ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections

Ethics Ref: 13/SC/0149 (Oxford C Research Ethics Committee)

Date and Version No: 25 August 2014 v7.

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Sponsor: University of Oxford, Oxford.

Funder: Set up: Li Ka Shing Global Health Foundation, Core: MRC, Wellcome Trust

Name and Title	Signature	Date

1. Background and Objectives

1.1 Purpose of the Document

This document is a standardized protocol for the rapid, coordinated clinical investigation of severe or potentially severe acute infections. This includes pathogens of public health interest. Patients with a spectrum of emerging and unknown pathogens will be enrolled. This protocol has been designed to maximize the likelihood that data and biological samples are prospectively and systematically collected and shared rapidly in a format that can be easily aggregated, tabulated and analysed across many different settings globally. The protocol is designed to have some level of flexibility in order to ensure the broadest acceptance and has been initiated in response to the recent cases of novel coronavirus (nCoV) in 2012-2013, Influenza H7N9 in 2013 and viral haemorrhagic fever (Ebolavirus) in 2014. Information will be circulated via the CLRN each to clarify the eligibility criteria.

1.2 Background Information

Infectious disease is the single biggest cause of death worldwide. New infectious agents, such as the SARS coronavirus, MERS coronavirus, novel influenza viruses, and viruses causing viral haemorrhagic fever require new investigations 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 will require sampling that will not immediately benefit the participants. It will also require analysis of the host genome, which may reveal other information about disease susceptibility or other aspects of health status.

This study, while not a study of a medicine, does involve additional procedures (some minimally invasive), the retention of genetic material, collection of personal data and additional follow up. The ISARIC consortium are keen that this protocol serve as a generic template for adoption of this study in other countries and similar studies in the future. ISARIC also intend that this protocol and supporting documents can be used to support or run alongside future intervention studies. For these reasons we aim to fulfil the standards of consent required by Medicines for Human Use (Clinical Trials) Regulations 2004 and NHS NPSA NRES Guidance for Researchers & Reviewers (May 2009).

This protocol as now amended is designed to enrol patients with proven infection by Influenza A/H5N1, or A/H7N9 or MERS-CoV, or viral haemorrhagic fever.

Influenza A/H5N1.

Since 1997, strain A/H5N1 of highly pathogenic avian influenza (HPAI) has emerged as a global zoonosis, and has caused severe sporadic respiratory illness in humans that is associated with an extremely high mortality rate. As of June 2014, the total number of human A(H5N1) cases reported to WHO worldwide is 667; of these 393 have died resulting in a case fatality rate of just under 60%. http://www.who.int/influenza/human_animal_interface/HAI_Risk_Assessment/en/(accessed 06 August 2014).

Middle East Respiratory Syndrome coronavirus (MERS-CoV).

In September 2012 a novel coronavirus, MERS-CoV, was identified in a patient who died of severe acute respiratory syndrome in June 2012. Since then, large outbreaks have occurred in the Middle East and imported cases have been seen in many countries. As of 23 July 2014, the World Health Organization has been informed of 837 confirmed cases, including 291 deaths. http://who.int/csr/don/2014_07_23_mers/en/ (last accessed 06 August 2014). .

Influenza A/H7N9.

Two waves of human infection with novel avian influenza A(H7N9) have occurred since March 2013. As of 27 June 2014, 450 laboratory confirmed cases of human infection with influenza A(H7N9) have been reported to WHO. One hundred and sixty-five patients (37%) have died. The majority of cases presented with respiratory tract infection with progression to severe pneumonia and breathing difficulties. The vast majority of cases have been in mainland China.

Emerging Pathogens causing Severe Acute Respiratory Illness.

Novel pathogens, new strains of existing pathogens, and re-emergence of known dangerous pathogens are a frequent threat to global health. A coordinated clinical research response is critical to identify and describe pathogen and host characteristics to inform a clinical and public health response.

Emerging or re-emerging pathogens causing viral haemorrhagic fever.

Outbreaks of viral haemorrhagic fever (VHF) occur sporadically in Africa, Asia, Europe and South America. The scale and impact of VHF outbreaks vary, but a common feature is for infection to cause significant morbidity and mortality and considerable societal disruption including the provision of healthcare. Global travel means that cases of infection are exported to other countries, with the potential to cause outbreaks in outside endemic areas. Important VHF pathogens include Ebola virus, Lassa virus, Crimean-Congo haemorrhagic fever virus, and Marburg virus. In 2014, an unprecedented outbreak of Ebola virus has occurred in humans in West Africa, with large numbers of cases identified across multiple sites in Guinea, Liberia, Sierra Leone, and Nigeria.

1.3 Target Audience of this Document

This document is of primary interest to clinicians (including emergency and critical care providers) and others engaged in identification, triage and treatment of patients with severe acute or potentially severe infections due to the pathogens of interest. Any individuals or members of research units/networks are invited to use this document to facilitate their own studies and contribute data to the centralized database.

1.4 Source of this Protocol

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

1.5 Primary Objectives

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

- Describe the clinical features of the illness or syndrome
- 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 and other samples.

- Characterise, where appropriate and feasible, the host responses to infection and therapy over time, including innate and acquired immune responses, circulating levels of immune signalling molecules and gene expression profiling in peripheral blood.
- Identify host genetic variants associated with disease progression or severity
- Understand transmissibility and the probabilities of different clinical outcomes following exposure and infection

1.6 Secondary Objectives

Secondary objectives are to collect evidence in order to:

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

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

The study will be conducted at multiple sites (to be determined by the spread of disease and availability of resources). It is appreciated that settings will vary in terms of clinical infrastructure, resources and capacity. Distinction is made to allow for a resource appropriate implementation of the protocol and it is understood that data and/or specimen collection may be limited in certain settings. Participating centres, in many cases working in extremely challenging circumstances, will follow this protocol as much as possible within their means. Observational analyses will be stratified according to available samples and data.

