ISARIC/WHO Clinical Characterisation Protocol UK (ISARIC CCP-UK)

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1 Background and Objectives

1.1 Purpose of the Study

This is a generic protocol for the rapid, coordinated clinical research-based investigation of exposure to pathogens, chemicals, toxins, or potentially harmful energy sources of public health interest.

By necessity this Urgent Public Health Research protocol is flexible and comprehensive. A supplementary **guidance document** will be used to define the actual sampling frequency and specific samples in use for each site, for a given pathogen or noxious exposure. Likewise, the **Case Report Form** (CRF) used for data collection in any event will be generic and refined in-flight according to the nature of the event.

Patients with a spectrum of emerging and unknown pathogens or noxious exposures will be enrolled. This protocol has been designed to maximize the likelihood that data and biological samples are prospectively and systematically collated and shared rapidly with clinicians, public health agencies and policy makers in a format that can be easily understood and then aggregated, tabulated and analysed across many different settings both nationally and globally.

The protocol is designed to have flexibility in order to ensure the broadest acceptance. It has been initiated in response to UK cases of Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV) in 2012-2013, Influenza H7N9 in 2013, viral haemorrhagic fever (Ebolavirus) in 2014, Monkeypox & MERS-coronavirus in 2018, Tick-borne encephalitis virus (TBEV) in 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in 2020, and in 2022 Monkeypox, Lassa Fever and Severe Hepatitis in Children of unknown origin.

It is expected that activation in the UK will be done in collaboration with the Department of Health and Social Care via the UK Health Security Agency or National Institute for Health and Care Research (NIHR). Information will be circulated by the Investigators and disseminated by the NIHR Clinical Research Network to clarify the eligibility criteria in the event of activation. Due to their nature, cases of and exposure to High Consequence Infectious Diseases (HCID) as agreed jointly by UK HSA and NHSE will remain eligible by default (Appendix s8.3)

The study is recognised by the NIHR as being an Urgent Public Health Research study and sits within a portfolio of such studies that will be given priority support in the event of emergence of a pathogen of public health interest (UK CRN ID 14152).

1.1.1 Test activation of data collection (internal pilot) to maintain readiness.

Recognising the value of maintaining a sleeping study such as this in a state of readiness and to test the readiness of the study, this protocol includes as an activation exercise, an internal pilot for a community-acquired severe acute respiratory infection (SARI). It is intended that this internal pilot will be conducted no more frequently that on an annual basis and for one week only, subject to funding.

Previous outbreaks of pandemic and zoonotic influenza viruses (H1N1pdm2009, H5N1 & H7N9), SARS-CoV, MERS-CoV and Ebola revealed that there is a significant time lag between the start of a disease outbreak and the availability of the data needed to inform

clinical management and public health interventions. There is also a lack of contemporary information about the epidemiology and management of SARI patients globally, and a recognised need to establish research infrastructure to gather information rapidly during an outbreak of public health interest such as the emergence of a new cause of SARI with epidemic potential. Regular test activations will provide the background or baseline characteristics of SARI immediately prior to any future outbreak and maintain the study in a state of readiness.

For the test activation eligibility criteria will include people of any ages and sex including pregnant women and young children with very severe community acquired pneumonia requiring admission to nominated level 3 intensive care units for mechanical ventilation and or ECMO support. This internal pilot is not a separate study in itself, but an important aspect of the study to test the activation that involves collation of data from routine data sources with consent (whether deferred or not) or with proxy assent. It is intended that the 'activation' will be conducted on an annual basis and for one week only.

Pseudonymised data collated will be also shared with an international project on SARI patients – SPRINT-SARI study, led by Dr Srinivas Murthy and Prof. Steven Webb, and coordinated by the ANZIC-RC (Australia) and ISARIC Coordination Centre (Oxford). This study aims to characterise SARI patients globally to better inform management strategies, to improve and inform clinical management of emerging infectious causes of SARI.

The specific guidance for the internal pilot study is included in Appendix A.

1.2 Background Information

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

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

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

This study, while not a study of a medicine, may involve additional procedures (some minimally invasive), the retention of genetic material, collection of personal data and additional follow up. The ISARIC consortium is 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, where samples are collected, 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 also enrol people with exposure to or infection by any pathogen on the High Consequence Infectious Diseases list (see UK HSA website), exposure to or infection by any other pathogen or syndrome of public health interest as yet unspecified, and any exposure to a noxious chemical, toxin or potentially harmful energy source of public health interest.

1.2.1 SARS-CoV-2 and COVID-19

SARS-CoV-2 caused a devastating global pandemic of the disease COVID-19. Previous versions of this protocol made a critical contribution to clinical and mechanistic understanding of this infection, informing clinical and public health countermeasures, beginning with the first report of clinical characteristics among patients in Wuhan in January 2020, and continuing throughout the pandemic, worldwide[1].

1.2.2 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 14 December 2015, the total number of human A(H5N1) cases reported to WHO worldwide is 844; of these 449 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 11 January 2016).

1.2.3 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 7th January 2016, the World Health Organization has been informed of 1,626 confirmed cases, including 586 related deaths. http://www.who.int/csr/don/7-january-2016-mers-oman/en/ (last accessed 11 January 2016).

1.2.4 Influenza A/H7N9.

Two waves of human infection with novel avian influenza A(H7N9) have occurred since March 2013. As of 23 February 2015, 571 laboratory confirmed cases of human infection with influenza A(H7N9) have been reported to WHO, including 212 deaths. 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.

[1] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5. Epub 2020 Jan 24. Erratum in: Lancet. 2020 Jan 30; PMID: 31986264; PMCID: PMC7159299.

1.2.5 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.

1.2.6 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 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.

1.2.7 Tick borne encephalitis virus (TBEV) and other emerging CNS viruses.

TBEV is a flavivirus spread by ticks to humans in endemic areas across large regions of Europe and Asia. Subtypes of the virus include: European (TBEV-Eu), Far Eastern (TBEV-FE), Siberian (TBEV-Sib), Baikalian (TBEV-Blk), Himalayan (TBEV-Him), and the recently-identified TBEV-UK. TBEV may cause (meningo)encephalitis, with or without myelitis, which can result in death or severe neurological sequelae and often leads to substantial impairment in quality of life. TBEV is a growing public health concern, as the number of human tick-borne encephalitis (TBE) cases continues to increase globally and endemic areas spread northwards and to higher altitudes.

In 2019, ticks carrying TBEV were identified in both Thetford Forest, Norfolk and on the Hampshire/Dorset border; the virus was thought to be imported by bird migration and to be established in the UK. In July 2019, a probable case of serologically-confirmed TBE was reported in an infant in the New Forest, Hampshire. Improved understanding of the epidemiology and clinical features of this disease is essential to inform clinical management and policy, particularly as vaccination against TBEV is available. Other emerging CNS viruses, such as West Nile Virus, Usutu virus, enterovirus D68, Nipah virus and Borna disease virus 1, also cause considerable morbidity and mortality and are a public health priority.

1.2.8 Children with Severe Acute Hepatitis of unknown origin

Clinicians in Scotland noticed an exceedance in cases of sever acute non-A-E Hepatitis in children, some of whom required emergency liver transplant as a lifesaving procedure for fulminant liver failure. ISARIC4C Investigators were notified by Public Health Scotland on 1st April 2022 and this protocol was activated. Since then, we have been working with public health agencies across the UK to characterise this outbreak, which has seen many more cases in the UK and abroad.

1.2.9 Monkeypox

Monkeypox is listed by the joint NHS-England and UK government Advisory Committee on Dangerous Pathogens (ACDP), so UK sporadic (mostly imported) cases have by default been eligible for recruitment. In May 2022 ISARIC4C investigators published the first report of human-to-human transmission outside of Africa including transmission within a family and separate transmission to a Health Care Worker[2]. In 2022, there has been a rise in the number of cases of monkeypox in the UK and abroad. Since then, ISARIC4C investigators have been working with public health agencies to characterise this outbreak.

1.2.10 Other emerging or re-emerging pathogens of Public Health Interest and exposure to noxious chemicals, toxins and harmful energy

These pathogens will be identified by the investigators taking into consideration position statements issued by of World Health Organisation, UK Health Security Agency (UK HSA) as successor to Public Health England and the relevant public health authorities in the UK devolved Nations.

1.3 Target Audience of this Document

This document is of primary interest to clinicians (including public health, emergency and critical care providers) and others engaged in identification, triage and treatment of people with exposure to or infection by any pathogen on the High Consequence Infectious Diseases list (see UK HSA website), any other pathogen or syndrome of public health interest as yet unspecified, and any exposure to noxious chemical, toxin or potentially harmful energy source of public health 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 an active collaboration between the World Health Organization (WHO) and the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC). It builds on a global consensus on observational research in emerging infections of public health interest. The protocol has been revised, often at short notice and in response mode, to address important gaps in public health and clinical knowledge and support clinical trials in response to outbreaks and exposures of public health importance.

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 featured by the outbreak of public health interest regardless of exposure, be that infection, toxin, chemical or potentially harmful energy.

[2] Adler H et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK, The Lancet Infectious Diseases, 2022, https://doi.org/10.1016/S1473-3099(22)00228-6.

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

1.6 Secondary Objectives

Secondary objectives are to collect evidence in order to:

- Facilitate effective triage and clinical management of people with exposures to pathogens, toxins, chemical or harmful energy as relevant to this protocol
- Determine infectivity and appropriate infection control measures of the various pathogens or noxious exposures
- Develop clinical guidance documents and offer clinical recommendations to policy makers on the basis of evidence obtained
- Understand the broader epidemiology of an emerging infection or exposure event through studying potential contacts and asymptomatic individuals

1.6.1 Specific objectives of Annual Activation (internal pilot)

These objectives are only for the annual activation and are complementary to the above objectives:

- To assess the barriers and enablers to being prepared for and conducting research during an outbreak of a pathogen or noxious exposure of public health interest and or pandemic at participating sites
- Evaluate the operational characteristics of this study
- Evaluate impact on incidence of alternative case-definitions
- Incidence
- Disease severity and risk factors for severe disease
- Case Fatality Proportion
- Duration of ICU/hospital stay
- Microbiology of, including variability in testing
- Treatments received during hospitalization

For further details see appendix A

1.6.2 Specific objectives of comparison group activations

Small-scale activations of the CCP will be initiated, when necessary, to recruit hospitalised patients with confirmed infection with pathogens related to the objectives of this study to provide comparison groups for the above objectives.

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

The study will be conducted at multiple sites including the community (to be determined by the nature of disease or exposure 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. 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. In UK events, a UK study specific CRF will be used. The CRF will initially be generic and refined in-flight according to the nature of the event, as was needed in response to the COVID-19 pandemic, for children with acute severe hepatitis of unknown origin and the increase in Monkeypox cases outside of Africa associated with human-to-human transmission.

Each additional tier builds on the preceding one:

- **Tier 0 (Clinical data collection only)** – Clinical data, and data derived from clinical samples of the pathogen or other putative causal agent, including pathogen genome sequence, will be collected. No additional 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 (Simple and stable biological samples)** – Limited samples, which do not require laboratory processing at the recruiting site, will be obtained for research. Residual diagnostic material will be retained for research purposes with consent.
- **Tier 2 (Serial biological sampling)** - Clinical samples and data will be collected on day of recruitment (*R* - Day 1; ideally at initial presentation to a health care facility), serial samples will be obtained (*S*), and samples will be obtained during convalescence (*C*) (see below).
- **Tier 3 (Local studies and population pharmacokinetics of antimicrobial/immunomodulatory drugs**) – local studies consistent with the aims of this protocol and the information provided to patients in the patient information sheet will be supported by provision of additional samples where appropriate, within the limits specified below. This could include measuring levels of drugs in body fluids for population pharmacokinetics and pharmacodynamic modelling, where such measurements are being made outside of the remit of a clinical trial of an investigational product.

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.

The internal pilot study will only collect clinical data and laboratory results for TIER ZERO – data collection only, for one week, and no more frequently than on an annual basis – there will be no additional biological sampling for research purposes. This in turn will inform participating sites about the challenges for collecting data and ensure that participant sites are better prepared for the activation of the full Clinical Characterisation Protocol in case of an outbreak.

