Appendix A
Annual Activation – Internal Pilot Study
for maintenance of the UK Clinical Characterisation Protocol (SPRINT SARI)

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1. Specific Aim & Objectives for Annual Activation (internal pilot study)

The aim of this annual activation – internal pilot study is a maintenance exercise of the ISARIC/WHO UK Clinical Characterisation Protocol (UK CCP (UK CRN ID14152). This will ensure the readiness of the research response for a future outbreak of a pathogen of public health interest and or pandemic at participating sites. The exercise will be a Severe Acute Respiratory Infection (SARI) observational study.

The specific objectives of the internal pilot study (annual activation), as per section 1.6.1 of main protocol are:

- To assess the barriers and enablers to being prepared for and conducting research during an outbreak of a pathogen of public health interest and or pandemic at participating sites
- Evaluate the operational characteristics of the study
- Evaluate the impact on incidence of alternative case-definitions of SARI
- To understand the incidence of SARI
- To understand the disease severity and risk factors for severe disease due to SARI
- To determine the Case Fatality Proportion of SARI
- Determine the duration of ICU/hospital stay due to SARI
- Identify the microbiology of SARI, including variability in testing
- Identify the treatments received during hospitalization for SARI

2. Overall Pilot Study Design

The annual activation is a multi-centre, prospective, observational study of patients in the ICUs of participating hospitals, with SARI. The study aims to recruit more than 100 patients in the UK per activation period. There is no maximum number of patients that can be recruited from any one site. The study period will be 7 consecutive days during which patients meeting a SARI case-definition who are admitted to the in-patient intensive care unit of interest will be recruited into the study.

The planned start dates will be agreed per site with the ISARIC coordination centre. Patients will be studied from time of admission to hospital until the time of hospital discharge (censored at 60 days). Information will be collected on demographics, co-existing illnesses, severity of illness, source and type of clinical specimens (upper versus lower respiratory tract and collection date), results of microbiological tests, administration of major therapies (including mechanical ventilation, vasoactive therapies, hypoxaemia rescue therapies, and dialysis), administration of antibiotics and antivirals (and adjunctive therapies, e.g. immunomodulators, corticosteroids) and outcomes at ICU (if applicable) and hospital discharge. We encourage sites to participate each year but an alternative, and equally acceptable option, is for sites to rotate on a year-by-year basis.

2.1 Study Population

2.1.1 Inclusion Criteria

All patients newly admitted at participating hospitals to the intensive care unit of interest, of any age, including pregnant women, presenting with SARI during the study period, commencing at 00:00 or at the start of the chart day and concluding 7 days (168 hours) later. Patients will be eligible for the study if the patient meets the case definition for SARI, as follows (4, 9):

A suspected or proven acute respiratory infection requiring new inpatient admission with:

- Onset within the past 14 days; With one or more of

the following:

- A history of fever or measured fever of ≥ 38^{o} C;
- Cough;
- Dyspnoea (shortness of breath) or Tachypnoea*

*Tachypnoea defined as a respiratory rate of ≥50 breaths per minute for participants who are aged less than one year; ≥40 breaths/minute for 1-5 years, ≥30 breaths per minute in patients five through 12 years of age, and ≥20 breaths per minute for patients aged 13 years and older (22). For children and adults who are able to report dyspnoea, the presence of either dyspnoea or tachypnoea can be used to meet entry criteria.

This study utilises a longer onset time than the WHO definition (14 as opposed to 10 days) and a broader case definition including dyspnoea and tachypnoea to allow evaluation of the operational characteristics of the current WHO definition. The Case Report Form (CRF) requires the documentation of the inclusion criteria met by each participant at the time of admission. This will allow for a detailed analysis of different SARI case definitions and the associated operational characteristics.

2.1.2 Exclusion Criteria

There are no exclusion criteria.

3. Participating Study Sites

In the first year, it is anticipated that a minimum of 2 and maximum of 15 hospitals will take part in this study in the UK. The number of participating sites are expected to increase in subsequent years to increase coverage across the UK. High Level Isolation Units, ECMO centres and regional adult and paediatric intensive care units (ITU/PICU) will be prioritise in the first year, with expansion to more site in subsequent years.

4. Ethics

4.1 Consent

As indicated in the Clinical Characterisation Protocol, all efforts will be made to obtain informed consent from each participant or from an appropriate consultee/guardian/carer/parent.

4.2 Confidentiality of Patient Data

As indicated in the Clinical Characterisation Protocol, no identifying data will be entered into the central database. The confidentiality of the participant will be maintained unless disclosure is required by regulations.