In all cases, a case report form (paper CRF or web-based electronic "eCRF") will be completed. In the initial stages of a global public health emergency, outside this research study, the WHO Natural History case report forms will be completed for audit and public health purposes. This extensive case report form contains all of the information needed for this study.

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 (Population pharmacokinetics** of antimicrobial/immunomodulatory drugs)

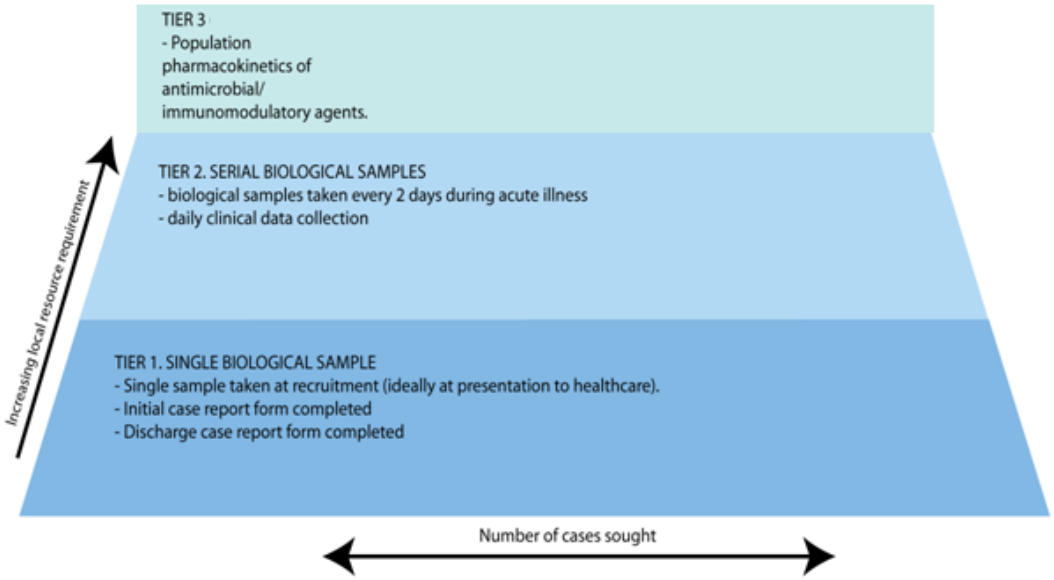

Figure 1. Tiered approach to recruitment in settings with different resources. This information is included to demonstrate the integration of this study with other studies following the same approach in other parts of the world.

As an outbreak progresses, and more cases occur, it is anticipated that both the research priorities and the local resource availability will change. It is therefore likely that, within a given institution, cases recruited later in an outbreak will be sampled at a lower intensity (see sample priorities, table 2) and may be recruited to a lower tier of the study.

1.8 Entry Criteria

This study will enrol eligible patients (children and adults) with confirmed infection with a pathogen relevant to the study objectives. Recruitment of patients with Day 1 (enrolment) data is the priority.

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

Inclusion criteria for SARI patients:

- Acute respiratory illness patients of all ages with a history of fever or measured fever of >38°C and at least one respiratory symptom
- AND suspected or confirmed infection with a respiratory pathogen relevant to the objectives of this protocol
- AND admitted to a healthcare facility

Inclusion criteria for VHF patients:

- Sudden onset high fever and known contact with a person with suspected or confirmed VHF
- OR sudden onset of fever with at least three of the following symptoms: headache; anorexia; lethargy; aching muscles or joints; breathing difficulties; vomiting; diarrhoea; stomach pain; dysphagia; hiccups
- AND suspected or confirmed infection with a VHF pathogen relevant to the objectives of this protocol
- AND admitted to a healthcare facility

Exclusion criteria for all patients:

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

2. Study Design

This protocol is for a prospective observational cohort study.

2.1 Sample Size

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

3. Methods

3.1 Identification of Potential Patients

Approval of the responsible ethics committee and institutional authority will be obtained before patients are recruited at any site. In the UK MREC approval has been given (Oxford C Research Ethics Committee 13/SC/0149) and local R&D approvals are being sought. Potential participants will be identified through hospital workers upon presentation at recruiting sites and through public health agencies. When resources limit the number of patients enrolled to less than the number of patients presenting, sites will establish procedures to minimize bias in the selection of participants.

3.2 Approach to Potential Participants

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

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

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

In view of the importance of early samples, participants or their parent/guardian/consultee will be permitted to consent and begin to participate in the study immediately if they wish to do so. Those

who prefer more time to consider participation will be approached again after an agreed time, normally one day, to discuss further.

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

3.3 Standard of Care

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

3.4 Data Collection and Sampling for Patients

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

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

Some samples should be processed and stored at -80°C. 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 ebolavirus, the biological sampling will at times be limited to extra volumes of blood taken at times to coincide when blood is being taken for clinical purposes and then only at the discretion of the clinical team.