1.8 Entry Criteria

This study will enrol eligible people (children and adults including pregnant women) with suspected or confirmed exposure or infection relevant to the study objectives, as specified below.

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

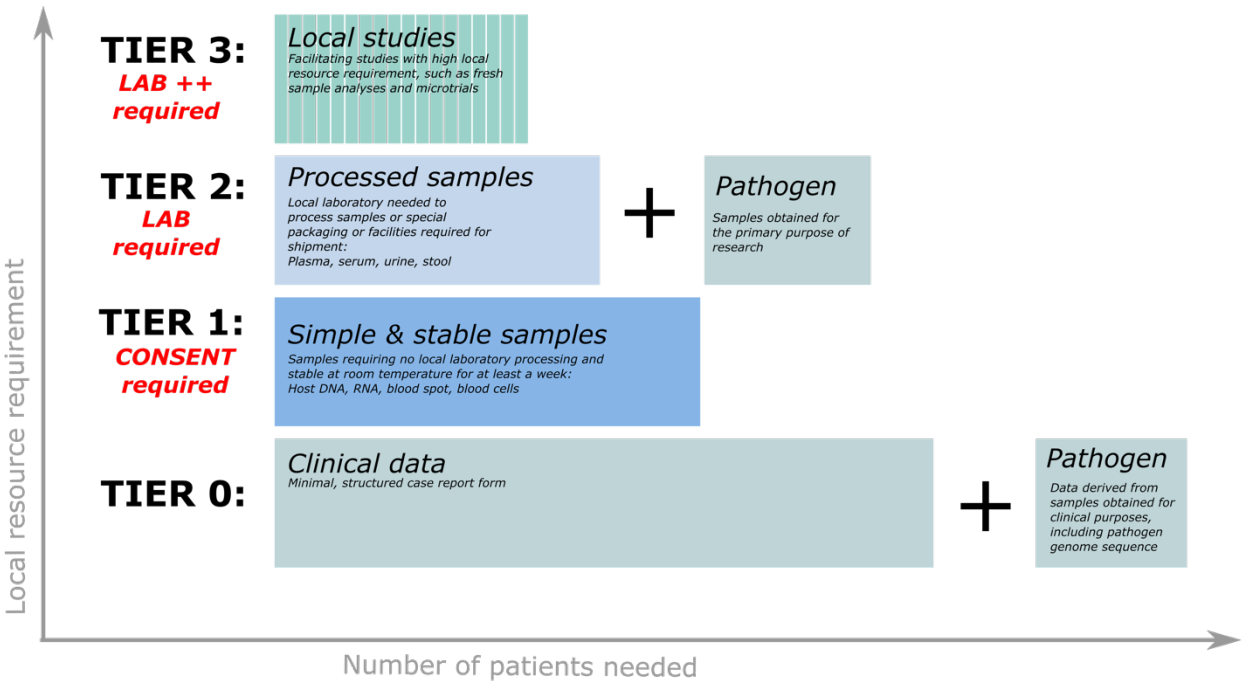

Figure 1: Recruitment Tier Structure. Note consent for Tier 1 may be wiaved by HRA CAG and other relevant authroities.

1.8.1 Inclusion criteria for SARI / HCID patients

- Proven or high likelihood of infection with pathogen of Public Health Interest or pathogen on HCID list
- **OR**
- Experience of the following symptoms during this illness episode: (one or more required for inclusion)
    - History of self-reported feverishness or measured fever of ≥ 38ºC

    - New Cough
    - Dyspnoea (shortness of breath) OR Tachypnoea*
- AND admitted to a healthcare facility (*including long term nursing care and residential mental health facilities)

Only SARI patients as defined in Appendix A will be included in the annual activation internal pilot study.

** Respiratory rate ≥50 breaths/min for <1 year; ≥40 breaths/min for 1-4 years; ≥30 breaths/min for 5-12 years; ≥20 breaths/min for ≥13 years*

1.8.2 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 high suspicion or confirmed infection with a VHF pathogen relevant to the objectives of this protocol
- AND admitted to any healthcare facility

1.8.3 Inclusion criteria for patients with CNS infection

- Fever >=38C or history of fever within 30 days in patients of all ages with one of:
    - altered consciousness (including reduced conscious level, confusion, or a change in personality or behaviour)
    - new onset of seizures (excluding simple febrile seizures)
    - new onset focal neurological deficit
    - Electroencephalographic (EEG), neuroimaging or cerebrospinal fluid examination findings indicative of central nervous system infection

• AND high likelihood of infection with a neuroinvasive pathogen of public health interest

• AND admitted to any healthcare facility

OR

• Confirmed infection with a neuroinvasive pathogen of public health interest

• AND admitted to any healthcare facility

1.8.4 Inclusion criteria for people exposed to or infected with pathogens, toxins, chemicals, and harmful energy of public health interest

This study will enrol any person with suspected or confirmed infection or exposure with a pathogen, or exposure to noxious chemical, toxin or potentially harmful energy source of public health interest regardless of setting be it in the community or a hospital admission. Pathogens, agents or exposures will be described by the investigators taking into consideration position statements issued by of World Health Organisation, UK HSA and other competent authorities. This includes but is not limited to the pathogens on the UK HSA / NHSE list of HCIDs (Appendix s8.3)

Agents and exposures are envisaged to include toxins, noxious substances, sources of radiation and potentially harmful energy. A case or outbreak of disease caused by these agents maybe natural, accidental, or deliberate.

1.8.5 Exclusion criteria

- Confirmed diagnosis of a pathogen unrelated to the objectives of this study and no indication or likelihood of co-infection with a relevant pathogen.

2 Study Design

This is a prospective observational cohort study with data collection and biological sampling for urgent public health research purposes.

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, agents or noxious exposures. Therefore, the sample size is not prospectively determined. Recruitment of participants will depend on the emergence and spread of the various pathogens consequences of noxious exposures balanced by 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, and then observe for changes in pathogen or population response over time.

This protocol will be opened at sites with capacity and capability to recruit to any tier of study intensity. The study will hibernate in the absence of any relevant cases. The study is exempt from NIHR high-level recruitment performance targets. The study has no set end date and no target to recruit to.

3 Methods

3.1 Identification of Potential Participants

Approval of the responsible ethics committee and institutional authority will be obtained before patients are recruited at any site. REC approval has been given for England and Wales by the Oxford C Research Ethics Committee (Ref. 13/SC/0149). Local R&D approvals were required from all Acute NHS Trust in England through an expedited process driven forward at the direction of the Chief Medical Officer for England in October 2013 and managed by the Manchester hub of the NIHR Comprehensive Research Network. This protocol has been approved in Scotland by the Scotland A REC (Ref. 20/SS/0028). Ethical approval has been extended to include sites in Northern Ireland.

In hospital, potential participants will be identified through hospital staff 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 should establish procedures to minimize bias in the selection of participants.

In the community, potential participants may be identified by Health Protection Teams and the study team notified through the relevant national public health authority.

In circumstances where residual material from diagnostic samples taken as part of routine clinical care is of critical research value, patients, their consultees or next of kin may be approached to consent to ISARIC participation and use of their pre-existing biological samples. Identification of potential participants via routine clinical samples will not be utilised unless the sample is critically valuable. Examples would include: a sample of pathogen implicated as an evolution of a resistant strain, a sample of value for development of a diagnostic assay, a sample obtained for routine diagnostic purposes from a case who has died before consent could be give, or for development of a seed strain of path for future research or commercial use (e.g. vaccine development or *in vivo* challenge study).

3.2 Approach to Potential Participants

Identification of potential participants will be made by usual care teams or dedicated research staff after screening admission data or through information shared securely by UK health agencies with the study team.

In most circumstances potential participants will be inpatients and will be approached by locally employed dedicated research staff or members of the usual care team. Given the nature of acute emergency and severity nature of many of the relevant disease, any approach will first be discussed with the usual/direct care team.

In some circumstances potential participants will have been discharged home well or with moderate disease for self-care and or isolation. Decision to discharge will be the responsibility of the usual care team and will have considered the domestic support and capacity.

Two methods of approach exist.

1. Potential participants may be identified by their usual care teams and research nurses familiar with the study objectives
2. Potential participants may be approached by the research team following sharing of personal identifiers by public health agencies, relying in England on Section 251 Regulation 3 of the NHS Act 2006 and the relevant legislation (where that exists) in the devolved nations.

3.2.1 Tier Zero: data collection

Tier Zero activity involves only data collection and requires collection of limited clinical data from the routine health record, pathogen data derived from clinical samples, participant National Health Service or Community Health Index numbers, date of birth and postcode.

Collection of personal identifiers along with clinical data will normally require consent, however an application will be made to the Health Research Authority (HRA) Confidential Advisory Group (CAG) for support to collect such data without consent under Section 251 Regulation 5 of the NHS Act 2006 in England and Wales, to the Public Benefit Privacy Panel approval (in Scotland), and to the Health and Social Care Privacy Advisory Committee (in Northern Ireland).

In the event that the HRA CAG issues approval under regulation 5, or other authority issues equivalence, the approval notice will be shared with sites' R&D offices for their records and the Case Report will highlight this change.

The justification for this waiver is the overriding public health interest, to allow timely linkage with other Health and Social Care Datasets, and to reduce data collection burden in support of other research activity including clinical trials. The collection of identifiers without consent will not take place in Northern Ireland if there is no applicable legislation to support this.

Tier zero participants can find more information about routine data linkage on the study website ISARIC4C.net.

Furthermore, subject to a successful application for support under regulation 5, the requirement to exclude people who have opted out of the National Health Data Sharing for personally identifiable data (Type 1 Opt-out) and deletion of such people's data where it has been collected by automated process will be waived. The justification for this waiver is the overriding public health interest, to avoid bias, specifically where personally identifiable data is required on a geographical basis to ensure comprehensive and accurate description of an affected population, and to permit comprehensive and timely linkage to other data sets such as ONS cause of death, or NHS Immunisation Management Service. Such data will be held within the Trusted Research Environment (Data Save Haven).

3.2.2 Tier One and Two: additional biological sampling

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

Data will be collected per Tier Zero. Tier one and two participants will be made aware of this activity via the information sheets and referred to the study website.

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.

Where adult patients lack capacity to consent to this Clinical Characterisation Protocol, an appropriate 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 consultee and allow them time to discuss and ask questions. The staff will review the informed consent form with the person giving advice and endeavour to ensure understanding of the contents, including study procedures, risks, benefits, the right to withdraw and alternatives to participation.

In some situations, the appropriate consultee, parent or guardian may be confined to a remote location under conditions of quarantine or self-isolation. In these circumstances' consent/consultee advice will be sought by telephone or voice-over-internet communication using a telephone-witnessed consent/consultee declaration form.

At sites working within a paperless environment (e.g. for infection control purposes) electronic consent is permitted only with prior agreement from the CCP-UK central team. Electronic consent systems must exactly mirror the content of the REC approved CCP-UK consent forms.

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 or consultee declaration form. If the patient is a child, the person with parental responsibility and the child, if competent, should both provide consent/ assent. Summary information sheets and consent forms have been produced to reduce the initial burden on patients, parents/guardians and consultees and these summary information sheets will be used as the basis for the consent discussion. The full study information sheets for adult patients, parents/guardians, and consultees will be provided for their information, subsequent to the initial consent discussion.

In view of the importance of early samples, participants or their parent/guardian/consultee will be permitted to consent/give advice 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.

An outbreak involving a pathogen of public health interest or noxious exposure is an emergency situation. Patients who are incapable of giving consent in emergency situations are an exception to the general rule of informed consent in clinical research. This is clearly acknowledged in the Declaration of Helsinki (2008). The process of consent will comply in England and Wales with the Mental Capacity Act 2005 (MCA 2005); in Scotland, with Section 51 of the Adults with Incapacity (Scotland) Act 2000; and in Northern Ireland with the 2016 Mental Capacity (Northern Ireland) Act.

