What is ISARIC?

ISARIC are an international consortium who investigates novel pathogens causing severe acute respiratory illness (SARI) and emerging infections of potential public health importance. Further information on ISARIC can be found at the following website www.isaric.org. Through the assistance of NRES-REC and the NIHR Clinical Research Network (NIHR CRN), a protocol has been developed allowing the rapid study of a pathogen should an outbreak arise (**NIHR CRN ID: 14152**). Amendments through the expedited study formally titled 'Novel Coronavirus Observational Study' (CSP ref. 126600) are now being made to address the emergence of the novel pathogens MERS-CoV, A/H7N9 and ebolavirus. The protocol is a "low-risk study" because it is limited to medical data and sampling, which would otherwise be done as part of routine care such as blood samples.

When an outbreak occurs, the Lead Local Clinical Research Network (Greater Manchester) will email those concerned with an update to the study and provide clarification to what the amendment entails. Queries should be sent to Greater Manchester Local Clinical Research Network in the first instance (contact details at the end of this documents).

The study is recognised by the NIHR CRN as being a 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. (see: https://www.crn.nihr.ac.uk/wp-content/uploads/publichealth/Urgent Public Health Research Process Summary.pdf)

Changes to any subsequent FAQ sheet will be highlighted in yellow

We are rolling this ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections (CCP) – as a sleeping study across all NHS acute and specialist trusts in the United Kingdom, and we are learning as we go of various issues at the many different sites.

Annual Activation

The annual activation pilot study will only be activated in nominated sites. Recognising the value of maintaining a study such as this in a state of readiness, and to test the readiness of the study, this version of the protocol includes as an activation exercise, a pilot study on community-acquired severe acute respiratory infection (SARI). The guidance for the annual activation pilot study is included in Appendix A

The protocol is generic to any novel SARI or VHF causing agent or emerging infection of potential public health importance. The first version circulated was populated with MERS-CoV. The amend v7 now also includes Influenza virus A/H7N9 & A/H5N1, and Ebolavirus. This list will change in response to identification of other emerging infections

of public health interest. The Protocol and MREC approvals recognise that this is in effect a generic protocol.

The annual activation pilot study involves collection of data from routine data sources with consent or proxy assent. This pilot study will be conducted on annual basis during the winter season for one week only.

What is the study title now?
The study was originally called the Novel Coronavirus Observational Study and later the ISARIC/WHO Severe Acute Respiratory Infection Biological Sampling Study. The scope has been widened to include both SARI and VHF emerging pathogens as these have recently presented threats to public health. To reflect this change the title has been changed to **ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections (CCP).** At present you may see information with any of these titles.

Which sites are involved in the CCP?
Any site handling a case of severe acute respiratory infection (SARI) or viral haemorrhagic fever (VHF) such as ebolavirus (VHF) in the UK may be involved as it is not possible to predict where confirmed cases of MERS-CoV, A/H7N9 or VHF will occur. It is expected the majority of cases will be on intensive care units or high dependency units or special isolation facilities.

Are all sites involved in the CCP also involved in the annual activation pilot study?
It is expected that in the first year, there will be between 2 and 15 sites (hospitals and intensive care units – ICUs, ECMO centres) ready to conduct the pilot study in the winter months for one week only (5 to 7 days). This number may increase in subsequent years. Taking part in the pilot study will help the site to test their readiness and activation procedures for the collection of data and samples for the CCP in case of an outbreak.