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

Table 1. Proposed 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, AND endotracheal aspirate if intubated, AND, where resources permit, Nasopharyngeal aspirate (NPA) OR (if NPA impossible) flocked nose and throat swab]; samples from infected sites/sores. Also store any residual from samples taken for clinical care.	Aliquot stored at -80°C*	Pathogen studies to reveal changes in pathogen during infection and during spread between individuals, detect development of resistance. #
	Blood sample in serum (clotted) tube (patients > 40kg only)	Serum (3 aliquots -80°C*)	Test for mediators and potential biomarkers
			Serology to detect development of antibodies
	Blood sample in EDTA tube	Plasma (3 aliquots -80°C*)	Test for mediators, metabolites and potential biomarkers Test for drug levels.
			Extract RNA/DNA from causative pathogen and other circulating pathogens.
		Cell fraction (1 aliquot -80°C*)	Extract host DNA for genomic studies
			Extract RNA/DNA from causative pathogen and other circulating pathogens.
	Blood sample in blood RNA tube	Freeze at -20°C; transfer to -80°C after 24h where possible	Microarray and CAGE analysis of host immune cell transcriptome
CASE REPORT FORM	Complete CORE CRF or WHO NATURAL HISTORY PROTOCOL (depending on local resources)	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, AND endotracheal aspirate if intubated, AND, where resources permit, Nasopharyngeal aspirate (NPA) OR (if NPA impossible) flocked nose and throat swab]; samples from infected sites/sores. Also store any residual from samples taken for clinical care.	Freeze at -80°C	Pathogen studies to reveal changes in pathogen during infection and during spread between individuals, detect development of resistance.
	Blood sample in serum (clotted) tube (patients > 40kg only)	Serum (3 aliquots -80°C*)	Test for mediators and potential biomarkers
			Serology to detect development of antibodies
	Blood sample in EDTA	Plasma (3 aliquots -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.
	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
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	Plasma (2 aliquots -80°C*)	Test for drug levels. Store aliquot for other studies.

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

Table 2. Sampling pattern - In Patient Recruitment

		Serial samples.														
	Recruitment	Week 1						Week 2								Furth samp
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Week until max 100 days
>40kg	R		S		S		S		S		S					S
20 to 40kg	R		S		S		S		S		S					S
10 to 20kg	R		S		S		S		S		S					S
4 to 10kg	R		S		S		P		S		P					S
>4kg	R		S		S		P		S		P					S
Sample priority	1		2		5		7		3		8					6

R = recruitment samples. S = serial samples including pathogen samples; P = research pathogen s
C = convalescent samples (see Table 3). In the event that local resource limitations require sampl
to decrease, samples will be prioritised as shown (1=highest priority). Serial sampling will stop w
illness resolves or a patient is discharged from hospital: next samples taken will be the blood sam
months and 6 months post recruitment.

Table 3. Samples

Weight	Samples at recruitment (R)	Serial samples (S)	Convalescent samples	Total Volumes
>40kg	9ml (3x3ml) EDTA blood 3ml blood in serum(clotted) tube 3ml blood in blood RNA tube Research pathogen samples	3ml EDTA blood 3ml blood in serum(clotted) tube 3ml blood in blood RNA tube Up to 3 additional 1ml samples in EDTA or fluoride oxalate tubes spread throughout dosing schedule for pharmacokinetic/pharmacodynamic studies. Research pathogen samples	3ml EDTA blood 3ml blood in serum(clotted) tube 3ml blood in blood RNA tube Research pathogen samples	Maximum any (0.38ml/kg) Maximum any (maximum 2.4
20 to 40kg	6ml (3x2ml) EDTA blood 3ml blood in serum(clotted) tube 3ml blood in blood RNA tube Research pathogen samples	1ml EDTA blood 2ml blood in blood RNA tube Up to 3 additional 0.5ml samples in EDTA or fluoride oxalate tubes spread throughout dosing schedule for pharmacokinetic/pharmacodynamic studies. Research pathogen samples	1ml EDTA blood 3ml blood in serum(clotted) tube 2ml blood in blood RNA tube Research pathogen samples	Maximum any (0.6ml/kg) Maximum any (maximum 2.1
10 to 20kg	2ml (2x1ml) EDTA blood 2ml blood in serum(clotted) tube 2ml blood in blood RNA tube Research pathogen samples	1ml EDTA blood 1ml blood in blood RNA tube Up to 3 additional 0.2ml samples in EDTA or fluoride oxalate tubes spread throughout dosing schedule for pharmacokinetic/pharmacodynamic studies. Research pathogen samples	1ml EDTA blood 1ml blood in serum(clotted) tube 1ml blood in blood RNA tube Research pathogen samples	Maximum any (0.6ml/kg) Maximum any (maximum 2.3

4 to 10kg	1ml EDTA blood 1ml blood in serum(clotted) tube ml blood in blood RNA tube Research pathogen samples	1ml EDTA blood Up to 3 additional 0.2ml samples in EDTA or fluoride oxalate tubes spread throughout dosing schedule for pharmacokinetic/pharmacodynamic studies. Research pathogen samples	1ml EDTA blood 1ml blood in serum(clotted) tube Research pathogen samples	Maximum any day: 2ml (0.5ml/kg) Maximum any 4 weeks: 9.4ml (maximum 2.35ml/kg)
< 4kg	0.5ml EDTA blood 0.1ml blood in serum(clotted) tube ml blood in blood RNA tube Research pathogen samples	0.2ml EDTA blood Up to 3 additional 0.1ml samples in EDTA or fluoride oxalate tubes spread throughout dosing schedule for pharmacokinetic/pharmacodynamic studies. Research pathogen samples	0.2ml EDTA blood 0.2ml blood in serum(clotted) tube Research pathogen samples	Maximum any day: 0.8ml (~0.27ml/kg) Maximum any 4 weeks: 2.4ml (maximum 2.4ml/kg)
Research pathogen samples (all patients)	**Pathogen samples taken solely for research purposes:** In all SARI or respiratory infection patients: combined nose and throat swab, otherwise a throat swab or nasopharyngeal swab alone In all intubated patients with SARI or respiratory infection: endotracheal aspirate also where resources permit in a respiratory case:: 1. Nasopharyngeal aspirate (NPA) OR (if NPA impossible) flocked nose and throat swab 2. Urine (up to 10ml in sterile universal container, if available) 3. Rectal swab or stool (up to 10ml in sterile universal container or stool specimen container, if available) 4. samples/swabs from infected sites or sores.			No patient will give more than 0.6ml/kg (>1% blood volume) on any one day, or more than 2.4ml/kg (approx 3% blood volume) in any four week period (MCRN recommendations).
Clinician-requested pathogen samples (all patients)	Where possible, we will obtain an aliquot of any residual and unwanted sample volume from specimens that have been sent by clinicians for pathogen detection, including those obtained before recruitment to the study: urine; stool; respiratory tract samples (NPA, ETA, BAL, sputum, ENT swabs); cerebrospinal fluid.			