4.3 Rule of Transfer

It is proposed that if a patient is transferred from a facility participating in the study to another facility that is also participating, the patient's previously allocated patient ID number will be documented in the CRF completed by the receiving hospital at time of admission.

It is the responsibility of each hospital to enter data pertaining to their component of the patient's hospital admission. If a patient is transferred to a non-participating hospital, further data collection will not be expected, but efforts will be made to contact these hospital and patients to identify outcome at study endpoint using the unique patient ID number assigned at enrolment.

5. Data Management

5.1 Data Collection Methods

The Principal Investigator at each site is responsible for maintenance of a securely held enrolment log linking the patient hospital record number and the study number as per UK research guidelines (24).

Streamlined data-collection instruments and procedures will be used in an attempt to minimise the work in study centres. Data will be collected from each site using the WHO ISARIC Severe Acute Respiratory Natural History and Biological Sampling CRF and eCRF – data collection only.

To account for the varying capacity, resources and infrastructure of sites the UK CCP has a tier approach to data collection and biological sampling. For this pilot study; only clinical and laboratory data corresponding will be collected. There will be no additional biological sampling 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. The sites research capacity will determine which CRF or combinations of CRFs that are to be completed, at the site's discretion. The eCRF will be available on the data management system at https://www.cliresdms.org .

The CRF is comprised of four tiers:

CRF Tier	Site Resource Level	CRFs completed for each patient
Tier 0.0	Sites that do not have the resources to collect Tier 1	Rapid CRF
Tier 0.1	Sites that do not have the resources to collect additional daily data outlined in Tier 2	Core CRF; and Daily CRF (day 1 only).
Tier 0.2	Sites with available resources to complete daily forms	Core CRF; Daily CRF, day 1 & 2: • Hospital admissions and • Daily CRF, day 1 & 2 of ICU admission (if applicable)
Tier 0.3	Optional additional CRFs, sites can choose to complete according to their scientific interest	Epidemiology CRF

All data will be collected at each study site by nominated individuals who will enter all required anonymised data described in the protocol into the CRFs directly from the source data. Trained staff at sites with the IT capabilities can enter all required data directly into the protected online database, known as the eCRF; paper CRFs are the alternative option for direct data entry with subsequent transcription, upon completion, into the eCRF. Information recorded in the CRF should accurately reflect the participants medical / hospital notes. The local Site Investigator will have the ability to choose the process they use to enter data into the eCRF, where data may be entered at one time or intermittently. If used, the original paper based CRF will be stored within a locked office in each study site. The intent of this process is to improve the quality of the clinical study by providing prompt feedback to the Investigators on the progress of the submitted data and to enhance the ability to collect early safety information in a more timely fashion to fully comply with the intent of GCP requirements.

5.2 Data Collection

The data that has entered by the online eCRF will be held and managed by the University of Oxford in the UK. Each site will be identified by a 3 digit site code, and each patient will be assigned a 4 digit sequential patient code making up the patient ID number. The site code is obtained by registering on the eCRF, 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. Alpha characters can also be used (e.g. Intensive Care Unit will assign A01 onwards, in-patient ward will assign B001 onwards). The patient identification number will therefore be a 10 or 7 digit number, with the format of the following: The site code – individual patient number [_][_][_]-[_][_][_][_](eg. -012-0001).The register of patient names and study numbers will not leave the participating hospital.

Access to the data entry system is 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, paper CRFs, participant list and enrolment log.

5.3 Participants' Enrolment log

A participant list and enrolment log 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 list and enrolment log will be maintained locally and is not to be transferred to any other location.

The sites will compile the enrolment log including the patient's name, date of birth, hospital identification number and unique study number. Subsequently, patient data will only be identified by the unique study number. The enrolment log and study data will be kept separately.

5.4 Data Variables Collected

All tiers include all data points collected in Tier 0 (RAPID CRF). Data collection Schedule of Events provides a summary and time schedule of the data to be collected for each tier.

5.6 Data Sharing Principles

This study adds to the research and data sharing policies of The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), Sample and Data Sharing Policy, Version 4, 21 July 2014 (28). Clinical investigators contributing to the research efforts will be given full recognition for their efforts and will be given the opportunity to access data. Ownership of any data transferred to the eCRF will be retained by the site that contributed. The University of Oxford will act as custodian of the central database.