Local investigators at site are expected to lead the study at site and contribute as appropriate in collaboration with the chief investigator to the analysis of data. In addition they are responsible for the identification of eligible patients, overseen the collection of data – in paper and electronic format, and ensure the save guarding of all site documents such as protocol, appendix A, CRFs, list of participants and enrolment logs, and consent forms

We don't have facilities for caring for people with viral haemorrhagic fever (VHF) – Is this study relevant to our site?
Proven cases of VHF will most likely be managed in special isolation facilities in London, Liverpool or Newcastle. It is possible that patients may present to any NHS Trust and could be recruited. No biological sampling should be undertaken from any case with high suspicion of VHF unless there is expertise and facilities for BSL4 sample handling. Outside of specialist facilities it is the expectation that VHF cases would be recruited to

tier 0 of the protocol i.e. data collection and use of residual clinical material for research purposes. For this reason separate laboratory SOPs and consent forms have been prepared for SARI cases and VHF cases.

How are local investigators being identified?
Identification of principal investigators is being supported through the NIHR CRN Clinical Specialty Leads and Local Clinical Research Networks, however assistance from research directorates may be required and is appreciated. The site list will be updated with investigator details as they become available.

Which Specialty Groups are involved?
This study is supported by the NIHR CRN: Critical Care, Infectious Diseases and Microbiology, and Children Specialties.

Site File
At present we are not sending out site files, but inviting the documents to be down loaded from CSP (please look in the zip folder ISARIC SARI 170613 uploaded 21st August 2013).
The most up-to-date site files will also be found in the study *dropbox*. This is the link:

https://www.dropbox.com/sh/cobctnn2wsz47cw/AADKS5fhRY7JXNt8rvegmQQFa?dl=0

A zip file can be sent on request to out where trusts or individual have difficulty accessing CSP or the *dropbox*, but there is an inherent risk that such documents will be out-of-date. Please make requests to

Raul Pardinaz-Solis raul.pardinaz-solis@ndm.ox.ac.uk or
Kajsa-Stina Longuere kajsastina.longuere@ndm.ox.ac.uk

Eligibility
This study now enrolls proven cases of MERS-CoV, A/H7N9, A/H5N1, or other novel emerging or re-emerging pathogens such as Ebola virus which present a threat to public health as notified through a protocol revision.

What cases should be included?
As of the 24th of August 2014 the cases to recruit would be confirmed cases of Middle-East Respiratory Syndrome Coronavirus (MERS-CoV), Influenza A Virus Subtype H7N9 and Viral Haemorrhagic Fever (eg Ebola virus). Novel emerging pathogens may be added as they emerge, a notification will be issued each time this happens. Cases can be in patients of any age and capacity, so children, those lacking capacity to consent and those unable to understand written English are to be included.

How many cases are expected?

Based on current knowledge only a handful of cases are expected across the acute and specialist Trusts in the UK. However it is not possible to predict where or how many cases will present given the nature of respiratory infections, viral haemorrhagic fever infections or other novel pathogens.
At present we do not expect to recruit more than a handful of cases from across all - acute and specialist trusts in England, Wales, Scotland and Northern Ireland.

The annual activation pilot study is expected to enroll as many patients as possible but it is difficult to predict where or how many cases will be enrolled in the study

Recruitment and Accrual
This study is one of the Pandemic Preparedness Studies and is exempt from NIHR recruitment targets and recruitment updates.

Where is the Case Report Form (CRF)?
The CRF is here https://www.cliresdms.org/ . Sites must register

How do I generate a patient number to enter on the eCRF
Patient numbers consist of a 3-digit site code and a 4 digit patient number. You can obtain a site code by registering on the data management system at https://www.cliresdms.org. Patient numbers should be assigned sequentially for each site beginning with 0001. In the case of a single site recruiting patients on different wards, or where it is otherwise difficult to assign sequential numbers, it is acceptable to assign numbers in blocks. E.g. Out-patient 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 the pilot study, each site will be identified via a 3 digit site code, and each patient will be assigned a 4 digit sequential patient code making up the patient ID number at time of enrolment. The site code is obtained by registering on the eCRF, data management system at https://www.cliresdms.org. The patient identification number will therefore be a 7 digit number, with the following: site code – individual patient number [_][_][_]-[_][_][_][_](eg. 012-0001).