3.6 Enrolment Procedures for Patients

Patients who meet the inclusion/exclusion criteria and who have given informed consent to participate directly, or have been consented by a parent/guardian or whose wishes have been declared by a consultee, 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, infected sites/sores, sputum, respiratory tract specimens, urine and stool or rectal swab. Any research pathogen samples which have not been taken for clinical care will be collected.
2. Take a blood sample (0.8 - 15ml dependent on weight).

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

3.7 Case report form and Patient Numbers

Ideally the WHO Natural History Protocol Case Report Form will be used to collect data at, enrolment to this study. The SARI CRF or VHF CRF for this study can be completed after site registration at https://www.cliresdms.org . Patient numbers consist of a 2-digit site code and a 4 digit patient number. You can obtain a site code by registering on the data management system at https://www.cliresdms.org. 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. Please enter the patient identification code at the top of each and every sheet. For settings or circumstances in which resources are constrained, an abbreviated core case report form is provided.

3.8 Follow-Up Procedures for Patients

Follow-up procedures 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 hospitalization and outcome. Some of the samples described below will coincide with clinical management. The number of these will depend on the applicable care guidelines, the treating physician and the health of the patient.

Procedures for serial sampling as shown in table 2: Collection of clinical information, blood sample (volume dependent on weight - see Table 3), 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, sampling will discontinue until the 3 month and 6 month visits. All patients will be asked to return for a convalescent visit and blood sample at 3 months and 6 months post recruitment.

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

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

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

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

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

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

3.9 Withdrawal of Patients

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

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

4. Specimens and Laboratory Analysis

4.1 Specimen Sampling and 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.

Public Health England (PHE) is a co-applicant on this study and has made the following recommendation: The study requires collection of research samples in addition to samples used for clinical and public health management. Well-established hospital protocols may be used to collect samples, however guidance on the collection of samples from SARI patients is also found in the WHO draft document "Collecting, preserving and shipping specimens for the diagnosis of influenza virus infection" (2011).

Guidance on the collection of specimens from VHF patients can be found in the WHO document “Interim infection prevention and control guidance for care of patients with suspected or confirmed Filovirus haemorrhagic fever in health-care settings, with focus on Ebola” (2014).

It is expected that BSL3 SARI pathogens will be sent to PHE Colindale or the local HPRU in Liverpool (University of Liverpool) or London (Imperial College London). It is expected that BSL4 VH pathogen samples will be sent to PHE Porton Down however BSL4 clinical and research capacity has also been commissioned at the Royal Liverpool Hospital and the HPRU in Liverpool University.

In dealing with novel respiratory 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.

Trusts should follow the usual sources of advice regarding laboratory containment of the pathogen. In an emerging infection this may include information from ACDP and PHE, which would support a local, risk assessment and SOP covering the handling of samples from the affected patient. Novel respiratory infections may be classified as requiring BSL3 or BSL4, as is the case for the currently included pathogens, novel coronavirus MERS-CoV, influenza A/H7N9, A/H5N1 and viral hemorrhagic fever ebolavirus. Laboratories planning to participate in the study should consider how they would fulfill a requirement to handle research samples in addition to clinical samples.

All samples collected must be labelled as per hospital procedure with appropriate identification and hazard labelling according to local policy and marked with a freeze-proof ISARIC research label. Samples collected in the household will be labelled with pseudoanonymised patient study codes. Samples will be processed as per the table below. Testing that cannot be done in country will be exported with the permission of the patient/parent/guardian/consultee. Any samples sent to external research laboratories will be anonymised with unique coded identifiers to protect the identity of the patient at the site level at the point of enrolment. When required, national guidance will be adhered to for the transport of specimens.

Standard laboratory information systems (LIMS) will be used for all clinical and research samples. Clinical samples will be labelled with standard hospital information, including the date and sent with the standard lab request forms.

In the UK, Clinical and Research samples will be transported to PHE laboratories at Colindale or Porton Down or the Health Protection Research Units in Liverpool and London using a BSL3 /BSL4 approved courier certified to GCP standards (PDP Couriers http://www.pdpcouriers.com).

Patient submitted on the CRF (SARI or VHF) or eCRF data must be anonymised using the following procedure. Patient numbers consist of a 2-digit site code and a 4 digit patient number. You can obtain a site code by registering on the data management system at https://www.cliresdms.org. Patient numbers should be assigned 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. Please enter the patient identification code at the top of each and every CRF sheet. Patient numbers and full identifiers must be shared with the ISARIC secretariat. Patient identifiers will not be shared with research institutes.

A unique alphanumeric code for patient samples will be given to each patient at PHE laboratories at Colindale or Porton Down or the Health Protection Research Units in Liverpool and London, and the only link between the patient's identifying data and this code will be held securely and shared only with the ISARIC secretariat. The ISARIC secretariat will link patient data numbers with sample identifiers. The ISARIC patient identifiers will not be shared with any party.

