | Test for mediators and potential biomarkers |
| Serology to detect development of antibodies |
| Blood sample in EDTA/Heparin | Centrifuge 1500g for 10mins at 4°C.  Plasma (3 aliquots -80°C\*) Cell fraction (1 aliquot -80°C\*) | Test for mediators, metabolites, and potential biomarkers  Test for drug levels. |
| Serology to detect development of antibodies |
| Extract RNA/DNA from causative pathogen and other circulating pathogens. |
| Cell fraction (1 aliquot -80°C\*) | Extract RNA/DNA from causative pathogen and other circulating pathogens; leftover cellular fractions from research or clinical samples can be used for PBMC isolation if feasible. |
| Blood sample in blood RNA tube | Freeze at -20°C; transfer to -80 after 24h where possible | Microarray and CAGE analysis of host immune cell transcriptome |
| Blood Sample in Mononuclear Cell Preparation tube (CPT) | Centrifugation and separation and storage of plasma at -80°C Separation and cryobanking of peripheral blood mononuclear cells; cells from 4x 10ml CPT stored at -80°C | Development of international serum standards. Perform functional cellular immunological studies including T cell stimulation assays; identification of virus specific T and B cells. Generation of monoclonal antibodies for research diagnostic and potentially therapeutic uses. |
| Oral fluid (saliva) sampling with convalescent sample sets | Determination of IgG and IgA. | Non-invasive determination of humoral immune response |
| Cerebrospinal fluid sample (if suspected CNS disease)  If after recruitment a lumbar puncture is clinically indicated, an additional sample of up to 5mls will be collected in a universal sterile tube, provided it is deemed appropriate by the supervising clinician. | 3 aliquots stored at -80°C\* | Extract RNA/DNA from causative pathogens and other circulating pathogens for molecular testing, genomic studies and virus isolation |
| Perform serological testing for pathogen- specific antibodies |
|  | Any residual CSF from samples taken as part of routine clinical care will be collected and stored if available. |  | Test for mediators, metabolites and potential biomarkers |
| SERIAL CLINICAL DATA | Complete ISARIC DAILY RECORD FORM | Site file | Clinical data |
| ADDITIONAL SAMPLES FOR POPULATION PHARMACOKINETICS STUDIES | Blood sample in EDTA or fluoride oxalate tubes | Centrifuge 1500g for 10mins at 4°C.  Plasma (2 aliquots -80°C\*) | Test for drug levels. Store aliquot for other studies. |
| FOLLOW UP SURVEY | Complete follow up survey from ISARIC COVID-19 follow up study | Site file | Short questionnaire to assess risk factors of long term physical and psychosocial consequences of COVID-19 and immune response over time. |

\*freeze at -80°C where possible, or at least at -20°C. #Detailed pathogen analysis will be organised by local authorities, clinicians or reference laboratory.

#### Table 2. Sampling pattern - Inpatient Recruitment

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Serial samples. | | | | | | | | | | | | | | |  |
|  | Recruitment | Week 1 | | | | | | Week 2 | | | | | | |  | Further samples | Convalescent samples |
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | Weekly until max 100  days | Taken after discharge |
| Volume to be adjusted for  <40kg | R |  | S |  | S |  | S |  | S |  | S |  | S |  | S | S | C |
| Sample priority | 1 |  | 2 |  | 5 |  | 7 |  | 3 |  | 8 |  |  |  |  | 6 | 4 |

R = recruitment samples. S = serial samples including pathogen samples; P = research pathogen samples only; C

= convalescent samples (see Table 3). In the event that local resource limitations require sampling frequency to decrease, samples will be prioritised as shown (1=highest priority). Serial sampling will stop when acute illness resolves, or a patient is discharged from hospital: next samples taken will be convalescent samples, taken after discharge.

## Enrolment Procedures for Patients

Patients who meet the inclusion/exclusion criteria and who have given informed consent to participate directly, will be enrolled to the study.

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

At enrolment, sites with available resources will:

1. Separate and store an aliquot of all routine clinical samples taken at baseline/presentation including (as indicated) blood, cerebrospinal fluid (if CNS disease), infected sites/sores, sputum, respiratory tract specimens, urine and stool or rectal swab. Any research pathogen samples which have not been taken for clinical care will be collected.
2. Take a blood sample (according to applicable sampling schedule).
3. The Smell Identification TestTM (UPSIT): indication of smell loss (anosmia; mild, moderate, or severe). Self administered in 10-15 minutes, comprises 4 booklets, each containing 10 microencapsulated (scratch and sniff) odours.