All analysis of pooled data will be undertaken with the explicit agreement of each site who contributed the study. ISARIC will retain the right to use all pooled data for scientific and other purposes. All members of the study group will have the right to access the pooled data for research purposes provided the research proposal has been reviewed and deemed satisfactory by the management committee following publication of the primary manuscript. Only summary data will be presented publicly. Individual patient data provided by participating sites will remain the property of the respective institution.

Anonymised data from the annual activation – pilot study will be also shared with the international study SPRINT-SARI –a short term incidence study of SARI. This study is coordinated by the ANZIC-RC (Australia) and ISARIC Coordination Centre (Oxford).

References

1. Bolotin S, Pebody R, White PJ, McMenamin J, Perera L, Nguyen-Van-Tam JS, et al. A new sentinel surveillance system for severe influenza in England shows a shift in age distribution of hospitalised cases in the post-pandemic period. PloS one. 2012; 7(1):e30279.
2. Dawood FS, Iuliano AD, Reed C, Meltzer MI, Shay DK, Cheng P-Y, et al. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. The Lancet infectious diseases. 2012; 12(9):687-95.
3. Simonsen L, Spreeuwenberg P, Lustig R, Taylor RJ, Fleming DM, Kroneman M, et al. Global mortality estimates for the 2009 Influenza Pandemic from the GLaMOR project: a modeling study. PLoS medicine. 2013; 10(11):e1001558.
4. Huang Q, Baker M, McArthur C, Roberts S, Williamson D, LeComte L, et al. Implementing hospital-based surveillance for severe acute respiratory infections caused by influenza and other respiratory pathogens in New Zealand. . Western Pacific Surveillance and Response Journal. 2014; 5(1).
5. Investigators AI, Webb SA, Pettila V, Seppelt I, Bellomo R, Bailey M, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. The New England journal of medicine. 2009; 361(20):192534.
6. Peiris JS. Severe Acute Respiratory Syndrome (SARS). Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology. 2003; 28(3):245-7.
7. Guery B, Poissy J, el Mansouf L, Sejourne C, Ettahar N, Lemaire X, et al. Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: a report of nosocomial transmission. Lancet. 2013; 381(9885):2265-72.
8. Gao HN, Lu HZ, Cao B, Du B, Shang H, Gan JH, et al. Clinical findings in 111 cases of influenza A (H7N9) virus infection. The New England journal of medicine. 2013; 368(24):2277-85.
9. Turner N, Pierse N, Bissielo A, Huang QS, Radke S, Baker MG, et al. Effectiveness of seasonal trivalent inactivated influenza vaccine in preventing influenza hospitalisations and primary care visits in Auckland, New Zealand, in 2013. Euro Surveillance. 2014; 19(34): pii=20884.
10. WHO regional office for Europe. WHO regional office for Europe guidance for sentinel influenza surveillance in humans. Internet communication. Copenhagen, Denmark: World Health Organization, May 2011.
11. Nachtnebel M, Greutelaers B, Falkenhorst G, Jorgensen P, Dehnert M, Schweiger B, et al. Lessons from a one-year hospital-based surveillance of acute respiratory infections in Berlin- comparing case definitions to monitor influenza. BMC public health. 2012; 12:245.
12. Canadian Critical Care Society. Guidance for the Management of Severe Acute Respiratory Infection in the Intensive Care Unit. Ontario, Canada: Canadian Critical Care Society, 2014 January Report No.
13. Infection Control Subcommittee. The control and prevention of MRSA in hospitals and the community SARI infection control subcommittee. Ireland: HSE 2005 0954017773.
14. Blasi F, Garau J, Medina J, Avila M, McBride K, Ostermann H, et al. Current management of patients hospitalized with community-acquired pneumonia across Europe: outcomes from REACH. Respir Res. 2013; 14:44.
15. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Critical care medicine. 2013; 41(2):580-637.
16. The World Health Organization. INTERIM GUIDANCE DOCUMENT: Clinical management of severe acute respiratory infections when novel coronavirus is suspected: What to do and what not to do. Geneva, Switzerland: World Health Organization, Diseases DoPaE; 2014.
17. Department of Health and Ageing Pandemic Influenza. Interim Infection Control Guidelines for Pandemic Influenza in Healthcare and Community Settings. Commonwealth of Australia, Canberra: Department of Health and Ageing, 2006 2006. Report No.: Contract No.: 3842.
18. Influenza Specialist Group (ISG). Discussion Paper: Treatment of Influenza in interpandemic periods2006 2 October 2014: [8 p.]. Available from: http://www.isg.org.au/assets/assets/Discussion-Paper-low-res.pdf.