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

4.2 Additional Data Collection – Pharmacokinetic/Pharmacodynamics Studies

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

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

4.3 Sample Processing –

Table 5 Sample Initial processing Aliquots Analysis Blood samples (serum) Centrifuge 1500g for 10mins. Supernatant:

Sample	Initial processing	Aliquots	Initial transfer	Further processing	Ultimate use
Blood samples (serum)	Centrifuge 1500g for 10mins.	Supernatant: freeze at -80°C*	Public Health England (PHE) or Health Protection Research Units (HPRU)	PHE or HPRU	Serology
		Supernatant: freeze at -80°C*		Imperial College London	Circulating mediators by multiplex cytokine/chemokine assays
		Supernatant: freeze at -80°C*			
Blood samples (EDTA)	Centrifuge 1500g for 10mins at 4°C.	Supernatant: freeze at -80°C*		PHE or HPRU	Serology
		Supernatant: freeze at -80°C*		Imperial College London	Circulating mediators by multiplex cytokine/chemokine assays
		Supernatant: freeze at -80°C*		Imperial College London	Other studies (eg pharmacokinetics/ pharmacodynamics)
		Cell pellet: freeze at -80°C*		Roslin Institute (DNA extraction)	1mcg: high-throughput genotyping and/or high coverage genome sequencing (Wellcome Trust Sanger Institute) 1mcg: targeted resequencing (Roslin Institute)
Blood samples (fluoride oxalate)	Centrifuge 1500g for 10mins at 4°C.	Supernatant: freeze at -80°C*		Imperial College London	Other studies (eg pharmacokinetics/ pharmacodynamics)
Blood samples (Tempus RNA)	Freeze at -20°C	Where possible, freeze at -80°C* after 24hrs		Wellcome Trust Sanger Institute (RNA extraction)	1mcg: microarray analysis and/or RNA seq analysis (Wellcome Trust Sanger Institute) 1mcg: high-throughput sequencing (CAGE)(Roslin Institute)
Pathogen samples	Aliquots where appropriate	Freeze at -20 or -80 °C*		PHE or HPRU	Pathogen detection, quantification and viral genome sequencing

*freeze at -80°C where possible, or at least at -20°C .

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

laboratories at Colindale or Porton Down or the Health Protection Research Units in Liverpool and London, and later distributed to reference laboratories.

4.4 Use of Stored Samples

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

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

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

Research Plan for samples

This document is a standardized protocol for the rapid, coordinated clinical investigation of any emerging infections causing severe acute illness. The protocol is designed to have some level of flexibility in order to ensure the broadest acceptance and has been initiated in response to the recent cases of novel coronavirus (nCoV) in 2012-2013, Influenza H7N9 in 2013 and viral haemorrhagic fever in 2014. However it is not prescriptive to these pathogens. This protocol has been designed to maximize the likelihood that data and biological samples are prospectively and systematically collected and shared rapidly in a format that can be easily aggregated, tabulated and analysed across many different settings globally. Likewise the research plan is likely to vary to address disease and pathogen specific issues. For the purposes of securing a Material Transfer Agreement in advance of an outbreak, a high level overview of research intentions by research institution is given here.

> Public Health England Laboratories at Colindale (PI Maria Zambon and Meera Chand) Porton Down (Tim Brooks) and the Health Protection Research Units in Liverpool (Calum Semple) and London (Peter Openshaw) will be responsible for the primary processing and storage of samples obtained from patients (with appropriate biological safety measures in place) and pseudoanonymisation of samples prior to forwarding to other research institutions. Studies will include serology, pathogen detection, quantification and viral genome sequencing both for diagnostic, public health and research purposes.
>
> The Centre for Respiratory Infection (CRI) at Imperial College London (PI Peter Openshaw) will quantify soluble immune mediators using multiplex technology, in blood and respiratory tract samples obtained. Cytokine, chemokine and biomarker profiles will be correlated with clinical data and outputs from other laboratories within the study. Additionally, whole blood transcriptomics analyses will be performed to assess patients' gene expression profiles.

Together, these data can be used to help understand pathogenesis, measure biological responses to novel treatments and help identify new therapeutic strategies. CRI will also contribute to the primary processing and storage of samples obtained from patients (with appropriate biological safety measures in place).

The Roslin Institute University of Edinburgh will conduct genotype comparisons of affected individuals with population controls to identify, characterise and confirm genetic associations with susceptibility to infection or severity of infection. Sequence-driven gene expression profiling of whole blood RNA to identify and explore the interaction of host and viral factors during the course of infection.

The Wellcome Trust Sanger Institute laboratory of Virus Genomics, (PI Paul Kellam) will undertake human genome characterisation by DNA and RNA sequencing of the somatic human genome and the variable B cell receptor locus DNA and RNA from samples obtained under this document. We aim to identify human genetic variants that correlate with clinical data and disease pathogenesis data from the participating patients, and correlate these data with sequence variation in the pathogen. We intend to test the function of such genetic variants in relevant biological assays.

Institute of Translational Medicine, University of Liverpool (CI Calum Semple,) will conduct clinical characterisation studies based on clinical features and outcome in collaboration with ISARIC Clinical Coordination team (PI Gail Carson, Laura Merson and Trudie Lang). The University of Liverpool (CI Calum Semple), will if required provide additional capacity to contribute to the primary processing and storage of samples and then quantify soluble immune mediators using multiplex technology, in blood and respiratory tract samples. Pharmacology studies (PI Saye Khoo) if included will be conducted at the University of Liverpool. We will measure drug exposure, and to relate this to patient characteristics (eg disease severity, liver or renal impairment, dialysis, children, pregnancy) and treatment response. Drug levels will be measured in plasma and other relevant samples.

4.5 Future Use of Samples

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

Any database detailing clinical data will only identify participants by a participant number. Participant names or any other identifying details will NOT be included. Data may be used alone or in combination with data from related studies in secondary analyses. The database containing personal identifiers and patient number (i.e. the key) will be held securely and encrypted by the ISARIC secretariat on a University of Oxford server in a digitally distant location unlinked to that containing the clinical data and research data.

5. Medical Management and Safety Reporting

5.1 Medical Management

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

6. Data Management

6.1 Data Collection

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

6.2 Data Management

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

6.3 Data Access

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 centralized database will be retained by the site that contributed it. All analysis of pooled data will be undertaken with the explicit agreement of each site who contributed.

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

7. Ethical Considerations

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

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

7.1 Regulations, Guidelines and Ethical Review

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

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

7.2 Informed Consent

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

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

Parents or guardians of children under the age of 16 will give consent for their child. Study staff obtaining consent will consider the ability of the child to understand the basic principles of the study and will discuss the study with the child in age appropriate language. Where appropriate, children will be invited to give assent, which will be recorded on the informed consent form. The right to withdraw at any time without negative impact will be reinforced with the child and their parent/guardian.