The day of initial sample collection will be counted as Day 1. All study days will be counted from this point forward. Clinical information will also be collected on discharge (for patients admitted to the hospital).

## Case Report Form and Patient Numbers

Case Report Forms (CRFs) completed after site registration will be stored in SHMS. Coordination will be Nationally and internationally as part of the ISARIC global response <https://isaric.tghn.org/>

Patient numbers consist of a 3-digit site code and a 4-digit patient number. Local investigators should be assigned patient numbers sequentially for each site beginning with 0001. In the case of a single site, recruiting patients on different wards, or where it is otherwise difficult to assign sequential numbers, it is acceptable to assign numbers in blocks. E.g. Outpatient ward will assign numbers from 0001 onwards. In-patient ward will assign numbers from 5001 onwards. The patient identification code is entered at the top of each and every sheet. For settings or circumstances in which resources are constrained, an abbreviated core case report form (Rapid CRF) is provided.

## Follow-Up Procedures for Patients

Follow-up procedures will be conducted in line with the ISARIC Follow-up Study Protocol. Follow-up procedures (e.g. serial sampling) will be undertaken only when resources allow according to Tier 2 sampling outlines in Table 1. Follow-up procedures will only be undertaken if appropriate biological safety measures can be maintained. Sites unable to perform daily follow-up as described below may reduce the frequency of follow-up procedures or exclude follow-up if necessary.

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

##### Procedures for serial sampling as shown in table 2

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

##### Procedures for pathogen-only serial sampling as shown in table 2

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

Once acute illness is resolved, or once patients are discharged from hospital, intensive serial sampling will discontinue. Patients may be asked to return for a convalescent visit and blood sample at 1, 3, 6, 12, 18 and 24 months post recruitment. For participants recruited in the recovery phase (including close contacts) the timing of these visits will be scheduled from the onset of illness or exposure.

Patients will also be contacted by study team following discharge from hospital/clinic for an optional follow-up survey based on ISARIC Follow-up Study Protocol. This short survey assesses the risk factors for long-term physical and psychosocial consequences of COVID-19 and immune response over time. Patients may be asked to perform this survey every 3 to 6 months for a maximum of 3 years after post-discharge. This survey can be collected either through telephone or paper form.

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

Any additional sampling within the Tier 3 clinical trials will be according to individual trial protocols.

**Follow up contact with participants**

Following discharge from hospital/clinic, the study team may contact the participant to request further information or samples regarding any care they received or health changes after discharge, or to invite the participation to take part in future research studies (pending relevant ethical approval for those studies). Any participation in further research studies is entirely voluntary.

## Withdrawal of Patients

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

Patient autonomy to withdraw from the study at any time must be respected. Patients can request to have their data and/or samples removed from the dataset or destroyed at any time.

# Specimens and Laboratory Analysis

## Specimen Sampling, Storage Procedures and Transport

Appropriate selection and timely collection of high-quality specimens, proper storage procedures and comprehensive diagnostic testing will ensure the quality of data. Local hospital protocols will be used to collect and handle specimens. Guidance on the collection of specimens from patients with emerging infections can be found on the WHO website.

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

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

All samples collected must be labelled according to local hospital policy with appropriate identification (full patient identifiers) and hazard labelling and ideally marked as research samples with a solvent resistant marker. Samples will be processed as per the laboratory manuals and SOPs for the study. Testing that cannot be done in country may be exported. Samples sent to laboratories other than those listed in the Protocol and Material Transfer Agreement will be anonymised with unique coded identifiers to protect the identity of the patient.

National guidance must be adhered to for the transport of specimens.

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

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

Additional urine samples will be collected but the testing protocol for this has not yet been finalised.

## Sample Processing

Samples will only be processed if authorised biological containment and laboratory facilities appropriate to the relevant pathogen are available, such as within the pathology,hospital or university template (e.g. the Perkins North and South Buildings or UWA sites)

## Use of Stored Samples

Samples will be stored in a de-identified manner at the University of Western Australia. Access to samples for additional analyses will be governed by a committee comprising the clinical lead investigator and scientific investigators for this study (Scientific Committee). Linked anonymised data generated during the course of these studies will be stored at the secure University of Western Australia data repository may be shared between investigators. Each local site will also hold their own data.

