Setting up research studies.

The World Health Organisation (WHO) supports the conduct of investigator-led clinical research in outbreaks of emerging infection. In order to facilitate this, the following two options are recommended for the use of this research protocol:

1. Use these documents independently of, and with no obligations to, WHO. Studies using this protocol will be compatible with other studies around the world, enabling future collaboration on data analysis as needed.
2. Use these documents in collaboration with WHO and ISARIC to ensure rapid set up and analysis. ISARIC can help to link investigators to laboratories currently working on relevant analyses, and access to a secure online database for clinical data collection; WHO can provide additional resources in low- and middle-income countries to enable collection of data and/or biological samples.

ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections

18 August 2014, Version 3.0

Sponsor: **[***Insert name of sponsor***]**

Chief Investigator: **[***Insert name of chief investigator***]**

Co-Investigators: **[***Insert names***]**

Funder: **[***Insert details***]**

License.

Note:

The structure of this document outlines a stratified recruitment according to local resource. To facilitate understanding of the tier stratified approach of this protocol, colour codding has been used in the body of the document as follows:

- For all Tiers including Tiers 0 and Tier 1 - in **back.**
- For Tier 2 - **blue**.
- For Tier 3 -
  - **Tier 3A - green**
  - **Tier 3B - brown**
  - **Tier 3C - lily**

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. 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 cases of MERS-CoV in 2012-2013, Influenza H7N9 in 2013 and viral haemorrhagic fever (Ebola) in 2014.

1.2 Background Information

Infectious disease is the single biggest cause of death worldwide. Emerging, re-emerging and recently emerged infectious agents, such as the SARS coronavirus, MERS coronavirus, novel influenza viruses, and viruses causing viral haemorrhagic fever, require detailed studies 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, and factors underlying individual susceptibility.

The ability to conduct clinical research in this area will be influenced by factors such as locally available resources, the nature of the pathogen being studied, and the scale of the outbreak. Therefore, a flexible protocol has been designed that is flexible and can accommodate different demands.

This protocol permits enrolment of patients with suspected *or* confirmed infection with pathogens of interest. However, it will be made clear by the study team/network that has adopted the protocol whether laboratory confirmation of infection is required for enrolment.

Influenza A (H5N1)

Since 1997, highly pathogenic avian influenza (HPAI) A(H5N1) has caused outbreaks of severe 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 ebolavirus, Lassa virus, Crimean-Congo haemorrhagic fever virus, and Marburg virus. In 2014, an unprecedented outbreak of ebolavirus 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. 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.

This document may also be of interest to other researchers and health care workers conducting basic research into the pathogenesis and treatment other severe or potentially severe emerging infections.

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.

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, where appropriate and possible, associated with disease progression or severity

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 Interaction with public health.

In all cases, a case report form (CRF) will be completed. In many cases, out with this research study, case report forms will be completed for audit and public health purposes. The data collected will be the foundation for subsequent analyses described here, following informed consent from a patient or appropriate consultee.

Likewise, the public health considerations in a novel outbreak suggest that autopsies should be performed on all fatal cases as soon as possible after death. However, appropriate infection control measures must be in place to ensure the safety of clinical, research and laboratory staff. Tissues should be collected and fixed in formalin or embedded in paraffin. Particular attention should be paid to relevant organs of cases in which complications developed (e.g. myocarditis (heart), rhabdomyolysis (muscle), encephalitis (CNS tissues) as well as any other tissues with gross or microscopic abnormalities. Where such samples are used for research, appropriate consent must be obtained.

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

The study may 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. For any tier that includes collection of biological specimens, sampling will only take place when appropriate and internationally recognised biological safety measures can be guaranteed for the safe collection, storage and later analysis of specimens. Additionally, infection prevention and control measures will be in place for the collection of clinical data.

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. Intensity of sampling will be varied according to local conditions.
- **Tier 3 Additional research modules** –
    - Tier 3A Sampling of contacts of confirmed cases
    - Tier 3B Sampling from healthcare workers
    - Tier 3C Population pharmacokinetics of antimicrobial/immunomodulatory drugs – appropriate samples will be collected

For patients with highly transmissible 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.