In the United Kingdom (England, Wales, Northern Ireland and Scotland); where competent young people age 16 years and older (but younger than 18 years old) have given consent, their parent(s) or person(s) with parental authority should be informed of the young person's decision and they should be given a copy of the study information. A contemporary record should be made in the clinical notes that this information has been shared with the parent(s) or person(s) with parental authority. In other countries local ethical regulations will apply

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

7.3 Alternatives to Participation and Withdrawal

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

7.4 Risks to Participants

Inconvenience.

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

Phlebotomy.

Participants may have blood drawn more often than is required for standard care. Phlebotomy can be associated with pain at the draw site and rarely with infection. Daily blood draw volumes have

been restricted according to weight so that combined clinical and research sampling is within recommended limits. Discomfort will be minimized by having expert staff obtain blood samples, and by combining research sampling with routine clinical sampling, where possible, which normally occurs daily in acutely unwell patients in hospital.

Discomfort of respiratory swabs.

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

Incidental findings in genetic testing.

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

Specific risks for VHF patients

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

7.5 Benefits to Participants

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

7.6 Participation in Other Research Studies / Co-enrolment

Particularly in the case of emerging infections, it is likely that other research projects, including clinical trials, will also recruit participants in this study. In fact it is important that they do so, and great effort has been expended to ensure that this observational study is compatible with, and complementary to, other possible research projects. However in the UK this study has been given NIHR Clinical Research Network expedited urgent public health study status. In the event of an outbreak the study will be given priority by the Clinical Research Network. All Comprehensive Local Research Networks (CLRN) have Urgent Public Health plans, which will be activated in the event of an outbreak. In practical terms this means that where research resources are limited, this study may take precedence over others.

7.7 Confidentiality

This study will be conducted by clinical staff and those involved in the study will ensure that each study participant's privacy and confidentiality is maintained. Participants will not be identified in any published reports of this study. All records will be kept confidential to the extent provided by international and local law. All laboratory specimens, evaluation forms, reports, study protocol,

documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party.

Minimal personal data will be entered into the database for analysis. The patient's identifying personal information will be logged separately and stored securely. The patient might be asked to take part in future research, and therefore their identifiers need to be retained for contact at a future date, subsequent to the appropriate ethical approvals. The stored research data is also likely to be of significant value in the future for other studies and therefore permission is sought for this storing of the research data that does contain minimal patient identifiers such as age, sex and ethnicity.

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 pseudoanonymised before transfer by eCRF.

At the Public Health England Laboratories and Health Protection Research Units in Liverpool all research samples will be labelled with a unique, non-identifiable subject number. The patient's name and subject number will be recorded on the consent form. This will preserve the link between anonymous and identifiable data. Data and samples obtained from routine clinical care will be anonymised. The only link to identifiable data will be the consent form. Further research questions, subject to appropriate ethical approval, may be answered in retrospect in the future. Since the samples and data generated by this work may be irreplaceable after an outbreak of infectious disease has passed, it is essential that future work is not impeded by unnecessary data loss.

Anonymised data will be stored on managed computer systems in Imperial College, London, the PHE, the Wellcome Trust Sanger Institute, and the Roslin Institute relevant to the laboratory tests they have done. Only the ISARIC office in Oxford will hold the complete data set and this will be separated from the personal identifiers. Data will be encrypted before transfer on portable devices. Multiple backups will be maintained on institutional servers. Critical data will be stored in encrypted form in a stable storage format (e.g. DVDs), with the passwords recorded on paper in securely held site files in these locations.

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 indefinitely.

7.8 Custody of Data and Samples

Custody of site data will remain with the responsible physician at the site. Samples will be shipped (depending upon pathogen of interest) to a central laboratory (the Public Health England Laboratories at Colindale or Porton Down or the Health Protection Research Units at Liverpool and London), for processing and pseudoanonymisation and later forwarded to research institutions for analysis as approved by the appropriate ethics/institutional review committee. Any residual samples will remain in the custody of the site until use can be decided upon according to ISARIC policies/procedures. Centralized data will be in the custody of Oxford University (ISARIC Coordination Centre c/o Dr G Carson). A data sharing policy will be put in place between Universities of Liverpool, Oxford and the research laboratories.

7.9 Additional Ethical Considerations

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

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

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

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

7.10 Insurance

The University of Oxford has arrangements in place to provide for non-negligent harm arising from participation in the study for which the University is the Research Sponsor. However, if the study involves minimal deviation from normal clinical care, non-negligent harm cover may not apply.

7.10 Scientific and Peer Review

The proposed research is the product of a year-long 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) comprises senior clinical scientists from 5 continents, and aims to promote and harmonise observational research during outbreaks of severe infectious disease.

7.11 Material Transfer Arrangements (MTA)

Given the nature of the study and the number of institutions that are potentially involved it is not practical to enter into separate material transfer agreements. The principles of the Brunswick Group Human Tissue Material Transfer Agreement will be applied between "the Provider Institutions" being the NHS Trusts giving local R&D approval to this protocol, PHE and the Research Institutions through inclusion of appropriate definitions in the appendix to this protocol. Local NHS R&D approval of this protocol will serve as agreement to the specimen Brunswick MTA attached as an appendix below.

This approach is consistent with the Proportionate and Pragmatic Approach to Human Tissue regulation taken by the National Institute of Health Research Clinical Research Network (NIHR CRN) and its member NHS organisations. Details of this approach and the associated research management and governance training for staff within member NHS organisations are available from the regional clinical research networks.

7.12 Revision History

Changes since v6.1

Change in protocol title: from “Novel Coronavirus Observational Study” to “Clinical Characterisation Protocol for Severe Emerging Infections” to reflect need for flexibility in protocol application and more accurately describe the purpose of the protocol.