Where possible and within the constraints of international law and specific requirements of local ethical and institutional management approvals, deidentified data will be shared centrally as part of the ISARIC network.

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

## Future Use of Samples

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

Collaborating centres must have appropriate biological safety measures and regulatory approvals in place in order to receive samples.

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

# Medical Management and Safety Reporting

## Medical Management

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

# Data Management

## Data Collection

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

## Data Management

When available, data collected by staff at each site will be submitted electronically to a protected online database. Anonymised data may be entered by study staff in order to minimise the workload on site clinical staff. Quality checks will be built into the data management system and there will be quality control checks of critical data points entered into the CRFs to ensure standardisation and validity of the data collected. Patients' identities will be protected, and their information held securely within the SMHS firewall.

For the Clinical Characterisation Protocol, access to the data entry system will be protected by username and password. Username and password will be assigned during the registration process for individual Site Investigators. All electronic data transfer between study site and database will be username and password protected. Each centre will maintain a trial file including a protocol, ethics approval documentation, and paper CRFs. A participant list will be used in each study site to match identifier codes in the database to individual patients in order to record clinical outcomes and supply any missing data points.

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

With regard to data privacy, a deidentifying study number will be assigned to each study participant. This code will be maintained in a secure REDCap database accessible only to the principal investigator and co-investigators. Others working with the data will only have access to the study number.

The study will be conducted in accordance with the Privacy Act 1988 including guidelines pertaining to section 95. All information will be stored securely at Fiona Stanley Hospital and will only be accessible to people directly involved with the study. Personal data identifying trial patients will be held securely at the recruitment site and the coordinating centre. All trial related documentation would be kept for a minimum of 15 years following trial closure in a secure environment according to regulatory and ethical requirements for each site.

## Data Access and Data Sharing

This study will adhere to the research policies of ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium, www.isaric.org). A fundamental principle of this work is that clinical investigators contributing to research efforts, often in extremely difficult circumstances, must be given full recognition for their efforts and the opportunity to access data and samples. Ownership of any data transferred to the eCRF and centralised database will be retained by the site that contributed it. All analysis of pooled data will be undertaken with the explicit agreement of each site who contributed.

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

## Data Quality

This study will be reviewed by the site Human Research Ethics Committee (HREC) and Research Governance Office (RGO). This project will be conducted in accordance with the submitted protocol and conform to the standards of The National Statement on *Ethical Conduct in Human Research (2007)*, The ***Australian Code for the Responsible Conduct of Research***, 2018 and Good Clinical Practice as well as meeting all legal and applicable regulatory requirements. Informed consent will be sought from each patient following a full discussion of potential benefits, disadvantages and study procedures.

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

* + - A detailed data dictionary will define the data to be collected on the case report form;
    - Quality checks will be built into the data management system and there will be quality checks of critical data points entered into the CRFs to ensure standardisation and validity of the data collected;

Data queries may be generated, depending on resource availability. Any information that is not available for the investigator will not be considered as missing. No assumptions will be made for missing data.

### 6.4.1 Monitoring

The trial investigators and associated institutions will permit trial-related monitoring, audits, and regulatory inspections, providing direct access to source data and study documents. This may include, but is not limited to, review by external sponsors, Human Research Ethics Committees and institutional governance.

The clinical trial sponsor and/or associated institutions may nominate the form of monitoring and auditing and will indicate the times of audit visits to the Chief Investigator and study team. Direct site visits will not be feasible, given the scope of the study.

# Ethical Considerations

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

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

## Regulations, Guidelines and Ethical Review

This study will be conducted in compliance with the principles set out in the Declaration of Helsinki. Where applicable, the principles of Good Clinical Practice (ICH 1996, E6 R2) and other applicable regulations and guidelines will be used to guide procedures and considerations.

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

A Human Research Ethics Committee (HREC) reviews all research in Australia involving humans. The ethical aspects of this research project have been submitted to the HREC of the South Metropolitan Health Service, Fiona Stanley Hospital. This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

To help participants decide whether or not to be part of the study, a member of the research team (CPI (delegate or Research practitioner) will explain the details of the study to the participant. The allocated member of the study team will also provide the participant information and consent form and explain details about the study such as its purpose, duration, required procedures, risks and potential benefits. Participants will have the opportunity to ask about anything that is not clear, or they do not understand. Participants can take their time including time to talk it over with their family, friends or own doctor before deciding whether to take part.