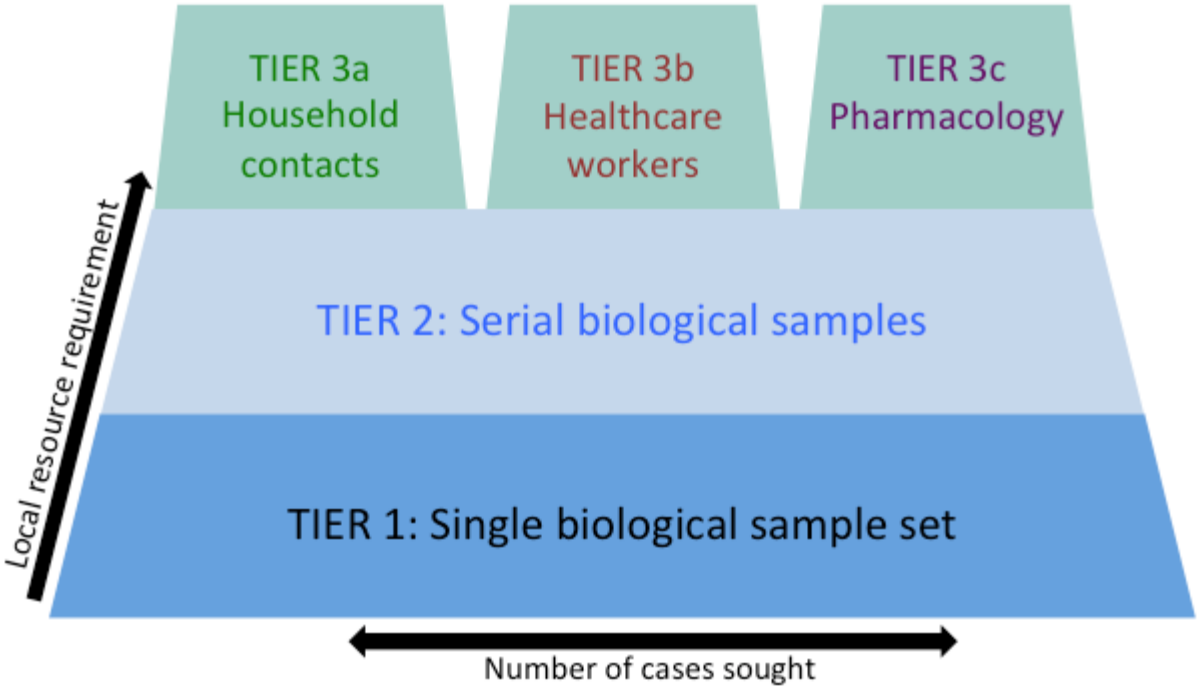

Figure 1. Tiered approach to recruitment in settings with different resources.

1.9 Modification of sampling and data collection during the study.

As an outbreak progresses, and more cases occur, it is anticipated that both the research priorities and the local resource availability will change. Therefore within a given institution, cases recruited later in an outbreak will be sampled at a lower intensity and may be recruited to a lower tier of the study. After the first 50 cases of a given outbreak are registered, it is likely that sufficient information will have been collected to answer key epidemiological questions regarding the outbreak. In normal circumstances, therefore, for severe respiratory disease the WHO SARI New Outbreak data collection forms will be used only for the first 50 cases. Following this phase, the shorter ISARIC SARI Core data collection forms will be used. Further details on the progression of the study during an outbreak are provided in section 3.7 of this protocol. For e.g. for an Ebola virus outbreak only clinical data collection may be advised.

1.10 Inclusion and Exclusion Criteria

This study will enrol eligible patients with confirmed or suspected infection with a pathogen relevant to the study objectives. The study team will dictate whether laboratory confirmation of infection is required prior to enrolment.

Inclusion criteria:

- A history of fever or measured fever of >38°C; AND
    - at least one respiratory symptom OR at least three symptoms of viral haemorrhagic fever*
    - OR
    - known contact with a suspected or confirmed case of infection with a pathogen relevant to the objectives of this protocol
- AND suspected or confirmed infection with a pathogen relevant to the objectives of this protocol
- AND admitted to a healthcare facility

- For the purpose of this protocol the following symptoms of viral haemorrhagic fever are included: headache; anorexia; lethargy; aching muscles or joints; breathing difficulties; vomiting; diarrhoea; stomach pain; dysphagia; hiccups.

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

[TIER2] Daily follow-up and convalescent visits of patients (Table 1 - Tier 2) should proceed according to local resources.

[TIER3A] Recruitment and follow-up of household contacts (Table 4) will be conducted where resources allow.

[TIER3B] Recruitment and follow-up of healthcare workers (Table 5) will also be undertaken if possible.

[TIER 3A] Inclusion criteria for contacts:

Any individual whose primary residence during the preceding two weeks is the same household as an enrolled patient with a confirmed diagnosis of a pathogen relevant to the study objectives.

[TIER3B] Inclusion criteria for healthcare workers:

Any healthcare worker directly involved in the care of a patient with confirmed infection with a pathogen relevant to the objectives of this protocol.

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.

Exclusion criteria for contacts:

Refusal by participant, parent or appropriate representative.

Exclusion criteria for healthcare workers:

Refusal by healthcare worker 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 and unknown 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 [*** insert - three years or five years – as appropriate ***] in the first instance.