For studies that collect or collate only pseudonymised data that is normally collected, as part of routine care consent may not be required. The internal pilot study will only collate data that is being recorded or generated as part of routine clinical care (e.g. microbiology results). We will seek consent, be it deferred, proxy or assent, in order to test the processes within the overarching Clinical Characterisation Protocol, which include obtaining consent.

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 Consent

Informed consent is one of the founding principles of research ethics. Its intent is that human participants can enter research freely (voluntarily) with full information about what it means for them to take part, and that they give consent before they enter the research.

However, in the context of severe “high consequence” infection or exposure to pathogens, chemicals, toxins or harmful sources of energy, where there is an overriding public health interest, rapid collection of routine clinical data is required along with linkage to secondary data sets, and it is often not practicable to obtain consent. For this reason, during the COVID-19 outbreak the CCP-UK did not obtain consent to collect personal identifiers and clinical data and instead relied on the Secretary of State for Health and Social Care’s notice under

Regulation 3(4) of the Health Service Control of Patient Information Regulations 2002 (COPI Reg 3(4) for short).

We have now ceased collection COVID-19 data. The Health Research Authority (HRA) Confidentiality Advisory Group (CAG) have reviewed our COVID-19 work and measures we have taken to ensure the security of participants'' data. They have also taken account of the views of patients and the public on how our work was conducted. With HRA CAG approval (CAG reference: 21/CAG/0125), we have transitioned to rely on Section 251 Regulation 5 of the NHS Act 2006 from 30th June 2022, which permits the study to collect and retain personal identifiers with clinical information without consent for the purpose of conducting COVID-19 research (last reviewed by ISARIC4C investigators 18 May 2022).

As of 18th May 2022, and until such time as the HRA CAG gives additional approval, all tiers of research activity for the CCP-UK require consent.

Many potential participants in this study will be very unwell, which poses further difficulties with obtaining consent, particularly as visitation is limited to reduce infection and contamination risks, thus limiting the opportunity to approach relatives for consultee discussions. There is a need to avoid bias in the research sample, which excluding the most unwell due to inability to obtain informed consent would introduce. For this reason, an application to HRA CAG for support under on Section 251 Regulation 5 of the NHS Act 2006 for collection of personal identifiers and clinical data including pathogen information has been made. This application has the support of the UK HSA. That application will also include permission to be exempt from the National NHS Data Opt-Out process to avoid bias in data collected and permit timely analysis of the data.

3.5 Sampling from Patients

Prospective sampling of people for research purposes must only be done after gaining consent or assent. After consent is obtained, residual samples may be used for research and development.

Samples required for medical management will always 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 according to the study Laboratory Manual which is subject to change due to the nature of the pathogen of interest and as national guidance is developed.

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

3.6 Sample and Data Collection Schedules

Tier of activity for sampling will reflect local recruitment and laboratory capacity and circumstances of the exposure and disease for example; a single community case with mild disease following exposure to a noxious agent may be supported by public health physicians and primary care research network whereas an outbreak of severe disease affecting many people may be supported by secondary care and their research network.

The below schedules may be modified, depending on the circumstances of a particular outbreak or event, by omitting some samples in order to conserve resources. This will be done by providing all sites with a specific modified schedule, in the format below, with some elements removed. Since this would in all cases result in a reduced burden to patients and recruiting sites, no explicit ethical or management approval will be sought for these omissions.

3.6.1 TIER ZERO schedule – Data only

Collect personal identifiers and clinical data per CRF and facilitate collection of data pertaining to clinical samples of pathogens detected, including viral sequence and pathogens excluded.

3.6.2 TIER 1 schedule [samples sent at room temperature by mail]

In addition to collecting data as in TIER ZERO, a limited sample set is obtained at, or as soon as practical after, recruitment. Samples in tier 1 require no laboratory processing at the recruiting site. To facilitate recall to study long-term sequelae participants who are willing to be contacted will be asked to provide their mobile phone number on the consent form.

Blood sample volumes will be limited by the estimated weight of the patient. In the absence of a measured weight, people age 18 years and over may generally be assumed to be over 40kg unless there is other clinical concern.

3.6.2.1 Throat swabs

Swab both palatopharyngeal arches, making sure they come into direct contact with the tip of the swab; ensure the sample is labelled throat swab

3.6.2.2 Skin, genital, and perianal swabs

If lesions are present on the body swab that lesion with the second swab. Make sure it is labelled to indicate which lesion has been swabbed e.g. lesion left cheek

If a genital or peri-anal lesion is present, use a third swab to sample that lesion, and label the sample so it is clear which lesion was sampled e.g. lesion head of penis

Table 1. Sampling schedule 4 (the primary schedule in use in the UK. See Appendix 2)

	Recruitment	**Week 1**						**Week 2**							**Convalescent sample**
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	>28 days after hospital discharge

Sample set	R		S						S					**S**	C
Priority	1		2						3					5	4

If local resource limitations require sampling frequency to decrease, samples will be prioritised as shown (1=highest priority). Sample sets refer to the tables below: R – Recruitment samples; S- Serial samples; C – convalescent samples.

Where a patient is otherwise medical fit for discharge and symptoms have resolved but the patient remains an in-patient for other reasons the convalescent sample should be taken at day 28 after symptom resolution or shortly thereafter.

Table 2. Maximum blood samples to be obtained at each sampling point in TIER1 (simple, stable samples)

	Blood Samples at tier 1 (simple, stable samples)
>40kg	**6ml** EDTA blood **3ml** blood in blood RNA tube
20 to 40kg	**3ml** EDTA blood **3ml** blood in blood RNA tube
10 to 20kg	**2ml** EDTA blood **2ml** blood in blood RNA tube
4 to 10kg	**1.5ml** EDTA blood **0.5 ml** blood in blood RNA tube
< 4kg	**0.7ml** EDTA blood **0.2ml** blood in blood RNA tube

3.6.3 TIER 2 schedule [laboratory work at site required]

In addition to data and samples collected as in TIER 1 acute serial sample sets and one convalescent set are obtained. Residual material from clinical care, including diagnostic samples, excised tissue/organs, and other materials, may be retained for research purposes, and specific samples will be collected according to the schedule below, including A) a pathogen or toxin detection sample from the relevant site e.g. throat, wound or skin swab, or hair sample B) blood samples C) urine and stool samples.

Table 3. Core sample set – to be obtained at each sampling point. This may be revised in response to specific conditions as some samples will not be necessary or useful.

TIER	CORE SAMPLE SET	Processing/ storage	Purpose
TIER1	**Blood** sample in EDTA tubes	Send by mail at room temperature in UN3373 packaging within one week	Host DNA genomics, methylation
	Blood sample in blood RNA tube (e.g Tempus™ or PAXgene®)		Microarray/RNA sequencing pathogen & host transcriptome

TIER2	Pathogen samples:
	• Respiratory samples:
	  ○ nasal **SAM** strip,
	  ○ throat swab in virus transport medium
	  ○ nose swab in virus transport medium,
	  ○ endotracheal aspirate if intubated,
	  ○ in infants/children who cannot tolerate a SAM strip take a nasopharyngeal aspirate
	• Urine (up to 10ml), do not fill the container.
	• Stool (up to 10ml) or rectal swab;
	• samples from infected sites/vesicles/ulcers/sores.
	• Also store any residual from samples taken for clinical care including bronchoalveolar lavage fluid.
		Do not process at site.
		Keep double-bagged.
		Store at -80°C*
			Pathogen studies to reveal changes in pathogen during infection and during spread between individuals, detect development of resistance.

	Oral fluid (Crevicular fluid)	Store at -80°C*	Non-invasive determination of humoral immune response
	Blood sample in serum (clotted) tubes	Serum (3 aliquots -80°C*)	Mediators/biomarkers
			Serology
	Blood sample in EDTA tubes	Plasma (3 aliquots -80°C*)	Mediators/ metabolites/ biomarkers
			Detect RNA/DNA from pathogens.
		Cell fraction (1 aliquot -80°C*)	RNA/DNA from pathogen, cellular immunology.
	Blood sample in 3.2% sodium citrate tube	Citrated plasma (2 aliquots -80°C*)	Coagulation function

*freeze at -80°C where possible, or at least at -20°C. If necessary (eg. weekends/public holidays) store in refrigerator until processing. For details, see Sample processing section.

Table 4. Maximum blood volumes by weight and schedule for recruitment in TIER2

	Samples at each scheduled time in tier 2 or above	Total volume of blood
>40kg	**3ml** blood in blood RNA tube [TIER1: send in mail] **3ml** (1x3ml) EDTA blood [TIER1: send in mail] **6ml** (2x3ml) EDTA blood **3ml** blood in serum(clotted) tube **3.5ml** blood in sodium citrate tube Research pathogen samples	Maximum any day: 18.5ml (0.46ml/kg) Maximum any 4 weeks: 96ml (max 2.4ml/kg)
20 to 40kg	**3ml** blood in blood RNA tube [TIER1: send in mail] **3ml** EDTA blood [TIER1: send in mail] **3ml** EDTA blood **3ml** blood in serum(clotted) tube **3ml** blood in sodium citrate tube Research pathogen samples	Maximum any day: 15ml (0.6ml/kg) Maximum any 4 weeks: 42ml (max 2.1ml/kg)
10 to 20kg	**2ml** blood in blood RNA tube [TIER1: send in mail] **1ml** EDTA blood [TIER1: send in mail] **1 ml** EDTA blood **2ml** blood in serum(clotted) tube **2ml** blood in sodium citrate tube Research pathogen samples	Maximum any day: 8ml (0.6ml/kg) Maximum any 4 weeks: 23.6ml (max 2.36ml/kg)
4 to 10kg	**0.5 ml** blood in blood RNA tube [TIER1: send in mail] **1ml** EDTA blood **0.5ml** blood in serum(clotted) tube **0.5ml** blood in sodium citrate tube Research pathogen samples	Maximum any day: 2.5ml (0.5ml/kg) Maximum any 4 weeks: 9.4ml (max 2.35ml/kg)
< 4kg	**0.2ml** blood in blood RNA tube [TIER1: send in mail] **0.5ml** EDTA blood **0.2ml** blood in serum(clotted) tube **0.2ml** blood in sodium citrate tube Research pathogen samples	Maximum any day: 1.1ml (~0.27ml/kg) Maximum any 4 weeks: 4.4ml (max 2.4ml/kg)

Blood sample volumes will be limited by the estimated weight of the patient. In the absence of a measured weight, people age 18 years and over may generally be assumed to be over 40kg unless there is other clinical concern.

Table 5. Data collection and documentation.

	Samples/documents
R – RECRUITMENT SAMPLE SET	Consent form OBTAIN SAMPLE SET Initiate CCP CASE REPORT FORM Complete ADMISSION and DAILY FORM
S- SERIAL SAMPLE SET	OBTAIN SAMPLE SET Complete another DAILY FORM
On hospital discharge	Complete OUTCOME FORM Plan convalescent visit
C – CONVALESCENT SAMPLE SET	OBTAIN SAMPLE SET Update OUTCOME FORM

Table 6. Samples to be taken for cases of topical exposure to toxins and chemicals.