Participants will then decide whether or not to sign the consent document. By signing the consent document (or verbally providing witnessed consent), the participant will be informed that this means they are agreeing to take part in the study and have understood what that will be involved. The allocated member of the study team will explain that the consent document is not a contract, and they may withdraw from the study at any time (and if they do withdraw from the study, the relationship between them and their doctor will not be affected).

The allocated member of the study team will also explain if there are any changes to the study or to the protocol, they will be kept informed and they may be asked to give their consent again before proceeding with the study.

## Informed Consent

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

Separate information and consent forms are provided for pregnant women and newborns, and paediatric patients and their parents/guardians.

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

## Alternatives to Participation and Withdrawal

Prospective participants are freely able to decline participation in this study or to withdraw from participation at any point without suffering any implied or explicit disadvantage. All patients will be treated according to standard practice regardless of if they participate. If patients withdraw, they can request to have their data and samples removed/destroyed.

## Risks to Participants

##### Inconvenience.

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

##### Phlebotomy.

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

Additional blood maybe taken during clinical blood draws, and in this case no additional blood draws will be required. Left over samples will also be utilised.

##### Discomfort of respiratory swabs.

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

##### Discomfort of lumbar puncture

##### Collection of cerebrospinal fluid with lumbar puncture will only be performed if clinically indicated, as decided by the responsible physician. Clinical investigations are the priority, with any remaining sample collected for use in research. Guidance on the safe recommended daily total volume of CSF to take is provided in table 3. Lumbar puncture can be associated with discomfort at the site of needle insertion, headache, and rarely bleeding or infection.

##### Incidental findings in genetic testing.

This study includes genetic testing to identify host genetic variants associated with disease progression or severity.

There is a very small chance that these tests may result in the incidental discovery of information that is relevant to the participant's health. Since the samples will be analysed anonymously in batches, and generally in non-clinical laboratories with investigational techniques, we will not attempt to identify and inform participants of any results from genetic tests. If we were to do so, there would be a considerable risk of accidental harm in the form of unnecessary anxiety and distress.

##### Specific risks for VHF patients

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

## Benefits to Participants

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

## Participation in Other Research Studies / Co-enrolment

Particularly in the case of emerging infections, it is likely that other research projects, including clinical trials, will also recruit participants in this study. In fact, it is important that they do so, and great effort has been expended to ensure that this observational study is compatible with, and complementary to, other possible research projects. This has been facilitated within Tier 3 of this protocol, with description of ‘sister’ studies where data sets can be shared.

## Confidentiality

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

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

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

It is important that data generated now is not destroyed unnecessarily, since they will be of considerable potential value to future generations faced with similar outbreaks of infectious disease. Electronic data and electronic copies of paper documents will be stored for at least 15 years.

## Custody of Data and Samples

Custody of site data will remain with the responsible Principal Investigator at the site. Samples will be shipped (depending upon pathogen of interest) to a reference laboratory for analysis as approved by the appropriate ethics/institutional review committee.

Any residual sample will remain in the custody of the site until use can be decided upon.

## Additional Ethical Considerations

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

**Perceived coercion because of individual responsibilities to society, and the implications of this research for public health.** We are sensitive to the fact that some patients or their representatives may feel under an unusually strong moral obligation to participate given the nature of this research and the wide, and often inaccurate, publicity surrounding emerging infections. In view of this, we have tried to make both the potential benefits and limitations of this observational study clear in the information sheet. In the informed consent form we also stress that participation is entirely voluntary and there is no penalty of any kind for declining to join the study.

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

**Risks to clinical and research staff treating the participants.** Staff who enrol, examine and take samples from study patients are at risk of infection. Care of study participants will require increased sampling and contact frequency added to normally heavy clinical workloads.

All staff must be trained in recognised infection control measures and have ready access to appropriate personal protective equipment. In collaboration with the public health authorities, there will be on-going communication with hospital staff to ensure the appropriate training is given, to support the work and to ensure that there is no excess burden on the health system. Where appropriate, dedicated research staff will be available to support the study activities.

## Scientific and Peer Review and Publication

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that individual participant data cannot be identified (i.e. study number 001).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.