3. Methods

3.1 Identification of Potential Patients

Approval of the responsible ethics committee will be obtained before patients are recruited at any site. 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. Translation services for alternative languages will be provided, as appropriate. 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.

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 for Patients

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 which samples will be obtained as a part of medical management or when they will be obtained. Participants in this study may have samples taken in addition to what is 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.

3.5 Sample and Data Collection Schedules

Sampling must only take place if appropriate biological safety measures are in place and can be maintained. This applies to the collection of samples, the storage and shipping of samples, and any subsequent laboratory analyses.

For patients with highly transmissible 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 and if the appropriate safe transport of samples to a laboratory with the appropriate biological containment can be guaranteed.

Table 1. Sample schedule.

REQUIREMENTS	Samples	Processing/ storage	Purpose
TIER 1			
CONSENT FORM		Site file	
SINGLE SAMPLE SET TAKEN AT RECRUITMENT	Pathogen samples: Urine (up to 10mls); stool (up to 10mls) or rectal swab; nasopharyngeal aspirate/nasal + throat swab‡; endotracheal aspirate if intubated‡; Samples from infected sites/sores. Also store other 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	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
			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 CASE RECORD FORM. For first 50 cases, use the WHO Initial Outbreak Case Record Form. Thereafter, use the ISARIC Core Case Record Form. For VHFs collect any amount of clinical data e.g. <50 cases.	Site file	Clinical data
TIER 2			
SERIAL SAMPLES THROUGHOUT ACUTE ILLNESS, CONVALESCENT SAMPLES WHERE POSSIBLE	Pathogen samples: Urine (up to 10mls) Stool (up to 10mls) or rectal swab Nasopharyngeal aspirate/flocked swab OR endotracheal aspirate if intubated Samples from infected sites/sores Also store other 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 FOLLOW UP FORM. For first 50 cases, use the WHO Initial Outbreak Follow Up Form. Thereafter, use the ISARIC Core Follow Up Form.	Site file	Clinical data
TIER 3C			
ADDITIONAL SAMPLES FOR POPULATION PHARMACOKINETICS STUDIES	Blood sample in EDTA	Plasma (2 aliquots -80°C*)	Test for drug levels. Store aliquot for other studies.

‡respiratory tract samples may not be required for VHF patients. *freeze at -80°C where possible, -20°C otherwise. #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								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	3 monthsand 6 months after recruitment
>40kg	**R**	P	**S**	P	S	P	S	P	**S**	P	S	P		P		S	C
20 to 40kg	**R**	P	**S**	P	S	P	S	P	**S**	P	S	P		P		S	C
10 to 20kg	**R**	P	**S**	P	S	P	S	P	**S**	P	S	P		P		S	C
4 to 10kg	**R**	P	**S**	P	S	P	P	P	**S**	P	P	P		P		S	C
>4kg	**R**	P	**S**	P	S	P	P	P	**S**	P	P	P		P		S	C
Sample priority	**1**	11	**2**	11	5	11	7	11	**3**	11	8	11		11		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).

Table 3. Samples

	TIER 1	TIER 2		
Weight	Samples at recruitment (R)	Serial samples (S)	Convalescent samples	Total Volumes of blood taken
>40kg	9mls EDTA blood 3mls blood in serum(clotted) tube 3mls blood in blood RNA tube Research pathogen samples	3mls EDTA blood 3mls blood in serum(clotted) tube 3mls 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	3mls EDTA blood 3mls blood in serum(clotted) tube 3mls blood in blood RNA tube Research pathogen samples	Maximum any day: 15mls (0.38mls/kg) Maximum any 4 weeks: 96mls (maximum2.4mls/kg)
20 to 40kg	6mls EDTA blood 3mls blood in serum(clotted) tube 3mls blood in blood RNA tube Research pathogen samples	1mls EDTA blood 2mls 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	1mls EDTA blood 3mls blood in serum(clotted) tube 2mls blood in blood RNA tube Research pathogen samples	Maximum any day: 12mls (0.6mls/kg) Maximum any 4 weeks: 42mls (maximum2.1mls/kg)
10 to 20kg	2mls EDTA blood 2mls blood in serum(clotted) tube 2mls blood in blood RNA tube Research pathogen samples	1mls EDTA blood 1mls 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	1mls EDTA blood 1mls blood in serum(clotted) tube 1mls blood in blood RNA tube Research pathogen samples	Maximum any day: 6mls (0.6mls/kg) Maximum any 4 weeks: 23.6mls (maximum2.36mls/kg)
<4 to 10kg	1mls EDTA blood 1mls blood in serum(clotted) tube mls blood in blood RNA tube	1mls 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	1mls EDTA blood 1mls blood in serum(clotted) tube Research pathogen samples	Maximum any day: 2mls (0.5mls/kg) Maximum any 4 weeks: 9.4mls (maximum2.35mls/kg)