At recruitment	**Sample**
	Hair sample
	Skin swab

3.6.4 For CNS infections only – residual cerebrospinal fluid from clinical sampling

Table 7. Cerebrospinal fluid sampling

Sample	Processing	Purpose
Additional cerebrospinal fluid sample during clinical lumbar puncture If after recruitment a lumbar puncture is clinically indicated, an additional sample of up to 5mls (Table 6) will be collected in a universal sterile tube, provided it is deemed appropriate by the supervising clinician. Any residual CSF from samples taken as part of routine clinical care will be collected and stored if available.	3 aliquots stored at -80°C, according to relevant UK HSA guidance.	Extract RNA/DNA from causative pathogens and other circulating pathogens for molecular testing, genomic studies and virus isolation
		Perform serological testing for pathogen-specific antibodies
		Test for mediators, metabolites and potential biomarkers

Table 8. Estimates of CSF production rate, total CSF volume and the safe recommended CSF volume taken at lumbar puncture for different age groups. Taken from the British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central

Age	Mean CSF production rate (ml/h)	Total CSF Volume (mls)	Safe CSF volume to take at LP (mls)
Adult	22	150-170	Maximum: 15-17
Adolescent	18	120-170	Maximum: 12-17
Young child	12	100-150	Maximum: 10-15
Infant	10	60-90	Maximum: 6-9
Term Neonate	1	20-40	Maximum: 2-4

3.6.5 Optional sub-studies

<table>
<tr><th>SUB-STUDY</th><th colspan="2">SAMPLE SET AND SAMPLE</th><th>Processing/storage</th><th>PURPOSE</th></tr>
<tr><td colspan="5">(Each sub-study will only operate in a small number of sites. Any site participating in a sub-study will alert staff to this fact in the TIER RECORD FORM at the front of the site file)</td></tr>
<tr><td rowspan="6">PHARMACOKINETICS*</td><td colspan="2">ADD TO R, S, & C SAMPLE SETS:
EDTA or fluoride oxalate blood sample</td><td rowspan="6">Separation and storage of plasma.</td><td rowspan="6">Test for drug levels. Store aliquot for other studies.</td></tr>
<tr><td colspan="2">Volumes</td></tr>
<tr><td>>40kg:</td><td>3ml</td></tr>
<tr><td>20 to 40kg:</td><td>0.5ml</td></tr>
<tr><td>10 to 20kg:</td><td>0.2ml</td></tr>
<tr><td>4 to 10kg:</td><td>0.2ml</td></tr>
<tr><td></td><td>< 4kg:</td><td>0.2ml</td></tr>
<tr><td rowspan="2">CELLULAR IMMUNOLOGY*</td><td colspan="2">ACUTE
Additional 24mL blood sample added to R and S sample sets</td><td rowspan="2">Separation and storage of plasma.

Extraction of PBMC.</td><td rowspan="2">Immune cell phenotyping, transcriptomics, T-cell epitope mapping, monoclonal antibody generation</td></tr>
<tr><td colspan="2">CONVALESCENT
Maximum 470mL blood over 16 weeks</td></tr>
<tr><td>LARGE-VOLUME CONVALESCENT SAMPLING*</td><td colspan="2">Up to 240mls of whole blood in fully recovered patients</td><td>Separation and storage of plasma.

Extraction of PBMC.</td><td>Serology tests, international standards, monoclonal antibodies</td></tr>
<tr><td>SERIAL SEROLOGY</td><td colspan="2">Sample set obtained up to monthly for up to 3 years per weight schedule
5-10mL clotted blood,
2.5mL blood in RNA tube,
3.5mL blood in sodium citrate tube
Oral crevicular fluid swab.
Throat swab in VTM
Nose swab in VTM</td><td>Table 9</td><td>Quantify nature and duration of humoral immunity.
T-cell and B-cell receptor sequencing.</td></tr>
</table>

SERIAL BAL DURING ECMO	120mL 0.9% saline BAL, performed on days 1, 3, and 9.	Centrifugation to obtain cell pellet and supernatant. Storage at -80°C.	Study host immune response, viral replication and co-infection
ENVIRONMENTAL (AIR & SURFACE) SAMPLING	Air samples and wabs of environmental surfaces from within patient vicinity	Air sample units and surface swabs will be stored at Imperial College London	Study spread of virus through air
THROAT, SEMEN, and VAGINAL SAMPLING	Semen sample and intra vaginal swab on day of discharge	Store intact at -80°C, or first-class post to laboratory according to activation and pathogen.	Describe infectious potential by sexual transmission using culture and molecular techniques
SERIAL THROAT, VESICLE, and SCAB SAMPLING	E-swab in UTM. Scabs in 30ml Universal container (one per day).	Store intact at -80°C, or first-class post to laboratory according to activation and pathogen.	Describe period of shedding of potentially infectious pathogen by using culture and molecular techniques
Monkeypox virus disease sampling	Per CCP-UK plus one additional sampling on d14	As per CCP-UK	To describe clinical, virological and safety outcomes in patients with monkeypox virus disease treated or not treated with tecovirimat.

*In order to limit excessive volume sampling, patients will **not be enrolled in more than one** of the pharmacokinetics, cellular immunology, or large-volume convalescent sampling sub-studies.

Table 9. Consent forms for biological sampling for sub-studies

Sub-study	**Sampling**	**Relevant PISC**
Serial BAL during ECMO	BAL	CCP-UK Consultee/Adult
Cellular Immunology	Acute (blood)	CCP-UK Consultee/Adult
	Convalescent (blood)	Extra Convalescent
Large Volume Convalescent Sampling	Blood	Extra Convalescent
Serial Serology	Core sample set	Serial Serology

3.6.5.1 Serial bronchoalveolar lavage during extra-corporeal membrane oxygenation

In small numbers of patients with refractory respiratory failure due to SARI receiving extra-corporeal membrane oxygenation (ECMO) in a specialist centre, the opportunity exists to safely perform serial bronchoscopy for research purposes without the risk of impairing oxygenation (in contrast to bronchoscopy performed when oxygenation is dependent on mechanical ventilation). This is also safer for the operator since the patient can be paralysed and ventilation can be temporarily discontinued, significantly reducing aerosol generation.

Broncho-alveolar lavage (BAL) specimens obtained in this context could be processed to allow analysis of viral load, bacterial or fungal co-infection, and host soluble immune mediators in the distal airway.

3.6.5.2 Cellular immunology

In selected centres with appropriate facilities and training, selected participants with a variety of severe and non-severe illness will be asked to donate additional larger blood volumes for PBMC isolation at one or more timepoints during acute illness and convalescence for detailed immune profiling. Acute samples will be obtained according to the Tier 2 biological sampling schedule (days 1, 3 and 9). Longitudinal convalescent samples obtained following discharge and recovery will not exceed 470ml in 16 weeks.

3.6.5.3 Large-volume convalescent sampling

In a small number of patients (likely to be around 100 patients for each emerging infection) there is a need for additional sampling after recovery from acute illness to enable generation of serological tests, setting of reference standards for serology, extraction and culture of peripheral blood mononuclear cells (PBMCs) for cellular immunology studies, and generation of monoclonal antibodies for research, diagnostic and therapeutic use. These studies are often extremely valuable in the global response to a new pathogen.

Immune cells, including monocytes, monocyte-derived macrophages, neutrophils and lymphocytes will be isolated from peripheral blood and studied immediately or following culture. Gene expression, protein synthesis and degradation, cytokine release and other functional studies will be measured in immune cells from cases and age- and sex-matched controls. Cells will be stored for future use and may be used in the generation of commercial products.

Patients who participated, with appropriate consent, in this study may be invited to provide additional samples under separate consent for this part of the study. All blood samples will be obtained by an experienced phlebotomist. Participants will be fully recovered, otherwise healthy individuals with no contraindications to blood donation, including:

- Infection with any blood borne diseases (e.g. HIV, Hepatitis B or Hepatitis C)
- Previous or current intravenous drug abuse
- Current anaemia
- Blood clotting disorders
- Current anticoagulant (blood thinning) drug therapy
- History of donations to the blood transfusion service (or any other donation) within the last 12 weeks.

Depending on the participant's weight, the following maximum volumes of blood will be obtained:

- >40kg: 240mls (6.0mls/kg)

- 20-40kg: calculated[3] at 2.4ml/kg
- <20kg: calculated at 2.4ml/kg

3.6.5.4 Long-term evolution of cellular and humoral immunity in survivors

In selected patients who give consent to be contacted after discharge, we will invite participation by telephone call and SMS reminders to participate in a three-year follow-up study of the evolution of cellular and humoral immunity. We will deliberately target survivors from centres supported by Clinical Research Facilities, and survivors who have identified themselves as Health Care Workers. Survivors with be invited and reminded by telephone and SMS to return to a clinical research facility at intervals not more than monthly and in most cases 3 monthly, to give a sample set not exceeding that described in the main protocol. Local travel expenses (by standard class fare if public transport) will be reimbursed. This study will involve people of all ages.

3.6.5.5 Long-term consequences of infection or exposure

Subject to resources being available: In those who give consent to be contacted after discharge, we will invite participation in a three-year follow-up study of the sequelae of infection or exposure. Participants will be initially invited at their 28-day post-discharge follow-up visit, or by post. Surveys will be completed at clinic visits (e.g. 28-day post-discharge follow-up) or via paper copies posted to the participants home address with a prepaid envelope for their return. Surveys will be sent not more than every 3 months. Interviews will be recorded and transcribed via professional transcription service. Consent for interview invitation is included as an optional statement on all relevant PISCs. Consent for interview participation and recording of the interview will be sought at the commencement of each interview and documented in the transcription.

3.6.5.6 Environmental sampling

In a small number of cases, samples from around the subject may be obtained using air-sampling devices which will be placed in unobtrusive locations in the subject's vicinity, and swabs will be taken from the environmental surfaces. These samples will be tested specifically for the pathogen or exposure of interest. This is in order to better understand the spread of a pathogen through the air. Results from this environmental analysis will be linked to subject data. We shall not seek formal consent for this additional sampling activity, as enhanced environmental sampling is part of infection or exposure prevention control in any outbreak.

3.6.5.7 Additional Semen, Meatal and Vaginal sampling

In a small number of cases at a limited number of sites, participants over the age of sixteen will be asked to provide genital samples to establish if the pathogen or agent of exposure is transmissible by that route.
We will ask men over the age of sixteen to provide a semen sample and swab from the meatal (urethral entrance at the tip of the penis) on the day of discharge from hospital. We will ask women over the age of sixteen to provide a vaginal swab on the day of discharge from

[3] Hawcutt DB et al. Points to Consider when Planning the Collection of Blood or Tissue Samples in Clinical Trials of Investigational Medicinal Products in Children, Infants and Neonates. In Rose K, van den Anker JN (eds): Guide to Paediatric Drug Development and Clinical Research. Basel, Karger, 2010, pp 97–110 (DOI:10.1159/000315578)

hospital. These samples will be collected in privacy. Swabs can be self-administered. We may ask participants to provide the same samples on the 28th day after discharge from Hospital.

3.6.5.8 Serial Throat, Vesicle and Scab sampling

In a small number of cases at a limited number of sites, participants will be asked to provide serially (daily or less frequent): a throat swab, swab from most recent vesicle, a swab from a specific lesion, scabs, and if lesions are present in these areas an external genital and or perianal swab. Digital photography may be involved to aid recording of lesion patterns and consistency of swabbing. According to pathogen and nature of disease the sampling schedule may be daily or reduced to a less frequent regime e.g. d1 (recruitment), d3, d7, d14, d21 and d28.

3.6.5.9 Monkeypox virus disease sampling

The Monkeypox ObServAtional Cohort (MOSAIC) is a REC approved multi-country, multi-centre research study that collects clinical data and biological samples on patients with laboratory-confirmed human monkeypox disease. [IRAS: 316821, East of England - Cambridge East Research Ethics Committee, approval 22/EE/0143, 27 June 2022]. MOSIAC will describe the clinical, virological and safety outcomes in patients with monkeypox virus disease treated or not treated with tecovirimat and other antiviral drugs.

A study related to MOSAIC was first opened in the Central African Republic in December 2021 by ISARIC Investigators, as an expanded access protocol [ISRCTN43307947]. With the recent spread of the West African Clade of Monkeypox, the MOSAIC protocol has been revised to run outside of Africa as an observational study. MOSAIC bears remarkable similarity to the CCP study which is running in many countries, and in the UK is supported by NIHR. MOSAIC has an additional sampling point at d14 not present in previous versions of the CCP and additional safety data will be collected by the MOSAIC study team. During the COVID-19 outbreak the CCP-UK protocol was harmonised with the Bio-AID study, allowing Bio-AID to co-enrol and rely on CCP-UK processes and infrastructure for data and sample collection. This smart working reduced research burden on participants and staff during a period of system stress. Likewise, we are now harmonising CCP-UK with MOSAIC.