SOP for Protocol for respiratory sampling from SARI cases
Respiratory virus diagnosis depends on the collection of high-quality specimens, their rapid transport to the laboratory and appropriate storage before laboratory testing. This link details the WHO standard SOP for respiratory pathogen sampling.

http://www.who.int/influenza/human_animal_interface/virology_laboratories_and_vaccines/guidelines_collection_h5n1_humans/en/

Who will anonymise the samples?
Samples must NOT be anonymised at source. Samples are transferred to PHE Colindale PHE Porton Down or the HPRUs in Liverpool or London labelled by the normal hospital identifiers. An anonymised unique alphanumeric code will be applied by this central laboratory before forwarding samples to research institutions.

Please confirm that the samples being transferred to HPE or HPRUs using the normal hospital identifiers and that the unique alphanumeric code (anonymisation) is applied by this central laboratory.
This is confirmed.

Do all samples need to be handled in containment level 3 / 4 facilities?
The current cases of interest are risk group 3 or 4 pathogens that should be handled in accordance with Public Health England (PHE) guidance on biosafety Level 3 or 4. Clarification is being sought from PHE regarding handling of respiratory secretions, urine and stool samples where local laboratories have as a minimum a Class 2 hood and staff experienced in handling potential BSL 3 samples within Good Laboratory Practice. Viral haemorrhagic virus samples such as ebolavirus may only be handled in BSL4 facilities

Are there any study-specific labels for samples?
Not at present. The possibility of producing a study specific research label that could be distributed to all centres in advance of recruitment is currently being explored. Given the number of sites centralised production of individual labels will not be feasible.

Are there any study-specific laboratory request forms?
We will provide a generic red ISARIC label to identify samples as research samples. These are not a substitute for completing full identifiers on the sample tubes.
It is hoped that the introduction of a study-specific research label will alert the local laboratory to the purpose of the sample. The sample management arrangements (SOPs) must be shared with the laboratory.

Is there a laboratory manual?
A laboratory manual is being revised following Public Health England feedback. SOPs have been developed for SARI cases. No biological sampling should be undertaken from any case with high suspicion of VHF unless there is expertise and facilities for BSL4 sample handling. Outside of specialist facilities it is the expectation that VHF cases would be recruited to tier 0 of the protocol i.e. data collection and use of residual clinical material for research purposes. For this reason separate laboratory SOPs and consent forms have been prepared for SARI cases and VHF cases

How quickly do samples need to be processed after collection?

The samples should be processed without delay and typically this would be between 30 minutes and 60 from sampling to reduce degradation of biomarkers. Processing consists of separating and making aliquots of whole blood and serum samples and bagging up respiratory, stool and urine samples.

Local capacity for sampling
Serial sampling (Tier 2) is dependent on local capacity and resources. In the absence of a pandemic we would hope to achieve a complete set of samples for each patient at each time point per the protocol schedule.

Sample handling in BSL2
PHE is a named investigator on this study and has reviewed and approved the protocol. We are seeking further clarification from PHE regarding handling of respiratory secretions, urine and stool where local laboratories have only a minimum a Class 2 hood and staff experienced in handling potential P3 samples within GLP.

Sample Labelling
The study protocol states 'All samples collected in hospital will be labelled as per hospital procedure with appropriate identification and hazard labelling according to local policy'. Study specific labels should be added to each sample tube at the bedside. Where these are not available we request that in addition ISARIC Research Sample is written in red on the primary sample container

Study Sample Request Forms
We are not producing specific lab request forms because of the many differences across the UK in how sample request are now handled, particularly by electronic ordering systems.

Is use of a refrigerated (+4°C) an absolute requirement?
No. Whilst strongly preferred, an alternative is to refrigerate the samples for 10 minutes prior to spinning at room temperature. Accurate calibration of rotor speed is not required; samples are only being spun for basic cell separation.