# References

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# Appendices

**Appendix A-Currently active ‘sister’ trials within Tier 3**

**Appendix B-Poster for display in clinical areas**

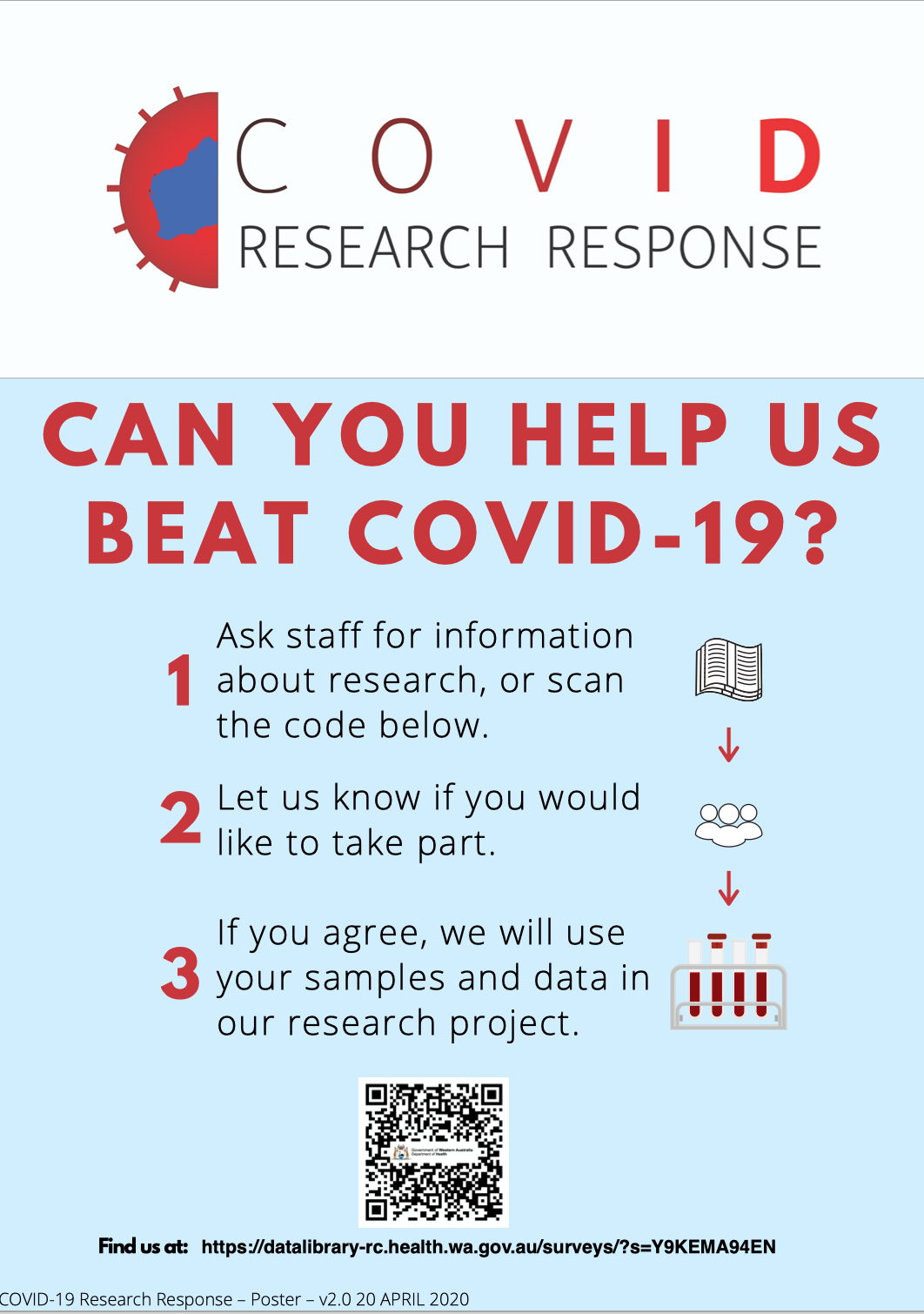
**Appendix C-Script to support verbal consent process**