	Research pathogen samples			
< 4kg	0.5mls EDTA blood 0.1mls blood in serum(clotted) tube mls blood in blood RNA tube Research pathogen samples	0.2mls 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	0.2mls EDTA blood 0.2mls blood in serum(clotted) tube Research pathogen samples	Maximum any day: 0.8mls (~0.27mls/kg) Maximum any 4 weeks: 2.4mls (maximum2.4mls/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: • Nasopharyngeal aspirate (NPA) OR (if NPA impossible) flocked nose and throat swab or nasopharyngeal swab • Urine (up to 10mls in sterile universal container, if available) • Rectal swab or stool (up to 10mls in sterile universal container or stool specimen container, if available) Samples/swabs from infected sites or sores.			No patient will give more than 0.6mls/kg (>1% blood volume) on any one day, or more than 2.4mls/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 Case report form

In the first 50 cases during a new outbreak caused by a respiratory tract pathogen, the WHO SARI New Outbreak data collection forms will be used to collect data at, or, in some conditions (such as a public health emergency) before, enrolment to this study. Following this phase, the shorter ISARIC-WHO SARI Core data collection forms will be used. [www.ISARIC/Protocol.org and https:/www.cliresdms.org]

For settings or circumstances in which resources are constrained, the ISARIC-WHO SARI Core data collection forms will be used from the outset. For a VHF outbreak, the ISARIC-WHO VHF case reporting form should be completed for all cases, and optional daily forms should be filled out when resources permit.

3.7 Modification of the sampling schedule.

The following planned changes in the sampling frequency are proposed following the declaration of a new outbreak by the study coordinating committee. Sampling frequency will decrease in order of the priorities shown in the sampling schedule, in which the highest priority is priority 1 (table 2):

1. After the first 50 cases, daily pathogen samples (Priority 11 in table 2) will not be required and will cease.
2. After the first 1000 cases (in total), serial sampling will cease and subjects will be recruited to genetic transcriptomic and biomarker studies at a single sample point at enrolment (i.e., Tier 1), unless there is another study ongoing (such as a clinical trial) that depends on data from serial sampling.
3. The local study team can adapt this protocol to exclude various tiers to produce a protocol relevant to their setting and the disease/pathogen they wish to study. Patients will notified of the selected sampling schedule at enrolment.

3.8 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 which have available resources AND appropriate biological safety measures in place 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 - 15 mls 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 recorded on discharge.

3.9 Follow-Up Procedures for Patients

Follow-up procedures (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 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.
Patients discharged from hospital will discontinue follow-up visits until the convalescent 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 pharmacokinetics studies [TIER 3C]. Up to 2 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 to on a case-by-case basis to fit in with clinical care; provided the precise times of administration 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 from SARI patients, a paired nasopharyngeal aspirate AND endotracheal aspirate if intubated is recommended. In settings where the necessary equipment is not available a combined flocked nasal and throat swab may be taken. A sputum sample will be collected when a productive cough is present and the patient is able to produce one. Paired upper and lower respiratory track samples should be collected when possible.

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.

3.10 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 no indication or likelihood of co-infection with a relevant pathogen will be withdrawn. No further follow-up will be conducted.

4. Specimen Sampling, Storage Procedures, Transport 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.

Well-established hospital protocols may be used to collect specimens. Guidance on the collection of specimens from SARI patients can be 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).

In dealing with 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. For either VHF or SARI studies, 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.

All samples collected in hospital will be labelled at the bedside as per hospital procedure with appropriate identification and hazard labelling according to local policy plus an additional marker identifying the sample as ISARIC RESEARCH. 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 laboratories will be anonymized with unique coded identifiers to protect the identity of the patient at the site level at the point of enrolment. When required, national and international guidance will be adhered to for the transport of specimens.

Standard local 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.

A unique alphanumeric code will be given to each patient at the local laboratory (not at the bedside), and the only link between the patient's identifying data and this code will be held securely.

Residual volumes available after clinical and research testing is complete will be stored centrally. All samples will be anonymised before storage. Only residual volumes which remain after the processing of the test for which the sample was taken will be stored.

4.2 Additional Data Collection - Pharmacokinetics Studies

Where local resources allow, additional information and samples will be sought daily 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 daily record form, and includes both the precise (to the minute) times of drug administration and the precise time of blood sampling.

4.3 Sample Processing

Table 5.