The purpose of MOSAIC is to provide augmented clinical data for patients with Monkeypox, particularly for patients who are receiving antiviral treatments given the paucity of human treatment data. Patients are not allocated to a treatment arm and the study is independent of decision to treat. Patients are offered enrolment at the time of their initial clinical consultation with suspected disease. Data collection includes clinical review, an online self-assessment symptom questionnaire, and biologic sampling in patients who present to hospital for review. Patients are followed up for six months (or until the end of pregnancy if they are pregnant).

The MOSAIC model and pre-existing infrastructure will be adapted to recruit all hospitalised patients undergoing MPXV testing at selected sites in the UK. Potential participants (or their consultees) will be approached by the local study teams to obtain informed consent for both MOSAIC and CCP-UK. For patients who are in hospital, biologic samples (blood, throat, and lesion swabs) will be taken at baseline, on day 3, 7, 14 and 28, with a +/- 48hr sampling window. This now aligns with the updated Tier 2 biological sampling schedule.

3.7 Enrolment Procedures for Patients

Patients who meet the inclusion 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, or be it deferred, proxy or assent, will be enrolled to the study. With due consideration to the circumstances of admission to a high-level isolation unit a summary information sheet will be used as the basis of the consent discussion and a full study information sheet will be given subsequent to the consent discussion.

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 obtain a core sample set (see above). 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.

During the one week of test activation for the internal pilot study, we will collect only pseudonymised data from patients that meet the selection criteria defined in Appendix A.

Regardless of consent, data from patients who meet inclusion criteria will be collected due to the overriding interest of public health. Where this data is routine and depersonalised then it can be collected without consent and without further approval. Where the data contains personal identifiers, that data will only be collected without consent while country specific approvals are in place to do so.

3.8 Case Report Form and Participant Numbers

Case Report Forms (CRFs), based on the WHO Natural History Protocol Case Report Forms, will be used to collect data at enrolment to this study. For this protocol, there are three sets of CRFs – Generic, Viral Haemorhagic Fever (VHF), and Central Nervous System (CNS). These can be downloaded and completed after site setup at https://isaric4c.net/protocols/ In instances where a patient is admitted alive but subsequently dies and an infection with a pathogen of interest is confirmed post-mortem, CRF data will be collected retrospectively.

Participant numbers consist of a 5-character digit ODS site code and a 4-digit patient number. A site Organisation Data Service (ODS) number (aka CMPS number) is known by your local R&D Office. 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 –Rapid CRF.

For the internal pilot study, TIER ZERO data collection only will be used at each site using the CRF. The eCRF is available by registering on the data management system at https://isaric4c.net/protocols/ by contacting ccp@liverpool.ac.uk. For the full study and internal pilot, each patient will be identified via a unique patient number consisting of a 5-character site code Organisation Data Service code [https://odsportal.digital.nhs.uk/Organisation/Search]), and each patient must be assigned a5-

digit sequential patient code. Sites must retain, in secure format, an enrolment log of all participant numbers and personal identifiers/

3.9 Follow-Up Procedures for Patients

Follow-up procedures will be undertaken only when resources allow according to TIER 2 sampling outlined 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.

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.

Follow-Up procedures may include contact by writing, telephone, SMS and contemporary communications media as may evolve, as stated in the PIS. These may lead to interviews or automated surveys as outlined in the *Post COVID-19 Sequelae* sub-study or further biological sampling (using sample sets included in main protocol or relevant sub-study to which the participant will have consented). The purpose of such activity is to invite to contribute in sub-studies to better understand the immune response and sequelae of infection or exposures of public health interest.

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.

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.

3.10 Withdrawal of Patients

Patients enrolled to the study whose illness is subsequently confirmed to be the result of infection with a pathogen or exposure which is not relevant to the objectives of this study, and who have no indication or likelihood of co-infection with a relevant pathogen or exposure, will be withdrawn. No further follow-up will be conducted. Samples collected prior to withdrawal will be retained unless the participant requests they be destroyed.

Patient autonomy to withdraw from sampling at Tiers 1 and 2 of study at any time must be respected, and residual samples will be destroyed.

Subject to a successful application for a Confidentiality Advisory Group s251 waiver or issue of a Control Of Patient Information (COPI) notice (in England and Wales) or Public Benefit Privacy Panel approval (in Scotland), or Health and Social Care Privacy Advisory Committee (in Northern Ireland), there will be no right for patients to withdraw data collected for the purpose of this study.

4 Specimens and Laboratory Analysis

4.1 Specimen Sampling, Storage Procedures and Transport

Appropriate selection and timely collection of high-quality specimens, proper storage procedures and comprehensive diagnostic testing will ensure the quality of data.

The UK Health Security Agency (as successor to Public Health England (PHE)) is a co-applicant on this study. PHE 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 and CNS pathogens will be sent to the Outbreak Laboratory in Liverpool (University of Liverpool). It is expected that BSL4 VH pathogen samples will be sent to UKHSA, however BSL4 clinical and research capacity may be commissioned at other places.

In dealing with novel pathogens where little is known about transmissibility and 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 UK HSA, which would support a local, risk assessment and SOP covering the handling of samples from the affected patient.

Novel respiratory infections or neurological infections may be classified into HG2, HG3 or HG4, as is the case for the currently included pathogens, novel coronavirus MERS-CoV, influenza A/H7N9, A/H5N1, viral haemorrhagic fever ebolavirus and known subtypes of TBEV, including European (TBEV-Eu), Far Eastern (TBEV-FE), Siberian (TBEV-Sib), Baikalian (TBEV-Blk), Himalayan (TBEV-Him) and TBEV-UK.

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

All samples collected must be labelled as per hospital procedure with appropriate identification (full patient identifiers) and hazard labelling according to local policy and ideally marked with a freeze-proof research label or with a solvent resistant marker. These samples that retain full identifiers will be stored within a home office approved high security facility. Samples collected in the household will be labelled with pseudonymised 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 (outside the HPRU and Outbreak Laboratory Liverpool and HPRU Imperial, UK HSA Colindale and UK HSA Porton) will be pseudonymised 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.

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

Research samples for SARI cases in England and Wales will be transported to the Health Protection Research Unit in Liverpool. In Scotland samples will be transported to the MRC Virology Unit in Glasgow. VHF samples will be sent to the UK HSA laboratories to be agreed at that time. The study team will organise couriers.

Patient data submitted on the CRF or eCRF must be pseudonymised using the following procedure. Participant numbers consist of a common 5-character Organisation Digital Service (ODS) site code and a unique 5-digit patient number. Your R&D Office will know your ODS site code. Your site must maintain a recruitment log linking consent to Participant ID numbers.

Patient numbers should be assigned sequentially by 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 UK HSA laboratory or the Health Protection Research Units in Liverpool and the only link between the patient's identifying data and this code will be held securely and shared only with the study

administrators. The study administrators will link patient data numbers with sample identifiers. The patient identifiers will not be shared with any party.

Residual volumes available after clinical and research testing is complete will be retained for future ethically approved research and this may include commercial purposes.

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

4.3.1 Tier 1 sample processing

No processing is required at site. Samples will be shipped at room temperature to the outbreak lab for processing and distribution.

4.3.2 Tier 2 sample processing

Table 9. Initial sample processing

Sample	Initial processing	Aliquots	Initial transfer	Further processing	Ultimate use
Blood samples (EDTA)	Post at room temperature in UN3373 packaging	No lab processing at site	**Core Genomics Laboratory, Western General Hospital, University of Edinburgh**	DNA extraction	Microarray genotyping, genome sequencing
Blood samples (RNA tube)	Post at room temperature in UN3373 packaging	No lab processing at site		RNA extraction	Microarray analysis and/or RNA seq analysis of host and pathogen RNA
Blood samples (clotted)	Centrifuge 1500g for 10mins.	Supernatant: freeze at -80°C*	**Outbreak Laboratory, Ronald Ross Building, University of Liverpool** **OR** **Outbreak Laboratory, Centre for Virology Research, University of Glasgow**	UK HSA or Outbreak Lab Liverpool	Serology
		Supernatant: freeze at -80°C*		Imperial College London	Circulating mediators by multiplex cytokine/chemokine assays and proteomics
		Supernatant: freeze at -80°C*		UK HSA or Outbreak Lab Liverpool	Mediators/proteomics other assays
Blood samples (EDTA)	Centrifuge 1500g for 10mins ideally at 4°C.	Supernatant: freeze at -80°C*		UK HSA or Outbreak Lab Liverpool	Serology
		Supernatant: freeze at -80°C*		Imperial College London	Circulating mediators by multiplex cytokine/chemokine assays
		Supernatant: freeze at -80°C*		Outbreak Lab Liverpool	Other studies (eg pharmacokinetics/ pharmacodynamics)
		Cell pellet: freeze at -80°C*		Roslin Institute (DNA extraction)	High-throughput genotyping and/or high coverage genome sequencing
Blood samples (3.2% sodium citrate)	Centrifuge 2600g for 10mins with brake off (or slow stop).	Supernatant (2 aliquots - 80°C*)		Outbreak Lab Liverpool	Coagulation function
CSF (if acquired)	Freeze at -80°C*	Aliquot if safe to do so into 3 aliquots Freeze at -80°C*		UK HSA or Outbreak Lab Liverpool	Pathogen detection, quantification, viral genome sequencing and isolation
					Serology

					Circulating mediators by multiplex cytokine/chemokine assays and proteomics
Pathogen samples (e.g. swabs & scabs	Do not process	Freeze at -80 °C*		UK HSA or Outbreak Lab Liverpool	Pathogen detection, quantification and viral genome sequencing and isolation.

*freeze at -80°C where possible, or at least at -20°C. If necessary (eg. weekends/public holidays) store in refrigerator until processing.

Sample processing should follow relevant UK HSA guidance.

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 pseudonymised 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, pseudonymised clinical 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 independent 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).

4.4.1 Research Plan for samples

This document is a standardized protocol for the rapid, coordinated clinical investigation of any emerging infections causing severe acute illness, or pathogen of public interest. 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, viral haemorrhagic fever in 2014 and tick-borne encephalitis virus (TBEV) in 2019. However, it is not limited 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.

A high-level overview of research intentions by research institution is given here. However, no such plan can be predictive of future research questions and priorities. Investigators will meet to plan any such work before it commences. Samples may be used for commercial purposes, with appropriate consent.

UK Health Security Agency Laboratories at Colindale (Maria Zambon, Meera Chand, Samreen Ijaz) Porton Down (Tim Brooks) and the Outbreak Lab in Liverpool (Calum Semple/Lance Turtle/ Tom Fletcher), Glasgow (Massimo Palmarini, Antonia Ho), London (Peter Openshaw) and Edinburgh (Kenneth Baillie, Clark Russell) will be responsible for the

primary processing and storage of samples obtained from patients (with appropriate biological safety measures in place) and pseudonymisation of samples prior to forwarding to other research institutions. Studies will include serology, proteomics, 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, proteomic and biomarker profiles will be correlated with clinical data and outputs from other laboratories within the study. Together, these data can be used to help understand pathogenesis, measure biological responses to novel treatments and help identify new therapeutic strategies. Serial serology tests will be used to characterise pre-existing and reactive adaptive immune responses.

Whole blood RNA tubes and EDTA blood tubes for DNA will be sent to the University of Edinburgh (PI JK Baillie) where DNA and RNA will be extracted. Host and pathogen transcriptomic analyses will be undertaken, including pathogen RNA and DNA sequencing and host gene expression profiling of whole blood RNA to identify and explore the interaction of host and viral factors during the course of infection. Where possible, genotype comparisons of affected individuals with population controls will be used to identify, characterise and confirm genetic associations with susceptibility to infection or severity of infection.