19. Butler C, Hood K, Kelly M, Goossens H, Verheij TJ, Little P, et al. Treatment of acute cough/lower respiratory tract infection by antibiotic class and associated outcomes: a 13 European Country Observational study in primary care. Journal Antimicrobial Chemotherapy. 2010; 65:6.
20. Lurie N, Manolio T, Patterson AP, Collins F, Frieden T. Research as a part of public health emergency response. The New England journal of medicine. 2013; 368(13):1251-5.
21. Gabriel LE, Webb SA. Preparing ICUs for pandemics. Current opinion in critical care. 2013; 19(5):46773.
22. Integrated Management of Childhood Illness (IMCI) (Revised). Improving child health IMCI: The integrated approach. Geneva, Switzerland: 2014.
23. ISARIC. Network and Council representatives [cited 2014 02 October]. Available from: https://isaric.tghn.org/about/council-network-membership/.
24. Therapeutic Goods Administration. The Australian Clinical Trial Handbook: A simple, practical guide to the conduct of clinical trial to International standards of Good Clinical Practice (GCP) in the Australian Context. In: Ageing DoHa, editor. Canberra, Australia Therapeutic Goods Administration; March 2006. p. 36.
25. Anzic Influenza Investigators, Webb SA, Pettila V, Seppelt I, Bellomo R, Bailey M, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. The New England journal of medicine. 2009; 361(20):1925-34.
26. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. The New England journal of medicine. 2004; 350(23):2343-51.
27. Dunning JW, Merson L, Rohde GG, Gao Z, Semple MG, Tran D, et al. Open source clinical science for emerging infections. The Lancet Infectious diseases. 2014; 14(1):8-9.
28. ISARIC. ISARIC Sample and Data Sharing Policy. Version 4. Oxford, London: ISARIC. p. 5.
29. ISARIC. ISARIC Publication Policy. Version 2. Oxford, London: ISARIC. p. 3.

Data collection Schedule of Events

Tier 0.0 Schedule of Events for Data Collection

Assessments / Procedures	Hospital Admission	Daily Hospital Admission	Daily Hospital Admission	ICU Admission	Daily ICU Admission	Daily ICU Admission	Hospital outcome (discharge, Death or transfer)
Inclusion & Exclusion criteria	X						
RAPID CRF							
1. Site	X						
2. Demographics	X						
3. Onset & Admission	X						
4. ICU or High Dependency Unit Admission				X			
5. Infectious Respiratory Diagnosis							X
6. Outcome							X

Tier 0.1 Schedule of Events for Data Collection

Assessments / Procedures	Hospital Admission	Day 1 Hospital Admission	Day 2 Hospital Admission	ICU Admission	Day 1 of ICU Admission	Day 2 of ICU Admission	Hospital outcome (discharge, death or transfer)
Inclusion & Exclusion criteria	X						
CORE CRF							
1. Demographics	X						
2. Co-morbidities & risk factors	X						
3. Signs & Symptoms at Hospital Admission	X						
4. Complications							X
5. Pathogen testing							X
6. Treatment				X			X
7. Medication							X
8. Outcome							X
Daily CRF							
1. Date of assessment		X			X		
2. Daily Treatment		X			X		
3. Daily Laboratory Results		X			X		
4. Chest X-Ray		X			X		

Tier 0.2 – Schedule of Events for Data Collection

Assessments / Procedures	Hospital Admission	Day 1 of Hospital Admission	Day 2 of Hospital Admission	ICU Admission	Day 1 of ICU Admission	Day 2 of ICU Admission	Hospital outcome (discharge, death or transfer)
Inclusion & Exclusion criteria	X						
CORE CRF							
9. Demographics	X						
10. Co-morbidities & risk factors	X						
11. Signs & Symptoms at Hospital Admission	X						
12. Complications							X
13. Pathogen testing							X
14. Treatment				X			X
15. Medication							X
16. Outcome							X
Daily CRF							
5. Date of assessment		X	X		X	X	
6. Daily Treatment		X	X		X	X	
7. Daily Laboratory Results		X	X		X	X	
8. Chest X-Ray		X	X		X	X	

Tier 0.3 – Schedule of Events for Data Collection

Assessments / Procedures	Hospital Admission	Day 1 of Hospital Admission	Day 2 of Hospital Admission	ICU Admission	Day 1 of ICU Admission	Day 2 of ICU Admission	Hospital outcome (discharge, death or transfer)
Epidemiological Investigation							
1. Exposures in previous 14 days	X						
2. Living arrangement	X						
3. Occupation	X						
4. Vaccination History	X						