Sample	Initial processing	Aliquots	Analysis
Blood samples (serum)	Centrifuge 1500g for 10mins.	Supernatant: freeze at -80°C	Serology
		Supernatant: freeze at -80°C	Circulating mediators by multiplex cytokine/chemokine assays
		Supernatant: freeze at -80°C	
Blood samples (EDTA)		Supernatant: freeze at -80°C	Serology

	Centrifuge 1500g for 10mins at 4°C.	Supernatant: freeze at -80°C	Circulating mediators by multiplex cytokine/chemokine assays
		Supernatant: freeze at -80°C	Other studies (eg pharmacokinetics)
		Cell pellet: freeze at -80°C	1mcg: high-throughput genotyping 1mcg: targeted resequencing
Blood samples (blood RNA tube)	Freeze at -20°C	Where possible, then freeze at -80°C after 24hrs	1mcg: microarray analysis 1mcg: high-throughput sequencing (CAGE)
Pathogen samples	Aliquots where appropriate	Freeze at -20 or -80 °C	Pathogen detection, quantification and viral genome sequencing

Samples will only be processed if authorised biological containment and laboratory facilities appropriate to the relevant pathogen are available. For sites/regions lacking specific laboratory facilities, an updated list of laboratories offering specific analyses of samples obtained through this protocol will be available at www.isaric.org Sites that do not have access to specific laboratory facilities are encouraged to contact investigators through the ISARIC network in order to arrange analysis.

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 database which will be fully compliant with standard data management processes and local regulations. 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).

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 with consent. The standard consent form will request consent from subjects for sample storage and/or export of 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 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.

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 completed by a study staff. There are two sets of standardised CRF for SARI and VHF to be used as appropriate according to the emerging severe or potentially severe emerging infection. 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. Centrally maintained electronic records 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 should 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 current revision of 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 should 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.

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 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 swab may 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 and such procedures may also expose staff to risk of infection. The decision to perform venepuncture or collect other samples 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. Venepuncture will be minimised, where possible, by combining research venepuncture with clinical venepuncture.

7.5 Benefits to Participants

There will be no direct benefit to research participants. The study might 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

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.

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 anonymised before transfer.

All samples that go to research facilities will be labelled with a unique, non-identifiable subject number. Patient are not anonymise at bedside, 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.

Data will be encrypted before transfer on portable devices. Multiple backups will be maintained on institutional servers. Critical data will be stored in a stable storage format.

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 to the named reference laboratories 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 and the appropriate ethical approvals.

7.9 Additional Ethical Considerations

Recruitment of critically ill patients who are not able to consent.

This is a ubiquitous problem in critical care research. Personal or nominated consultees will be asked to provide an opinion on whether they believe the patient would object to recruitment to the study; recruitment will only take place if a favourable opinion is provided. 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.

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.

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 work-loads. All staff will be trained in recognised infection control measures and will have ready access to appropriate personal protective equipment. In collaboration with public health authorities, there will be on-going communication with hospital staff to ensure that 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 study activities.

7.10 Scientific and Peer Review

The proposed research is the product of years of work within a group of international experts who began to work 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.

ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections Study

INFORMATION SHEET FOR PATIENT

18th August 2014. Version 3.0

We are undertaking a research study involving people with severe [*** insert as appropriate 'respiratory infection (H5N1 or H7N9 or Mers-CoV)', or 'viral haemorrhagic fever'***], which is why we have approached you.

You are invited to take part in this study.

Before you decide it is important for you to understand why the research is being done and what it would involve for you. Please take time to read this information carefully. One of our team will go through the information with you. Please ask us if there is anything that is not clear or if you would like more information and time to decide. Your decision is completely voluntary. The decision you make will not affect your care or treatment in any way.

What is the study about?

Infectious diseases affect millions of people around the world every year. Most cases are mild, but some people become very unwell. There is a great deal that we do not understand about existing infections, and new infectious diseases continue to appear. This research study will gain important information about [*** insert as appropriate 'respiratory infections' or 'viral haemorrhagic fever infections' ***] so we can try to find better ways to manage and treat them in the future.

What will happen if I take part in this study?

We will collect information and possibly samples which are in addition to what would normally be collected for your medical care.

A blood sample may be taken now, together with a swab from your throat, a swab from any infected sites/sores, a sputum sample, urine sample and a stool sample or rectal swab. If samples are to be taken, you will be told in advance which samples are required and how often sampling will occur..

We may take the same samples again over the next two weeks, every second day and then every week for as long as you are unwell up to a maximum of 100 days. We will also invite you to return to the hospital or clinic in 3 months and 6 months to have a blood sample taken. Each sample will take less than 15mls (3 teaspoons) of blood.

If any other samples are taken from you for regular care, and if there is leftover sample after the tests requested by your doctors are done, we will store the leftover to be tested.

What will happen to the samples and information?

If samples are obtained we will use the blood samples to look at how the body fights the infection and how the treatments work in the body. We will also use the blood sample to analyse your DNA. We will examine your DNA together with DNA from many other people to try to find out what makes some people more susceptible to infection. Some of the tests may be done in different countries.