Liverpool (CI Calum Semple, Tom Solomon, Tom Fletcher & Lance Turtle) will conduct clinical characterisation studies based on clinical features and outcome in collaboration with ISARIC Clinical Coordination team (Gail Carson, Laura Merson). The University of Liverpool (CI Calum Semple, Tom Solomon & Lance Turtle), will if required provide additional capacity to contribute to the primary processing and storage of samples and then quantify soluble immune mediators using proteomics, multiplex technology, in CSF, blood and respiratory tract samples. Long read length sequencing using MinION will be used to characterize respiratory and pathogen samples from patients providing information on pathogen genotypes and the host transcriptome (Hiscox). This will be done either at the Royal Liverpool Hospital High Level Isolation Unit or within the CL3/CL2 laboratories at Liverpool, as appropriate.

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 (e.g. disease severity, liver or renal impairment, dialysis, children, pregnancy) and treatment response. Drug levels will be measured in plasma and other relevant samples.

UK Health Security Agency has a diverse portfolio of activity. It is anticipated that blood and oral fluid samples will be used to develop and validate diagnostic assays, and pathogen samples used to describe the molecular epidemiology of an outbreak.

Any use may include or lead to commercial development of diagnostic and therapeutic products and processes.

4.5 Future Use of Samples

All use of data and samples will be controlled by the Independent Data and Material Access Committee (IDAMAC; see below).

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, including commercial use.

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.

Future use may include commercial development of diagnostic and therapeutic products and processes.

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 study administrators 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 with the relevant CRF for SARI, VHF, CNS or other emerging infections of public health interest will be completed by a study staff as appropriate. The data will be pseudonymised at site and a study number issued.

The NHS, CHI or H&SC number, date of birth and postcode will be recorded for data linkage, subject to Confidentiality Advisory Group (CAG) section 251 regulation 5 support or presence of a Control Of Private Information (COPI) notice, or other relevant country approval. This will include linkage to information stored in NHS electronic medical records and national radiology databases. The participant's telephone number will be recorded at time of consent so they can be contacted to arrange convalescent samples and invited to participate in future studies or to provide SMS linked to health surveys.

6.2 Data Management

When available, data collected by staff at each site will be submitted electronically to a protected online database. Pseudonymised 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. The European Union General Data Protection Regulation (GDPR) and UK Data Protection Act 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.

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

The Participant List (enrolment log) is maintained locally and is not to be transferred to any other location, except the ISARIC coordinating centre to allow linkage with laboratory research findings. The sites will compile an enrolment log including the patient's name, date of birth, hospital identification number and unique study number. Subsequent data will be identified by the unique patient study number only (consist of a 3-digit site code and a 4-digit patient number; see section on Case Report Form and Patient Numbers). The enrolment log and study data will be kept separately.

6.3 Data Retention

The value of detailed clinical information about acute disease and outcome caused by exposure to novel pathogens and other agents of public health interest is immense, particularly as the long-term sequelae cannot be predicted with certainty. Thus, we do not intend to destroy the data. We shall archive the data in a trusted research environment (Data Safe Haven) and manage access through an Independent Data and Material Access Committee (for IDAMAC process see https://isaric4c.net/sample_access/)

We also note that this data will fall within 'Archiving in the public interest' as described in the Data Protection Act 2018 as an exemption to the usual GDPR provisions and therefore should allow for this (DPA Schedule 2, Part 6, paragraph 28).

6.4 Data Linkage

For the purposes of deeper clinical characterisation and timely, well-targeted clinical trials in the patient population it is essential to link the current ISARIC CCP-UK research records with routinely collected NHS and related health and care records. Prospective CCP-UK sampling is collecting NHS Number for patients in England, and CHI number is Scotland.

Participant identifiers (NHS/CHI/H&SC number, date of birth, postcode & gender) will be used to request health and social care data from the Health & Social Care Information Centre (H&SC IC) for HES, from the relevant hospital finance departments for hospital administrative data and ONS for deaths and in Scotland from Public Health Scotland (PHS),

GPs and NHS Scotland Boards for hospitalisation and testing data (SMR01, SMR00, SMR02 Prescribing, ECOSS (Covid-19 tests), SICSAG (intensive care data)), and National Records of Scotland (NRS) for deaths.

Provided such notices remain in force, consent for data release from NHS Digital will not be sought under the terms of the Control of Patient Information notice of 20/03/20 (https://digital.nhs.uk/coronavirus/coronavirus-covid-19-response-information-governance-hub/control-of-patient-information-copi-notice). Consent for data release from these routine data sources will not be sought under the terms of Public Benefit and Privacy Panel for Health and Social Care (PBPP) approval, as granted for this study on 17th April 2020, and any subsequent amendments or extensions to this approval as required.

Under the provisions of the existing COPI notice for COVID-19 and any subsequent CAGs251r5 approval, we will flow data from CCP-UK patients' records from NHS Digital and or NHSx into a secure intermediate CCP-UK database hosted by Arden and GEM Commissioning Support Unit (CSU), drawing on their experience of processing linked Secondary Uses Service and GP data, which we need to flow from NHS Digital and or NHSx. Under the provisions of the existing PBPP approval and any subsequent amendments to this approval, we will flow data from CCP-UK patients' records from NHS Scotland, GPs, PHS and NRS into a secure intermediate CCP-UK database hosted by Arden and GEM Commissioning Support Unit (CSU), drawing on their experience of processing linked Secondary Uses Service and GP data. The CSU staff will work with NHS Digital, Liverpool Clinical Trials Centre, and Oxford University who host the CCP-UK database, to run an intermediate database holding complete NHS records and transferring only the information needed to enhance disease characterisation into the secondary CCP-UK database.

Access to longitudinal patient records is vital for providing the fullest insights needed to respond to exposure to novel pathogens and other agents of public health interest in a timely and accurate manner. Researchers outside of the ISARIC CCP-UK investigators will only have access to the data relevant to their separately ethically approved research questions and it will be provided in a de-identified form, which will be held in an accredited safe haven (trustworthy analytic environment), minimising the risk of inappropriate access to identifiable information. Use of the data will be fully audited and controlled.

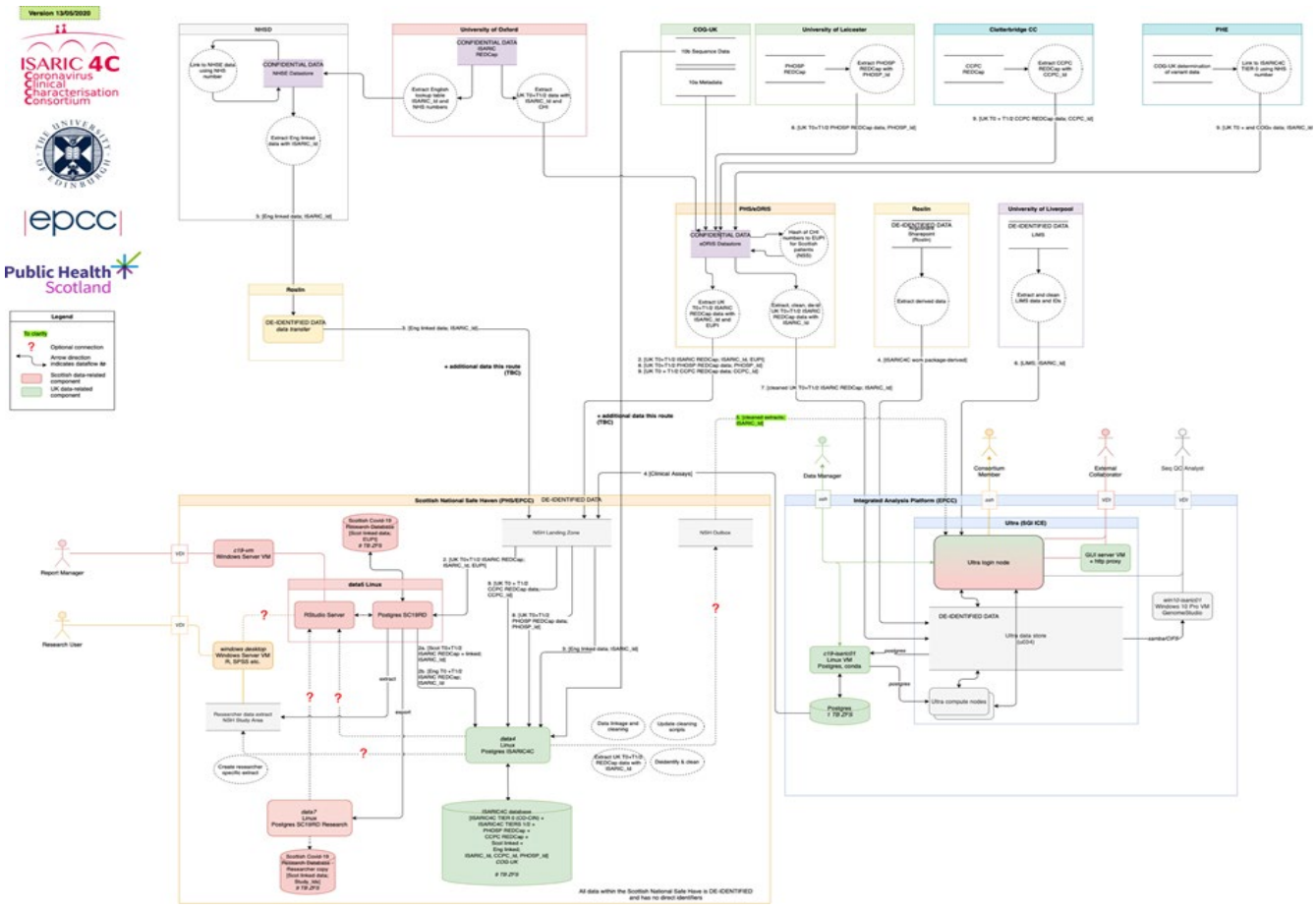

Figure 2: Data Flow for CCP-UK showing linkage with routine health data

6.5 Data Access and Data Sharing

All use of depersonalised data, data including limited identifiers (e.g. NHS number subject to National Confidentiality Panel approval) and biological samples will be controlled by the Independent Data and Materials Access Committee (IDAMAC).

6.5.1 Independent data and materials access committee (IDAMAC)

The IDAMAC will comprise seven senior, independent people with broad representation including research funders, academia, medicine, industry and public health. These individuals will not be involved in the acquisition or analysis of samples or data.

All samples, generated data and materials will be governed by the IDAMAC. The IDAMAC will authorise use of samples and dissemination of results. Disputes will be resolved by majority vote of the IDAMAC. The committee will meet virtually using teleconference every 3 months for the duration of the project, and on an ad hoc basis thereafter. New appointments to the IDAMAC to replace retiring members will be proposed by the chair and approved by majority vote of the committee.

6.5.2 Principles of data and materials access

The IDAMAC will facilitate and prioritise urgent investigations (from any sector, including public health, academic and commercial) with a high probability of impact in a given outbreak.

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.

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.

6.6 Data Quality

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

- An online start-up tutorial for all investigators prior to study commencement will be held to ensure consistency in procedures;
- A detailed data dictionary defines the data to be collected on the case report form;
- Quality checks will be built into the data management system and there will be quality checks of critical data points entered into the CRFs to ensure standardization and validity of the data collected;

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

6.6.1 Monitoring

Data monitoring will be conducted on a randomly selected subset (up to 5%) of cases, through discussion with the local site investigator to discuss data collection techniques. Direct site visits will not be feasible, given the scope of the study.

7 Ethical Considerations

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

Medical management of participants in this study and public health protection activities 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

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

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.

An outbreak involving a pathogen or other exposure of public health interest is an emergency situation. For patients who are incapable of giving consent in emergency situations, the process of consent will comply in England and Wales with the Mental Capacity Act 2005 (MCA 2005); in Scotland, with Section 51 of the Adults with Incapacity (Scotland) Act 2000; and in Northern Ireland, with the 2016 Mental Capacity (Northern Ireland) Act. These are exceptions clearly acknowledged in the Declaration of Helsinki (2008), the following process will be observed:

- All efforts will be made to have consent from appropriate consultee /guardian/carer when available, and from the patient at the earliest opportunity.
- If a patient is incapable of giving consent and there is no relative/representative present, two doctors (one independent of the study team with knowledge of the patient condition) will consider the patient’s eligibility criteria and any known views of the patient about his/her participation. Together they will decide whether or not is appropriate to enrol the patient in the study.