Investigators: Change of CI from Dr Gail Carson to Dr Calum Semple. Removal of Prof Jeremy Farrar and Prof Maria Zambon as CoI. Addition of Dr Meera Chand as CoI.

Clarification on expansion of study to include severe emerging infections and pathogens of public health interest.

Intention to expand study to the whole of UK.

Updated detail of “Background Information: Emerging, re-emerging and recently emerged infectious agents, such as the SARS coronavirus, MERS coronavirus, novel influenza viruses, and viruses causing viral haemorrhagic fever”

Criteria: Novel pathogens causing Severe Acute Respiratory Infection (SARI) i.e. Middle East respiratory syndrome coronavirus (MERSCoV), Influenza A/H7N9 & A/H5N1 and emerging or re-emerging pathogens causing Viral Haemorrhagic Fever (VHF). Two sets of documents including consent and assent forms, one set for SARI and other set for VHF.

Amends to reflect organisational change from Health Protection Agency (HPA) to Public Health England (PHE) and include Health Protection Research Units in Liverpool and London.

Update on A/H5N1, A/H7N9, MERSCoV and ebolavirus cases as reported by WHO.

Clarification of the primary objective of the study for severe emerging infections of public health interest in line with expansion of the observational protocol to cover SARI and VHF Clarification on eligibility that only proven cases of A/H5N1, A/H7N9, MERS-CoV or viral haemorrhagic fever (VHF) should be enrolled.

Inclusion of Tier 0 for collection of data only with no biological samples with the option to collect additional detailed clinical data at frequent intervals, according to local resources/needs and in response to needs of patients with VHF..

Clarification on eligibility that any person admitted to hospital with a proven infection with any of the pathogens of interest may be enrolled. This is to ensure that atypical presentations (such as those with predominantly gastrointestinal or neurological presentations and nosocomial presentations are included in the study.

Inclusion criteria for VHF patients in addition to the inclusion criteria for all SARI patients

Clarification that persons of all ages and capacity can be enrolled (correction and reissue of SSI)

Sample Labelling: Clarification that samples are sent from research sites to Public Health England Laboratories or Health Protection Research Units depending upon the pathogen.

Clarification that samples are sent from research sites to PHE and HPRU via secure courier labelled with full identifiers.

Clarification that ISARIC will commission and pay for BSL3 or BSL4 approved courier (PDP Couriers) and dry ice to transport samples to PHE Laboratories or HPRU.

Clarification on process of assent on behalf of participants who lack capacity due to acute illness and consent at the earliest opportunity in their recovery.

Clarification on data collection and management that there are two sets of CRFs, one set for SARI and one set for VHF patients.

Clarification on data management (including anonymisation and linkage), guardianship and sharing between Universities of Oxford, Liverpool and research institutions.

Clarification on follow-up procedures for patients to reflect expansion of the protocol for SARI and VHF.

Clarification of the specimen sampling, storage procedures and transport, following WHO guidance for safety and collection of samples for VHF

Clarification on the risk for participants with VHF

Adoption of English (UK) spelling conventions in the protocol

Adoption of SI units conventions in the protocol

Statement regarding no need for MTA's and Data sharing agreements for sites with R&D approval for this study as the conditions for MTA's and Data sharing are covered by this protocol and the attached Brunswick Group Human Tissue Material Transfer Agreement

Material Transfer Agreement for the Supply of Human Tissue Materials FOR USE where the material is human organs, tissue or cells (other than human gametes or embryos) but NOT where the intended use is transplantation or human application

This Agreement is made by and between:

a) "the Provider Institutions" being the NHS Trusts giving local R&D approval to this protocol

and

b) Dr Gail Carson, ISARIC Clinical Coordinator, University of Oxford

Dr Kenneth Baillie, Roslin Institute, University of Edinburgh

Professor Peter Openshaw, Professor of Experimental Medicine, Imperial College London

Ms Laura Merson, Head of Clinical Trials Unit, Oxford University Clinical Research Unit, Vietnam

Prof Paul Kellam, Wellcome Trust Sanger Institute

Dr Trudie Lang, Coordinator of the Global Health Network

Prof Maria Zambon, Director, Reference Microbiology Services, Public Health England

Professor. Saye Khoo, Institute of Translational Medicine, University of Liverpool

, these being "the Recipient Scientists and their respective Recipient Institutions")

This Agreement records the terms under which the Provider Institution will make available to the Recipient Institutions the Material identified in the protocol (the "Material"). The term "Material" means material, other than human gametes or embryos, which consists of, or includes human cells and which is considered "Relevant Material" for the purposes of the Human Tissue Act 2004[1] together with related data. The Recipient Institution will hold the Material on the terms of this Agreement and solely for the purpose of "the Study" and as described the protocol, within the research groups ("the Recipient Scientists"). The Recipient Institutions hereby agrees to comply and procure that the Recipient Scientists and all personnel who work with the Material comply with the following terms and conditions:

1. The Recipient Institutions will not use the Material for administration to human subjects or human application as that term is defined in the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (or equivalent as each may be replaced or amended from time to time), or for clinical or diagnostic purposes.[2]

[1] The Human Tissue Act 2004 applies to the "authorised activities" principally the removal, storage and use of "Relevant Materials" (as defined under the Act, including human cells, tissue and organs, but not cell lines) which come from a living or deceased person for "Scheduled Purposes" (these are set out in Schedule 1 of the Act, including, but not limited to, "research in connection with disorders, or the function of the human body", "education or training relating to human health", and "transplantation").