All information about you will be handled in confidence and only the people responsible for your care and for this study will know that you were a part of the study. We will review your medical records and keep limited information about you on a secure file. All information and samples will be labelled only with a number so that they cannot be directly linked to you personally. With your permission, we would also like to store your samples and use them for future ethically approved medical research. The data and samples collected during this study may be looked at by public health agencies.

Are there any benefits to taking part in this study?

There is no benefit to you personally. The information gained from this study may not be available in time to affect your care. Any results available while you are in hospital will be given to your treating doctor. The information we learn may help in caring for other patients in the future.

What are the risks of being in the study?
Being a part of this study means that if research samples are taken, then more samples will be taken than are needed for normal care. Whenever possible these samples will be taken at the same time as regular samples to reduce the extra procedures. There is a risk of pain or irritation when samples are taken.

When DNA testing is done, there is a small chance that the results will show a genetic condition that could affect your future health. Since the tests will be conducted anonymously, no-one on the study team will know that such a result applies to you, and in any case there is usually considerable uncertainty about the implications of any research DNA test result for individual health. For these reasons we would not attempt to identify you or inform you of any results from DNA testing.

Who is responsible and what if something goes wrong?
[***insert sponsor and contact details***]

Can I request that I be withdrawn from the study at any point?
Yes, you can withdraw at any time without giving a reason and without affecting your care. Any samples that have not already been analysed can be destroyed anytime you request it.

What if I have any problems or would like further information about the study?
[***insert details***]

[INSTITUTIONAL LOGO]

ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections Study

INFORMED CONSENT FORM FOR PATIENT

18th August 2014. Version 3.0

- I have read (or it has been read to me) the information sheet for this study. I understand the information and have had the opportunity to ask questions for clarification.
- I understand that my participation is voluntary and that I am free to withdraw from the study at any time, without giving any reason and without my medical care or rights being affected.
- I understand that data will be collected from my medical records by study staff during the study and that this information may be looked at by authorized individuals from public health agencies. I agree that these individuals may have access to my research records.
- I understand that my information can be collected, analysed, reported and shared with others within and outside the country as part of this study. I understand that my name will not be used and I will not be identified
- I agree that my samples may be sent elsewhere in the world to be analysed.
- I agree that DNA from my blood sample will be analysed to determine whether any genetic factors have made me susceptible to severe infection.
  OR IF YOU DO NOT AGREE, CHECK HERE ❑
- I agree that my blood sample, including my DNA, may be used in additional research in the future, if necessary in different parts of the world, as long as appropriate ethical approval is in place.
  OR IF YOU DO NOT AGREE, CHECK HERE ❑
- I agree to be contacted directly by the investigators with an invitation to participate in future research studies.
  OR IF YOU DO NOT AGREE, CHECK HERE ❑

Patient name:_____ Signature/fingerprint:_____
Date:_____

Person taking consent:_____
Signature:_____ Date:_____

Witnessed Consent

If the consenting party cannot read the form: I have no interest or involvement in this research study and I attest that the information concerning this research was accurately read and explained to the patient in language they can understand, and that informed consent was freely given by the patient.

Witness name:_____ Signature/fingerprint:_____
Date:_____

ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections Study

INFORMATION SHEET FOR CONSULTEE

18th August 2014. Version 3.0

We are undertaking a research study involving people with severe [*** insert as appropriate 'respiratory infection (H5N1 or H7N9 or Mers-CoV)', or 'viral haemorrhagic fever'***]. We are asking you about the participation of an individual who is not able to consent for themselves, because he/she lacks the legal capacity to do so. To help decide if he/she should join the study, we would like to ask your opinion whether or not he/she would want to be involved.

Before you decide it is important for you to understand why the research is being done and what it would involve for the participant. Please take time to read this information carefully. One of our team will go through the information with you. Please ask us if there is anything that is not clear or if you would like more information and time to decide. Your decision is completely voluntary. The decision you make will not affect the participant's care or treatment in any way.

What is the study about?

Infectious diseases affect millions of people around the world every year. Most cases are mild, but some people become very unwell. There is a great deal that we do not understand about existing infections, and new infectious diseases continue to appear. This research study will gain important information about [*** insert as appropriate 'respiratory infections' or 'viral haemorrhagic fever infections' ***] so we can try to find better ways to manage and treat them in the future.

What will happen if I take part in this study?

We will collect information and possibly samples which are in addition to what would normally be collected for the participant's medical care.

A blood sample may be taken now, together with a swab from the participant's throat, a swab from any infected sites/sores, a sputum sample, urine sample and a stool sample or rectal swab. If samples are to be taken, you will be told in advance which samples are required and how often sampling will occur..

We will take the same samples again over the next two weeks, every second day and then every week for as long as the participant is unwell up to a maximum of 100 days. We will also invite the participant to return to the hospital or clinic in 3 months and 6 months to have a blood sample taken. Each sample will take less than 15mls (3 teaspoons) of blood.