Is provision of -80°C refrigeration an absolute requirement?
No. Please store samples frozen at the lowest temperature available prior to courier.

How long after the sample has been obtained would it need to be processed?
The samples should be processed without delay and typically this would be between 30 minutes and 60 from sampling to reduce degradation of biomarkers.

How long will the Trust be required to store the samples before they require transfer?
Once frozen, there is no great urgency for transfer. A weekly batch transfer using the PHE BSL3 approved courier (www.pdpcouriers.com) on dry ice as specified and paid for

by the study would suffice. We understand the same courier is required for the transfer of the high risk clinical samples to PHE Colindale and we expect that our provision of this service will offset a cost that would otherwise need to be met by the trust.

How will samples need to be packaged prior to transfer?
All samples will need to be packaged to Biosafety Level 3 (BSL 3) standards.

Will packaging be provided?
No. Local laboratories are responsible for the safe packaging of samples to BSL3 standards.

Will courier services be provided?
Courier services and dry ice will be provided for the study. Local laboratories will be responsible for the safe packaging of samples to Biosafety Level 3 standards. The courier service is being provided by PDP Couriers www.pdpcouriers.com.

Is there a lab manual or study specific lab standard operating procedure for this study?
Yes available from the CSP and dropbox site, but a revision is being prepared to address situations where labs do not have full BSL3, or a class 2 hood for handling or no such capacity. No biological sampling should made from cases of VHF outside of specialist facilities.

How long will samples have to be stored before they are transferred?
Once frozen, samples are stable and transfer could be arranged as convenient for the Trust. A weekly batch transfer would suffice for the study. It is expected that one week would be the maximum period of storage required at any given NHS organisation.

Will a material transfer agreement be required as the protocol contains minimal information on the sample transfer arrangements?
No. On the advice of the NIHR CRN there is no need for 159 individual MTAs after a single site sign off. The primary recipient laboratory (Public Health England) and end research laboratories (research institutions) will be detailed in the revised laboratory SOP, which will be subject to scrutiny at a future single site sign off for England. By a technicality, having made expressly clear the guardianship of samples and their use, we are compliant with the HTA code.

Will there be a material transfer agreement?
No, as this is a study on respiratory viruses that could be reported from any secondary care site receiving severe acute respiratory cases it is not proposed that separate agreements be entered into for every NHS organisation. The requirements of the Human Tissue Act are met by including the purpose of collection and fate of tissue

samples in the obtaining of informed consent and by detailing the responsibilities of sites and receiving organisations in the laboratory manual.

Research Contracts (NIHR CRN approved)
With the knowledge and support of the NIHR CRN we will not be establishing individual research contracts with each of the 159 acute and specialist trusts.

What costs have been identified and will they be covered?
The following costs have been attributed to the study on a per patient basis. Cost of dry ice and courier services have not been included as these are provided by ISARIC. Storage is of a small volume incidental to transportation and therefore has not been included.

Research costs (NIHR CRN approved)
Laboratory and sample handling costs will be covered on a per patient basis.
Tier one costs are for a single patient and one sample set = £32.37
Tier two costs are for a single patient and ten sample sets =£334.69

Service support costs (NIHR CRN approved)
Identification, Recruitment and Consent - Time estimate: 30 minutes clinician, 45 minutes nurse = £59.25
Arrangements to support consent from individuals unable to understand written English (translation or similar) would also be attributed as a service support cost if required for a particular patient.

Treatment costs
The initial identification of cases will follow the standard clinical care pathway for respiratory infection. Samples taken as part of this clinical care pathway will continue to be a treatment cost. No additional treatment costs are anticipated as a result of this study, however the courier can transport clinical samples to PHE Colindale alongside research samples, so there is a potential treatment cost saving in relation to this study.