[2] The Human Tissue (Quality and Safety for Human Application) Regulations 2007 apply to the procurement, testing, processing, storage, distribution, and import or export of tissues and cells (including cell lines). "Cells" mean human cells (whether individually or in an unbound collection) including cell lines, but not including

2. The Recipient Institution may use the Material for the purposes of the Study and as described in the protocol, from the date of receipt of the Material. The Recipient Institution will comply fully with all applicable environmental, health and safety laws, the Human Tissue Act 2004 and other Applicable Laws[1] with respect to its use (including, but not limited to, disposal or return).

3. The Recipient Institution shall use a courier with suitable skill and experience to safely transport the Material in accordance with all Applicable Laws. The Recipient Institution will bear the cost of carriage and any necessary insurance. The Provider Institution makes no charge for the Material / the Material is provided subject to the reimbursement by the Recipient Institution to the Provider Institution for its costs of extracting from storage and preparing the Material as set out in the protocol. Risk in and responsibility for the Material shall pass to the Recipient Institution once it is loaded onto transport as organised by the Recipient Institution. If so requested by the Provider Institution the Recipient Institution shall provide it with written confirmation of the safe receipt of the Materials promptly after their delivery to the Recipient Institution's laboratory.

4. The Recipient Institution understands that the Material may have hazardous properties, contain infectious agents or pose other health and safety risks. Subject to clause 9, the Provider Institution makes no representations and gives no warranties either express or implied in relation to it: for example (without limitation), no warranties are given about quality or fitness for a particular purpose, or freedom from infection. The Provider Institution will not be liable for any use made of the Material by the Recipient Institution. The Recipient Institution will use the Material in accordance with good laboratory practice standards, all due skill and care and with dignity, sensitivity and respect. The Recipient Institution will comply with all Applicable Laws, approvals, rules, codes of practice and regulations governing the transportation, storage, use and disposal of the Material. The Recipient Institution warrants that it will only use, or permit the use of the Material in work that has ethical approval, as stated in the protocol.

5. Except to the extent prohibited by Law and subject to clause 9, the Recipient Institution assumes all liability for damages which may arise from its receipt, use, storage or disposal of the Material. The Provider Institution will not be liable to the Recipient Institution for any loss, claim or demand made by the Recipient Institution, or made against the Recipient Institution by any other party, due to or arising from its use, storage or disposal of the Material by the Recipient Institution, except to the extent the law otherwise requires.

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gametes, embryos outside the body, blood or blood components. "Tissue" for the Regulations, means all constituent parts of the human body formed by cells, but not including gametes and embryos outside the body (which are regulated by the Human Fertilisation and Embryology Authority pursuant to the Human Fertilisation and Embryology Act 1990), or organs.

[1] Applicable Laws means all laws, rules, regulations, codes of practice, research governance or ethical guidelines, or other requirements of any Regulatory Authority, that may apply to the use of the Material by the Recipient Institution from time to time, including (but not limited) the Human Tissue Act 2004 or the Human Tissue (Scotland)_Act 2006, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the Human Fertilisation and Embryology Act 1990 (as amended), the EU Tissues and Cells Directive (2004/23/EC) and Commission Directives 2006/17/EC and 2006/86/EC. The Human Tissue Authority Directions and Codes of Practice, and the Medicines for Human Use (Clinical Trials) Regulations 2004, as updated and amended from time to time and, where relevant, the national implementations of the same.

6. The liability of either party for any breach of this Agreement, or arising in any other way out of the subject matter of this Agreement, will not extend to loss of business or profit, or to any indirect or consequential damages or losses.

7. The Recipient Institution agrees to obtain the written consent of the Provider Institution if there is any material change to the proposed use of the Material in the Study as described in the protocol.

8. The Recipient Scientist will acknowledge the source of the Material in any publication reporting on its use. If the Recipient Scientist wishes to include in a publication any information which has been provided by the Provider Institution with the Material and which was clearly marked as “confidential” and “proprietary” at the point of disclosure (“Confidential Information”), the Recipient Scientist must obtain written permission from the Provider Institution, providing a copy of the text to allow a reasonable period for review before publication takes place, such permission not to be unreasonably withheld or delayed. If so requested by the Provider Institution, the Recipient Institution shall provide the Provider Institution with a confidential copy of the findings of the Study.

9. The Provider Institution warrants that where required by Applicable Laws the Material has been obtained from humans with the appropriate consent as required by the Human Tissue Act 2004 and with ethical approval and the Provider Institution shall be liable for any claims arising due to the breach of this warranty. The Provider Institution hereby grants to the Recipient Institution a non-exclusive research licence to use the Material for the Study only. The Provider Institution further warrants that it has not provided any information (and does not intend to provide any information) which has led or may lead to the Recipient Institution being able to identify the person from whom the relevant material came.

10. The Recipient Institution undertakes to store the Material in accordance with all Applicable Laws and not to attempt to identify or contact the donor of the Material or to compromise or otherwise infringe the confidentiality of information on the donors and their right to privacy.

11. Nothing included in this Agreement shall prevent the Provider Institution from being able to distribute the Material to other entities as described in the protocol. If, as per the details included in the protocol, the Material is to be transferred to another institution for the purposes of the Study, the responsibility for compliance with the terms of this Agreement rests with the Recipient Institution.

12. The Provider Institution has the right to terminate this agreement forthwith at any time by means of written notice to Recipient Institution if the ethical approval is withdrawn or if the Recipient Institution is in breach of this Agreement. In the case of any termination, the Recipient Institution shall immediately discontinue all use of the Material and, at the Provider Institution's discretion, promptly return or destroy (at the Recipient Institution's own cost) all unused Material and provide written confirmation that this has been completed. If requested, the Recipient Institution must certify that it has complied in full with any such requirement of the Provider Institution. Should an individual donor or their next of kin rescind their consent, the Provider Institution will require and the Recipient Institution agrees to discontinue using the appropriately identified sample and return or destroy it in accordance with the Provider Institution’s instructions.

13. This Agreement shall be governed by English Law, and the English Courts shall have exclusive jurisdiction to deal with any dispute which may arise out of or in connection with this Letter Agreement.

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