If any other samples are taken from the participant for regular care, and if there is leftover sample after the tests requested by the participant's doctors are done, we will store the leftover to be tested.

What will happen to the samples and information?

If samples are obtained we will use the blood samples to look at how the body fights the infection and how the treatments work in the body. We will also use the blood sample to analyse the participant's DNA. We will examine the participant's DNA together with DNA from many other people to try to find out what makes some people more susceptible to infection. Some of the tests may be done in different countries.

All information about the participant will be handled in confidence and only the people responsible for the participant's care and for this study will know that the participant were a part of the study. We will review the participant's medical records and keep limited information about the participant on a secure file. All information and samples will be labelled only with a number so that they cannot be directly linked to the participant personally. With your permission, we would also like to store the participant's samples and use them for future ethically approved medical research. The data and samples collected during this study may be looked at by public health agencies.

Are there any benefits to taking part in this study?

There is no benefit to you or the participant personally. The information gained from this study may not be available in time to affect the participant's care. Any results available while the pariticipant is in

hospital will be given to your treating doctor. The information we learn may help in caring for other patients in the future.

What are the risks of being in the study?
Being a part of this study means that if research samples are taken, then samples will be taken than are needed for normal care. Whenever possible these samples will be taken at the same time as regular samples to reduce the extra procedures. There is a risk of pain or irritation when samples are taken.

When DNA testing is done, there is a small chance that the results will show a genetic condition that could affect the participant's future health. Since the tests will be conducted anonymously, no-one on the study team will know that such a result applies to the participant, and in any case there is usually considerable uncertainty about the implications of any research DNA test result for individual health. For these reasons we would not attempt to identify the participant or inform the participant of any results from DNA testing.

Who is responsible and what if something goes wrong?
[***insert sponsor and contact details***]

Can I request that I be withdrawn from the study at any point?
Yes, you or the participant can withdraw at any time without giving a reason and without affecting the participant's care. Any samples that have not already been analysed can be destroyed anytime you or the participant request it.

What if I have any problems or would like further information about the study?
[***insert details***]

[INSTITUTIONAL LOGO]

ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections Study

DECLARATION OF UNDERSTANDING FOR CONSULTEE

18th August 2014. Version 3.0

- I have been consulted about [ ]'s participation in this research project. I have read (or it has been read to me) the information sheet for this study. I understand the information and have had the opportunity to ask questions for clarification.
- I understand that the participant's participation is voluntary and that the participant is free to withdraw from the study at any time, without giving any reason and without my medical care or rights being affected.
- I understand that data will be collected from the participant's medical records by study staff during the study and that this information may be looked at by authorized individuals from public health agencies. I agree that these individuals may have access to the participant's research records.
- I understand that the participants' information and samples can be collected, analysed, reported and shared with others outside the country elsewhere in the world. I understand that participant's name will not be used and they will not be identified.
- I understand participant's samples may be sent elsewhere in the world to be analysed.
- I understand that DNA from the participant's blood sample will be analysed to determine whether any genetic factors have made him/her susceptible to severe infection.
  OR IF YOU DO NOT AGREE, CHECK HERE ❑
- I understand that participant's blood sample, including my DNA, may be used in additional research in the future, if necessary in different parts of the world, as long as appropriate ethical approval is in place.
  OR IF YOU DO NOT AGREE, CHECK HERE ❑
- I understand for the participant to be contacted directly by the investigators with an invitation to participate in future research studies.
  OR IF YOU DO NOT AGREE, CHECK HERE ❑

Patient name:_____ Signature/fingerprint:_____
Date:_____

Person taking consent: _____
Signature:_____ Date:_____

Witnessed Consent

If the consenting party cannot read the form: I have no interest or involvement in this research study and I attest that the information concerning this research was accurately read and explained to the patient in language they can understand, and that informed consent was freely given by the patient.

Witness name:_____ Signature/fingerprint:_____
Date:_____

ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections Study

INFORMATION SHEET FOR PARENT / GUARDIAN

18th August 2014. Version 3.0

We are undertaking a research study involving people with severe [*** insert as appropriate 'respiratory infection (H5N1 or H7N9 or Mers-CoV)', or 'viral haemorrhagic fever'***]. We are asking you about the participation of a child who is below the legal age at which he/she can consent to participate in research, because you are the parent or legal guardian of that child (hereafter referred to as your child). Where possible, we will also give your child the opportunity to express his/her views and assent to participate.

Before you decide it is important for you to understand why the research is being done and what it would involve for your child. Please take time to read this information carefully. One of our team will go through the information with you. Please ask us if there is anything that is not clear or if you would like more information and time to decide. Your decision is completely voluntary. The decision you make will not affect your child's care or treatment in any way.