Remuneration - What to do when costs are incurred
In the event of a confirmed case and where the study has incurred costs for recruitment and provision of data and or biological samples, tier 1 or 2 costs will be met as appropriate., invoices should be sent to YYY, please provide details of ZZZ (e.g. bank details) for the payment to be processed

What about the Data Protection Act and Caldicott procedures?
The Caldicott Guardian Manual 2010 specifically excludes from their remit data shared for purposes of medical research where ethical approval and informed consent has been given.

http://systems.hscic.gov.uk/infogov/links/2010cgmanual.pdf

Regardless, some trusts have a policy of applying a Caldicott review to research protocols prior to local approval.

"Flying Research Nurses"
We understand that we may need to establish access permissions for visiting NHS research staff for training or support during an outbreak. During the last pandemic this was facilitated by a direction from the director of R&D NHS to Trusts CEOs to cooperate. Your cooperation in this matter would be valued.

Co-enrolment.
The study protocol anticipates and the NRES permission approves co-enrolment. "Particularly in the case of emerging infections, it is likely that other research projects, including clinical trials, will also recruit these patients. In fact it is important 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 England this study has been given NIHR CRN expedited urgent public health study status. In the event of an outbreak the study will be given priority by the NIHR CRN. All Local Clinical Research Networks 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.

Basis for Costs (NIHR CRN approved)

Service Support
Identification, Recruitment and Consent - Time estimate: 30 minutes clinician, 45 minutes nurse.
Total Service support cost: £59.25

Research
Tier 1 Involvement

Collection of samples	Time estimate - 30 minutes nurse time	Cost Estimate -	£10.79 (Band 6 Spine Point 9)
Sample preparation	Time Estimate - 30 minutes technician time	Cost Estimate -	£10.79 (Band 6 Spine Point 9)
CRF completion	Time estimate - 30 minutes nurse time	Cost Estimate -	£10.79 (Band 6 Spine Point 9)

Total research cost Tier 1: £32.37

Tier 2 Involvement

Each sample collection	Time estimate - 30 minutes nurse time	Cost Estimate - £10.79 (Band 6 Spine Point 9)
Sample preparation	Time Estimate - 30 minutes technician time	Cost Estimate - £10.79 (Band 6 Spine Point 9)
CRF completion (day 0)	Time estimate - 30 minutes nurse time	Cost Estimate - £10.79 (Band 6 Spine Point 9)
Daily form completion	Time estimate - 15 minutes nurse time	Cost Estimate - £ 5.39 (Band 6 Spine Point 9)

For 10 sets of samples this would equate to

10 x sample collection	- 5 hours nurse time,	cost £107.90
10 x sample preparation	- 5 hours technician time,	cost £107.90
1 x CRF completion	- 30 minutes nurse time	cost £ 10.79
20 x daily form completion	- 5 hours nurse time,	cost £107.90

Total research cost Tier 2: £334.69

Key Contacts

Protocol
Dr Calum Semple, Chief Investigator (UK)
Senior Lecturer in Child Health University of Liverpool
m.g.semple@liverpool.ac.uk
T:0151 252 5440
M:07958335337

Permissions, Site files, Contact Lists
Dr Raul Pardinaz-Solis
Clinical Research Support Coordinator – ISARIC
Centre for Tropical Medicine and Global Health
University of Oxford, NDM Research Building.
Old Road. Oxford. OX3 7LE
raul.pardinaz-solis@ndm.ox.ac.uk

Project management & Data Management
Kajsa-Stina Longuere, Project Manager, ISARIC
Centre for Tropical Medicine and Global Health
University of Oxford. NDM Research Building
Old Road. Oxford. OX3 7LE
kajsastina.longuere@ndm.ox.ac.uk
T: 07718696412

NIHR CRN and Local Clinical Research matters
Richard Sherburn, RM&G Manager
NIHR CRN: Greater Manchester Research Management and Governance Team
Central Manchester University Hospitals NHS Foundation Trust
North Road, Manchester, M13 9WL
crngm@cmft.nhs.uk
T: 0161 7015598