Parents or guardians of children under the age of 16 years old will give consent for their child. Study staff obtaining consent will consider the ability of the child to understand the 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. Should the UK rules on consent by young people for research purposes alter during the period of this study to allow consent by competent minors, then these new rules will be applied to this study without further amendment.

In the United Kingdom (England, Wales, and Northern Ireland); 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. In Scotland, once someone has reached the age of 16, they are considered to be an adult. In Scotland if those aged 16-18 years of age who lack capacity to consent on their own behalf they would be classed as Adults With Incapacity (AWI).

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

Participants may be invited to participate in one or more of the optional sub-studies, if their site have sufficient capacity to conduct these. Table 8 details which consent forms are required for each sampling sub-study.

A copy of the informed consent form will be given to the person who gives consent, and a copy will be sent securely to the central study team for monitoring of informed consent and study administration. For those consenting via telephone a copy of the completed telephone consent form should be given to the participant at the earliest opportunity. In cases of electronic consent, the completed e-consent form should be given to the participant.

If the version of a consent form is updated after a participant gives their consent for participation, and that participant is returning for follow-up visits or further sample collection, every effort should be made for them to re-consent on the new version. There is no expectation that participants **not** remaining as hospital inpatients or returning for follow-up visits be contacted to re-consent.

Potential participants identified by residual diagnostic materials that present an important research opportunity will be contacted to consent to the use of their pre-existing samples for ISARIC and future research. In most cases this will involve an information sheet and consent form being posted to the potential participant by their usual clinical team, with a pre-paid envelope for return. The approach for consent could also take place in person if the potential participant remains in hospital.

If the potential participant is in hospital, local translation services may be used for patients who do not understand English, or the information sheet may be read to the patient, with consent appropriately witnessed, for illiterate patients. For potential patients being sent the information sheet to consent from home, these services will not be possible and therefore those known to be illiterate or not understand English should not be contacted.

If the potential participant is known to have lost capacity to consent since being discharged from hospital, the direct care team will identify the next of kin from the patient medical

records to ascertain whether they can act as a consultee. If no suitable consultee is identified, potential patients without capacity (in Scotland Adults with Incapacity) who have already been discharged from hospital will not be contacted to provide consent.

In cases where the potential participant is deceased their next of kin will be contacted using a specialist bereaved information sheet and asked to consider providing consent for their relative's samples to be used in ISARIC and future research.

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. A withdrawal form should be completed by the research team for any participants who choose to withdraw from this study after providing consent. 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 throat swabs. Collecting throat 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.

Discomfort of SAM strips. Collecting nasal fluid using SAM strips may be cause a transient tickling sensation during application and removal which can cause eye watering through a local reflex.

Oral (Crevicular) Fluid Collection. Oral crevicular fluid collection involves the participant or carer gently brushing a small sponge on a flexible plastic rod at the margin of the gums and teeth in exactly the same manner as is done for routine mouth care or teeth brushing. Apart from inconvenience and sensation, there is no expectation of and discomfort.

Lumbar puncture. Collection of cerebrospinal fluid with lumbar puncture will only be performed if clinically indicated, as decided by the responsible physician. Clinical investigations are the priority, with any remaining sample collected for use in research. Guidance on the safe recommended daily total volume of CSF to take in different age groups is provided (Table 6). Lumbar puncture can be associated with discomfort at the site of needle insertion, headache, and rarely bleeding or infection.

Incidental findings in genetic testing. This study includes genetic testing to identify host genetic variants associated with disease progression or severity. There is a very small chance that these tests may result in the incidental discovery of information that is relevant to the

participant's health. Since the samples will be pseudonymised and analysed 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.

Subject to a successful application for a Confidentiality Advisory Group s251 waiver or issue of a Control Of Patient Information (COPI) notice (in England and Wales) or Public Benefit Privacy Panel approval (in Scotland), or Health and Social Care Privacy Advisory Committee (in Northern Ireland) , the National Health Service or Community Health Index or Health and Social Care numbers, date of birth and postcode of participants will be collected to allow linkage with other Health and Social Care Datasets and to reduce data collection burden in support of other research activity including clinical trials. Consenting participants will be provided with a paper copy of their consent form (if consenting via telephone this will be provided at the earliest opportunity). Electronic consent forms will be printed to allow for participants to be given a copy. Electronic consent is only permissible with explicit permission from the trial team, and will rely on printing of consent forms being possible and storage facilities meeting trial requirements.

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 pseudonymised before transfer by eCRF.

At the UK HSA 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 pseudonymous and identifiable data. Data from routine clinical care will be pseudonymised and stored separately to laboratory samples. Samples obtained will be pseudonymised where possible however source samples containing high consequence pathogens of public health interest cannot be pseudonymised for important safety reasons so will be held under very strict security measures (a home office approved high security facility) by staff who do not have access to clinical data. The only link to identifiable clinical 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.

Pseudonymised research data will be stored on managed computer systems in Imperial College London, University of Liverpool, UK HSA, the University of Edinburgh, the Roslin Institute and other investigator sites relevant to the laboratory tests they have done. Only the study administrators will hold the data set key, 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 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 UK HSA 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 the University of Oxford (ISARIC Coordination Centre).

A research data sharing policy has been put in place between Universities of Liverpool, Oxford, Edinburgh, Imperial College and the public health agencies of the four nations. A framework for sharing names and contact details of people affected by outbreaks and events of public health interest has been put in place between UK HSA and Oxford acting as sponsor for this study.

7.9 Additional Ethical Considerations

Subject to a successful application for Health Research Authority Confidentiality Advisory Group section 251 regulation 5 support or issue of a Control Of Patient Information (COPI) notice (in England and Wales) or Public Benefit Privacy Panel approval (in Scotland), or Health and Social Care Privacy Advisory Committee (in Northern Ireland), limited personal identifiers including the National Health Service or Community Health Index or Health and Social Care numbers, date of birth and postcode will be collected along with clinical data relating to the event, to allow linkage with other Health and Social Care Datasets and to reduce data collection burden in support of other research activity including clinical trials. Otherwise, consent will be obtained for collection of patient information including personal identifiers.

Exemption (no intent) to apply National Data Opt Out process. Subject to a successful application for a Health Research Authority Confidentiality Advisory Group section 251 regulation 5 support, there will be an application for exception to apply the general opt-out to access of routine NHS personal date for the primary purposes of the study. The opt-out will however be applied to any secondary use of data outside of the named investigator group. To avoid doubt, this will prevent use of a data access request from a third party to gain back-door access to personal data, even when anonymised, where a person has requested opt out. Otherwise, National Data Opt Out will apply with a monthly removal of all who are registered for National Data Opt Out. This application to be exempt from National Data Opt Out is supported by UK HSA.

No right to withdraw data. Following on from no intent to seek consent to only use data and no intend to apply the National Out process, we do not intend to offer a mechanism to withdraw personal data.

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.

Use of digital photography and video. The outbreak of monkeypox has highlighted the need to characterise skin lesions and ensure consistency in swabbing from a given site or lesion. The wide availability of mobile video calls can now facilitate consent processes. We have included explicit consent to retain digital imagery of lesions. We will make best efforts to ensure that images are not disclosive of identity i.e. avoid face and distinguishing features such as tattoos and body piercings.

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.

7.11 Scientific and Peer Review

The proposed research began as the product of a year-long discussion (2011-2012) 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; Chair, JK Baillie) comprised senior clinical scientists from 5 continents, and aims to promote and harmonise observational research during outbreaks of severe infectious disease.

The protocol has been extensively reviewed by scientists and the sponsor research governance officers since 2012.

7.12 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) University of Liverpool
University of Oxford
University of Edinburgh
University Glasgow
University of Bristol
University of Cambridge
Crick Institute London
University of Newcastle
University of Cardiff
Liverpool School of Tropical Medicine
University of Sheffield
University of Birmingham
Imperial College London
University College London
Wellcome Trust Sanger Institute
Global Health Network, Oxford
Health Protection Scotland,
UK Health Security Agency (as successor to Public Health England)
University of Southampton
NHS Blood & Transplant Blood Borne Virus Unit

the above being "the 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[4] together with related data. The Recipient

[4] 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

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).[5]
2. The Recipient Institution may use the Material for the purposes of the Study (including for clinical diagnostic purposes and commercial development 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[6] 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

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to, "research in connection with disorders, or the function of the human body", "education or training relating to human health", and "transplantation").

[5] 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 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.

[6] 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.

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.
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.

END

7.13 Revision History

7.13.1 Changes since v10.1

Addition of Prof Judith Breuer of University College London as consortium investigator and in Section 7.12 Material Transfer Agreement, addition of University College London.

7.13.2 Changes since v10

Section 6.4 Data Linkage. Administrative addition of previously approved text to recognise role in Scotland of Public Health Scotland (PHS), Scottish GPs and NHS Scotland Boards for hospitalisation and testing data (SMR01, SMR00, SMR02 Prescribing, ECOSS (Covid-19 tests), SICSAG (intensive care data)), National Records of Scotland (NRS) for deaths, and Public Benefit and Privacy Panel for Health and Social Care (PBPP).

Section 7.2 Informed consent. Administrative addition of previously approved text to recognise legal status of Scottish young people age 16 year and older and language for Adults With Incapacity.

7.13.3 Changes since v 9.6

Administrative changes include:

1. all references to Public Health England (PHE) have been changed to UK Health Security Agency (UK HSA),
2. removal of COVID-19 specific directions to return protocol to generic and flexible form and
3. removal of reference to co-enrolment to Bio-AID, as that study has closed.

Substantive amendments

Section 1.8.4 - The most significant change to this protocol is the additional inclusion for eligibility of participation, and activation of the protocol for exposure to noxious chemicals, toxins, or potentially harmful energy sources of public health interest. Supporting documents (consent and information sheets) have been updated to reflect this.

Section 3.2.1 and 3.4 – reinstatement of need for consent for collection of personal identifiers and linked clinical data pending HRA CAG approval to extend s251 Reg 5 support to non-COVID activity. (CAG reference: 21/CAG/0125)

Section 3.6.2 & 3.6.5.9 Table 1 – addition of sampling point at d14 to harmonise with MOSAIC protocol and reduce research burden on participants and staff. Explanatory text on MOSAIC.

Section 3.6.5.7 - addition of sub-study in select participants for additional throat, meatal, and vaginal swab or Semen sampling in select circumstances.

Section 3.6.5.6 – addition of sub-study in select participant for serial throat, vesicle and scab sampling.

Section 5.3 - Table 5. Samples to be taken for cases of topical exposure to toxins and chemicals – details on these additional sampling given.

Section 7.9 – Pursuant to CAGs251r5 support being granted, intent to apply for exemption from National Data Opt Out Process to avoid bias and permit timely complete response to analysis of clinical information of public health interest. This application to be exempt from National Data Opt Out is supported by UK HSA.

Non-substantive amendments

Section 3.2– "approach to participants"; additional clarity to existing processes addition of section on

Section 3.8 - clarification that sites must retain in secure format an enrolment log.

Section 4.5 – clarification that personal identifiers will not be shared externally (i.e. not beyond source data-base in Oxford.

Section 6.3 - Data retention - Explanation is given as to the intent and justification to retain data in perpetuity and the need for 5 yearly reviews.

Section 7.2 – Material Transfer Agreement- addition of University of Cambridge, Crick Institute London, University of Newcastle, University of Cardiff, Liverpool School of Tropical Medicine, University of Sheffield, and University of Birmingham to recipient institutions.

Section 7.8 - Summary details of data sharing framework agreement between ISARIC4C and UK HSA added.