What is the study about?

Infectious diseases affect millions of people around the world every year. Most cases are mild, but some people become very unwell. There is a great deal that we do not understand about existing infections, and new infectious diseases continue to appear. This research study will gain important information about [*** insert as appropriate 'respiratory infections' or 'viral haemorrhagic fever infections' ***] so we can try to find better ways to manage and treat them in the future.

What will happen if I take part in this study?

We will collect information and possibly samples which are in addition to what would normally be collected for your child's medical care.

A blood sample may be taken now, together with a swab from your child's throat, a swab from any infected sites/sores, a sputum sample, urine sample and a stool sample or rectal swab. If samples are to be taken, you will be told in advance which samples are required and how often sampling will occur..

We will take the same samples again over the next two weeks, every second day and then every week for as long as your child is unwell up to a maximum of 100 days. We will also invite your child to return to the hospital or clinic in 3 months and 6 months to have a blood sample taken. Each sample will take less than 15mls (3 teaspoons) of blood.

If any other samples are taken from your child for regular care, and if there is leftover sample after the tests requested by your child's doctors are done, we will store the leftover to be tested.

What will happen to the samples and information?

If the samples are taken we will use the blood samples to look at how the body fights the infection and how the treatments work in the body. We will also use the blood sample to analyse your child's DNA. We will examine your child's DNA together with DNA from many other people to try to find out what makes some people more susceptible to infection. Some of the tests may be done in different countries.

All information about your child will be handled in confidence and only the people responsible for your child's care and for this study will know that your child were a part of the study. We will review your child's medical records and keep limited information about your child on a secure file. All information and samples will be labelled only with a number so that they cannot be directly linked to your child personally. With your permission, we would also like to store your child's samples and use them for future ethically approved medical research. The data and samples collected during this study may be looked at by public health agencies.

Are there any benefits to taking part in this study?
There is no benefit to you personally. The information gained from this study may not be available in time to affect your child's care. Any results available while your child is in hospital will be given to your treating doctor. The information we learn may help in caring for other patients in the future.

What are the risks of being in the study?
Being a part of this study means that if research samples are taken, then more samples will be taken than are needed for normal care. Whenever possible these samples will be taken at the same time as regular samples to reduce the extra procedures. There is a risk of pain or irritation when samples are taken.

When DNA testing is done, there is a small chance that the results will show a genetic condition that could affect your child's future health. Since the tests will be conducted anonymously, no-one on the study team will know that such a result applies to your child, and in any case there is usually considerable uncertainty about the implications of any research DNA test result for individual health. For these reasons we would not attempt to identify your child or inform your child of any results from DNA testing.

Who is responsible and what if something goes wrong?
[***insert sponsor and contact details***]

Can I request that I be withdrawn from the study at any point?
Yes, you can withdraw at any time without giving a reason and without affecting your child's care. Any samples that have not already been analysed can be destroyed anytime you request it.

What if I have any problems or would like further information about the study?
[***insert details***]

[INSTITUTIONAL LOGO]

ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections Study

PARENT and PARENTAL AUTHORITY CONSNET FORM

18th August 2014. Version 3.0

- I have been consulted about [ ]'s participation in this research project. I have read (or it has been read to me) the information sheet for this study. I understand the information and have had the opportunity to ask questions for clarification.
- I understand that his/her participation is voluntary and that I am free to withdraw him/her from the study at any time, without giving any reason and without his/her medical care or rights being affected.
- I understand that data will be collected from his/her medical records by study staff during the study and that this information may be looked at by authorized individuals from public health agencies. I agree that these individuals may have access to his/her research records and study results.
- I understand that his/her information and samples can be collected, analysed, reported and shared with others outside the country elsewhere in the world. I understand that his/her name will not be used and will not be identified.
- I understand his/her samples may be sent elsewhere in the world to be analysed.
- I understand that DNA from his/her blood sample will be analysed to determine whether any genetic factors have made me susceptible to severe infection.
  OR IF YOU DO NOT AGREE, CHECK HERE ❑
- I understand that his/her blood sample, including DNA, may be used in additional research in the future, if necessary in different parts of the world, as long as appropriate ethical approval is in place.
  OR IF YOU DO NOT AGREE, CHECK HERE ❑
- I understand that I might be contacted directly by the investigators with an invitation for him/her to participate in future research studies.
  OR IF YOU DO NOT AGREE, CHECK HERE ❑

Patient name:_____ Signature/fingerprint:_____
Date:_____

Person taking consent:_____
Signature:_____ Date:_____

Witnessed Consent

If the consenting party cannot read the form: I have no interest or involvement in this research study and I attest that the information concerning this research was accurately read and explained to the patient in language they can understand, and that informed consent was freely given by the patient.

Witness name:_____ Signature/fingerprint:_____
Date:_____