**Appendix D-Phone script invitation to attend in recovery phase**

##### Appendix A – Current ‘sister’ trials within Tier 3

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study Name | REC # | Lead Investigator | Location | Description |
| A Randomised, Embedded, Multi- factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP). | TBC | Dr Ed Litton | FSH | The broad objective of this REMAP is, over time, to determine and continuously update the optimal set of treatment for community-acquired pneumonia. REMAP-CAP uses a novel and innovative adaptive trial design to evaluate a number of treatment options simultaneously and efficiently. This design is able to adapt in the event of pandemics and increases the likelihood that patients will receive the treatment that is most likely to be effective for them. |
| Life AfTER covid-19 (LATER-19): a prospective, longitudinal, cohort study of symptoms, physical function and psychological outcomes | RGS4040 | Assoc Prof Dale Edgar | FSH, RPH, SCGH | Those affected by COVID-19 infection may be at high risk of increased symptoms that will result in reduced physical fitness and psychological function, both of which will impact their quality of life and ability to return to normal life afterwards.  The aims of LATER-19 are to: (i) document symptoms and the physical and psychological recovery of patients with COVID-19 during the acute phase of their disease and up to 12 months following treatment; and (ii) identify which factors are related to delayed or poor recovery. |
| Australasian COVID-19 Trial (ASCOT) | TBC | Dr Owen Robinson (FSH). Coordinating PIs: A/Professor Steven Tong, A/Professor Justin Denholm, Professor Joshua Davis  Sponsor: Melbourne Health | FSH | A multi-centre clinical trial to assess clinical, virological and immunological outcomes in patients with SARS-CoV-2 infection (COVID-19) treated with lopinavir/ritonavir and/or hydroxychloroquine compared to standard of care). Protocol number: 62646 |
| Western Australian COVID 19 Immunity Collaboration (WACIC) | TBC | Prof Dominic Mallon | WA Health (Public Health, PathWest, SMHS, NMHS, CAHS, EMHS) | A prospective observational cohort study of immune responses to SARS CoV 2 in subjects with documented infection and their close contacts |

**Appendix B-Poster for display in clinical areas**

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**Appendix C- Script to support verbal consent process**

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*Patient label goes here*

***Prospective Informed Consent Script***

***COVID-19 Research Response (CRR)***

***V2.0 22 May2020***

* You have come to the hospital and are suspected or diagnosed with the COVID-19 virus.
* We are collecting data and samples from patients to enable researchers and scientists to better understand the disease and treatments that may help you or others. We would like to invite you to participate.
* If you agree, we will collect information about your illness while you are in hospital and take extra blood tests. Ideally at the same time as you are having tests for normal clinical reasons
* Some discomfort may be involved when extra blood samples are taken. There are no direct benefits to you by participating other than contributing to the global understanding of how this virus works.
* The samples will be used by researchers and scientists to explore markers associated with this illness and look for information of how the disease effects normal body functions as well as responses to treatment. These tests may include chemical ‘phenomics’ and genetics.
* The blood samples and information we collect will be kept for **at least 15 years** and only be **used to investigate the effects of COVID-19**. Your information will be held in strict confidence. When the outcomes of this study are shared no individual participants will be identifiable. De-identified information may be shared with the national and international centres involved in this pandemic.
* Participation in this study is optional and will not change the treatment you receive. You will be able to withdraw from the study at any time. The study has been approved by the SMHS Ethics Committee.

**Do you have any questions?** *Answer all questions and give the participant time to consider.*

*Once you are well enough, a member of the research team will be in touch with you to discuss the study in more detail and confirm your choice to participate.*

**Would you like to participate?**

***Circle one: Patient agreed to participate OR Patient did not agree to participate***

Name:

Signature:

Date:

*Please file a copy of the completed form in participant’s medical record.*

**Appendix D– Phone script invitation to attend in recovery phase**

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***Recovery Invitation***

***COVID-19 Research Response (CRR)***

***V1.0 10 June 2020***

Hello, my name is [researchers name] and I am calling on behalf on the COVID research response team based at [name of hospital or Public Health unit].

We are collecting information and samples from people who were exposed to COVID-19 or in close contact with a known COVID-19 patient, to enable researchers and scientists to explore how the disease affects normal body functions and to understand the immune response.

If you are able to help us, we will arrange a clinic appointment where we will collect information about your illness, your recovery and physical function and take extra blood and saliva tests. Taking part is optional and your decision will not affect any ongoing treatment you may be receiving.

We would like to monitor your progress every 6 months for the next 2 years if possible to understand how the immunity changes over time, but even if you can visit us once now that would be very helpful.

**Do you have any questions?** *Answer all questions and give the participant time to consider.*

More information is available [online/email/post], a member of the research team will be in touch with you to arrange a follow up clinic appointment.