Section 8.3 – Addition of List of High Consequence Infections Diseases as jointly agreed by UK HSA and NHSE

7.13.4 Changes since v9.3

Section 1.7
Correction to Tiers at which residual material will be retained (previously listed for Tier 0 in error).
Section 1.8.1
Addition inflammatory multi-system syndrome as inclusion criterion.
Section 3.1
Approach of patient's post-discharge whose samples represent critical research value added.
Section 3.2
Clarification that identifiers will not be sought without consent in Northern Ireland due to lack of legal framework allowing this.
Section 3.5.3
Corrections made to Table 3. Sodium citrate tube added in last protocol amendment missed from several rows in error.
Section 3.5.4.6

Updates made to long-term follow-up survey to reflect decisions made for administration of surveys.
Section 3.9
Clarification added regarding retention of samples if participant withdraws.
Section 7.2
Clarification added about expectations for re-consenting participants if consent forms are updated.
Detail of process for approaching patients after discharge in exceptional circumstances for sample consent added.

7.13.5 Changes since v8.2

Date and Version No: 7th May, v9.3

Section 1.8:

Clarification of definition of healthcare facility.

Removal of exclusion by refusal as redundant.

Section 3.2:

Collection of NHS numbers and identifiers for linkage to trials and other data sets.

Explicit use of telephone consent as patients likely to be isolated.

Allowance of electronic consent at limited sites with explicit central approval.

Section 3.4:

Change to sample processing to reflect Health & Safety Executive guidance.

Section 3.5:

Addition of telephone numbers to consent forms.

Clarification around respiratory sampling and alternative (NPA) for children, addition of nose swab and specify collection of leftover BAL.

Addition of one further blood sample in the core sample set for analyzing coagulation function.

Addition of cellular immunology, serial serology, serial BAL on ECMO, COVID-19 BioAID, air/surface sampling and long-term follow-up sub-studies.

Section 3.6:

Clarification and justification for collection of data without consent.

Section 3.7:

Clarification that CRF data will be collected post-mortem if patient dies prior to confirmation of pathogen of interest.

Updated website and email address for eCRF.

Section 3.8:

Clarification on contact methods for patient follow-up.

Section 4.3:

Outbreak Laboratory, Ronald Ross Building, University of Liverpool listed as initial receiving laboratory for biological samples.

Sections 6.1 and 7.9:

Collection of NHS number (for data linkage) and telephone number (for follow-up).

Section 6.3:

Purpose of data linkage.

Section 7.2

Confirmation added that a consent form copy should be returned to the study team for administration.

Appendix 2:

Tables illustrating different Tier 2 serial sampling schedules.

7.13.6 Changes since v7.3

Date and Version No: v8.2 17FEB2020

In section 1.1 Purpose of the Study, expansion of study to include an annual one week activation – internal pilot study to maintain and test readiness of the study activation that includes data collection only on severe acute respiratory infection (SARI). The anonymised data collected from the annual activation will be also shared with an international project aimed at characterising SARI patients to better inform management strategies and ultimately to improve clinical management of emerging infectious causes of SARI (SPRINT-SARI).

The Background information of A/H5N1, MERS CoV and A/H7N9 in section 1.2 has been revised and updated.

Section 1.6.1 has been added with specific objectives of annual activation (internal pilot)

Amends in section 1.7 Structure of this document to reflect the inclusion of the pilot study for data collection only corresponding to TIER ZERO within the main tier structure of the Clinical Characterisation Protocol.

In section 1.8 updated detail Entry Criteria for SARI patients for the pilot study included in Appendix A. To be consistent with the background of this protocol, it has been added a clarification on the entry criteria for patients with suspected or confirmed infection with a pathogen relevant to public health interest.

Clarification in section 3.1 the sample size is not prospectively determined. The study has no set end date.

Inclusion in Section 3.2 Approach to Potential Participants of explanatory paragraph on the process for consent within emergency situation to enter a patient into the study when the patient is unconscious or incapacitated to give consent and there is no relative/representative present, a nominated consultee will be sorted. The process of consent will comply in England and Wales with the Mental Capacity Act 2005 (MCA 2005); in Scotland, with Section 51 of the Adults with Incapacity (Scotland) Act 2000; and in Northern Ireland, research provisions of the 2016 Mental Capacity Act (Northern Ireland).

This is acknowledged within the Helsinki Declaration (2008). Emphasising that every effort will be made to get consent from representatives where they become available and/or from the patient when he/she is able to do so.

It is explained that for studies that submit collect or collate only pre-identified pseudonymised data that is normally collected as part of routine care information and where involvement in the research carries no more than low risk, such as the pilot study, consent may not be required. In the annual activation pilot study in order to test the processes within the overarching Clinical Characterisation Protocol, consent will be obtained from patient/consultee/parent/guardian/career.

Clarification in Section 3.6 Enrolment Procedures for Patients that meet the inclusion criteria will be have their clinical information collected and entered in the study when consent has been obtained, be it deferred, proxy or assent. Clarifying that to annually activate the study for one week - the selection criteria and data collection will follow the procedures indicated in the in Appendix A

In section 4.1 Specimen Sampling, Storage Procedures and Transport, there is a clarification on the management of other merging pathogens, indicating that these pathogens may be classified as requiring BSL2, BSL3 or BSL4 for safety management and guidelines should be consulted as per hospital protocol. Samples that are not BSL3/4 may be stored locally at participating sites.

In section 4.2. Removal of need for consent for Tier Zero activity (collection of de-identified data only').

Inclusion in section 6.2 Data Management of explanatory paragraph to clarify that the entry of data for the Clinical Characterisation Protocol and pilot study user name and password are assigned during registration. Transfer of data is password protected. Each site will maintain a trial file including a protocol, ethics approval documentation, and paper CRFs. A participant list will be used in each study site to match identifier codes in the database to individual patients in order to record clinical outcomes and supply any missing data points. The Participant List is maintained locally and is not to be transferred to any other location. The enrolment log and study data will be kept separately.

Explanation in section 7.2 Informed Consent, in the case of an outbreak of public health interest, for patients who are incapable of giving consent in emergency situations, the process of consent will comply in England and Wales with the Mental Capacity Act 2005 (MCA 2005); in Scotland, with Section 51 of the Adults with Incapacity (Scotland) Act 2000; and in Northern Ireland, research provisions of the 2016 Mental Capacity Act (Northern Ireland).

These are an exceptions acknowledged in the Declaration of Helsinki (2008), the following process will be observed:

• If a patient is incapable of giving consent and there is not relative/representative present, two doctors (one independent of the study team with knowledge of the patient condition) will consider the patient's eligibility criteria and any known views of the patient about his/her participation. Together they will decide whether or not is appropriate to enrol the patient in the study.

•All efforts will be made to have consent from appropriate consultee /guardian/carer when they became available, and from the patient at the earliest opportunity.

Regarding consent by competent minors, should the UK rules on consent by young people for research purposes alter during the period of this study to allow consent by competent minors, then these new rules will be applied to this study without further amendment.

To reflect the above changes in protocol single patient information and consent / assent forms have been created instead of being virus specific.

At the end of protocol inclusion of APPENDIX A CCP Annual Activation Guidance (a separate document).

Reformatting of protocol and consent forms for easier maintenance and sharing.

At the request of the Chief Medical Officer, we have transferred governance of the samples to the IDAMAC. The protocol is updated to reflect this.

Additional optional sub studies are included describing the following samples and procedures:

- additional sample for isolation of PBMCs

- environmental transmission assessment.

- plasmapheresis for research, standards and product development

7.13.7 Changes from (Previous version v7.0 25AUG2014)

Date and Version No: 21 March 2016 v7.3

UK CRN ID14152 (now included in first page of Protocol)

The most significant change in the protocol "Clinical Characterisation Protocol for Severe Emerging Infections", is an amend to activate the sleeping protocol for one week in each winter season for data collection of SARI in nominated centres. This short-term activation of the protocol will maintain and test the protocol in order that it remain prepared to be activated in the event of an outbreak / pandemic of an pathogen of public health interest. This annual activation will serve as an internal pilot to test and maintain the main study processes.

In addition, there is a clarification on the inclusion criteria for patients presenting with an infection by a pathogen of public health interest.

Inclusion of new co-investigators: Prof Richard Tedder, UK HSA and NHS Blood & Transplant Blood Borne Virus Unit, and Prof Peter Horby, Professor of Emerging Infectious Diseases and Global Health, University of Oxford.

The institutional affiliation of two co-investigators has been updated to reflect their present role: Dr Jake Dunning is now at UK HSA, and Laura Merson, is now at University of Oxford in England.

8 APPENDICES

8.1 Appendix A: Test Activation Guidance – Internal Pilot Study for maintenance of the UK Clinical Characterisation Protocol

To be used in combination with this protocol

8.2 Appendix B: Examples of sampling schedule flexibility

Sampling schedule 1.

		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	>28 days after hospital discharge
>40kg	**R**																
20 to 40kg	**R**																
10 to 20kg	**R**																
4 to 10kg	**R**																
<4kg	**R**																
Sample priority*	**1**																

Sampling schedule 4.

		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	>28 days after hospital discharge
>40kg	**R**		**S**						**S**								**C**
20 to 40kg	**R**		**S**						**S**								**C**
10 to 20kg	**R**		**S**						**S**								**C**
4 to 10kg	**R**		**S**						**S**								**C**
<4kg	**R**		**S**						**S**								**C**
Sample priority*	**1**		**2**						**3**								**4**

Sampling schedule 6.

		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	>28 days after hospital discharge
>40kg	**R**		**S**		**S**				**S**							**S**	**C**
20 to 40kg	**R**		**S**		**S**				**S**							**S**	**C**
10 to 20kg	**R**		**S**		**S**				**S**							**S**	**C**
4 to 10kg	**R**		**S**		**S**				**S**							**S**	**C**
<4kg	**R**		**S**		**S**				**S**							**S**	**C**
Sample priority*	**1**		**2**		**5**				**3**							**6**	**4**

Sampling schedule 10.

		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	>28 days after hospital discharge
>40kg	**R**	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**	**S**	**C**
20 to 40kg	**R**	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**	**S**	**C**
10 to 20kg	**R**	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**	**S**	**C**
4 to 10kg	**R**	**P**	**S**	**P**	**S**	**P**	**P**	**P**	**S**	**P**	**P**	**P**	**S**	**P**	**P**	**S**	**C**
<4kg	**R**	**P**	**S**	**P**	**S**	**P**	**P**	**P**	**S**	**P**	**P**	**P**	**S**	**P**	**P**	**S**	**C**
Sample priority*	**1**		**2**		**5**		**7**		**3**		**8**		**10**		**9**	**6**	**4**

Key (refer to Table 2)**:**
R: recruitment sample set **S:** serial sample set**, P:** pathogen-only sample set **C:** convalescent samples
***In the event that local resource limitations require sampling frequency to decrease, samples will be prioritised as shown (1=highest priority). Serial sampling will stop when acute illness resolves, or a patient is discharged from hospital: next samples taken will be the blood sample at 3 months and 6 months post recruitment.**

8.3 List of high consequence infectious diseases (HCIDs)

A list of HCIDs has been agreed by a joint UK Health Security Agency (UKHSA) and NHS England HCID Programme:

Contact HCID	Airborne HCID
Argentine haemorrhagic fever (Junin virus)	Andes virus infection (hantavirus)
Bolivian haemorrhagic fever (Machupo virus)	Avian influenza A H7N9 and H5N1
Crimean Congo haemorrhagic fever (CCHF)	Avian influenza A H5N6 and H7N7
Ebola virus disease (EVD)	Middle East respiratory syndrome (MERS)
Lassa fever	Monkeypox
Lujo virus disease	Nipah virus infection
Marburg virus disease (MVD)	Pneumonic plague (Yersinia pestis)
Severe fever with thrombocytopaenia syndrome (SFTS)	Severe acute respiratory syndrome (SARS)*

*No cases reported since 2004, but SARS remains a notifiable disease under the International Health Regulations (2005), hence its inclusion here

**Human to human transmission has not been described to date for avian influenza A(H5N6). Human to human transmission has been described for avian influenza A(H5N1), although this was not apparent until more than 30 human cases had been reported. Both A(H5N6) and A(H5N1) often cause severe illness and fatalities. Therefore, A(H5N6) has been included in the airborne HCID list despite not meeting all of the HCID criteria.

The list of HCIDs will be kept under review and updated by UKHSA if new HCIDs emerge that are of relevance to the UK.