Short PeRiod IncideNce sTudy of Severe Acute Respiratory Infection (SPRINT-SARI)

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ABBREVIATIONS

ANOVA	Analysis of Variance
ANZIC-RC	Australian and New Zealand Intensive Care-Research Centre
ARDS	Acute Respiratory Distress Syndrome
CRE	Carbapenem-resistant Enterobacteriaceae
CRF	Case Report Form
EARL	Ethics, Administrative, Regulatory and Logistic
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
H1N1pdm09	Influenza A virus subtype H1N1pdm09
H7N9	Avian Influenza A virus subtype H7N9
H5NI	Avian Influenza A virus subtype H5N1
ICH	International Council on Harmonisation
ICU	Intensive Care Unit
InFACT	International Forum for Acute Care Trialists
ISARIC	International Severe Acute Respiratory and Emerging Infection Consortium
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MRSA	Methicillin Resistant Staphylococcus Aureus
OUCRU	Oxford University Clinical Research Unit
PK/PD	Pharmacokinetic/pharmacodynamics
PREPARE	Platform for European Preparedness Against (Re-) emerging Epidemics
PRIME	clinical PRotocols and guidelines for Infectious disease Management
RO	Reproduction Number
SARI	Severe Acute Respiratory Infection
SARS-CoV	Severe Acute Respiratory Syndrome Associated Coronavirus
WHO	World Health Organisation

SYNOPSIS

Background	Severe acute respiratory infection (SARI) continues to be of major relevance to public health worldwide. In the last 10 years there have been multiple SARI outbreaks around the world. The 2009 H1N1 pandemic was estimated to result in more than 200,000 respiratory deaths globally (1-3). The World Health Organization (WHO) defines SARI as an acute respiratory infection of recent onset (within 10 days) requiring hospitalisation, manifested by fever (≥38°C) or a history of fever and cough (4-7). There is international consensus that it is important to undertake observational studies of patients with SARI as an essential component of pandemic and epidemic research preparedness.
Aim	The primary aim of this study is to establish a research response capability for future epidemics / pandemics through a global SARI observational study. The secondary aim of this study is to describe the clinical epidemiology and microbiology profiles of patients with SARI. The tertiary aim of this study is to assess the Ethics, Administrative, Regulatory and Logistic (EARL) barriers to conducting pandemic research on a global level.
Methods	This is a multi-centre, prospective, short period incidence observational study of patients in participating hospitals and intensive care units (ICUs) with SARI. The study period will occur, in both Northern and Southern hemispheric winters. The study period will comprise a 5 to 7-day cohort study in which patients meeting a SARI case-definition, who are newly admitted to the hospitals / ICUs at participating sites, will be included in the study. The study will be conducted in 20 to 40-hospital/ ICU-based research networks globally. All clinical information and sample data will only be recorded if taken as part of the routine clinical practice at each site and only fully anonymised and de-identified data will be submitted centrally.
Outcomes	Primary Outcome: 1. To test the feasibility of conducting a global study of SARI. Secondary Outcomes: 1. Incidence of SARI 2. Disease severity and risk factors for severe disease due to SARI 3. Case Fatality Proportion of SARI 4. Duration of ICU/hospital stay due to SARI 5. Microbiology of SARI, including variability in testing 6. Treatments received during hospitalization for SARI 7. Evaluate impact on incidence of alternative case-definitions of SARI 8. Evaluate the operational characteristics of this study, including CRF, Completion Guidelines, and entry criteria to provide information by which iterative improvement in study design can be achieved. 9. Explore the feasibility of extrapolation of results obtained at participating sites to population levels Tertiary Outcomes 1. To assess the EARL barriers and enablers to being prepared for and conducting pandemic research on a global level.

LAY DESCRIPTION

SARI is a major public health problem. There have been multiple outbreaks of severe acute respiratory infection (SARI) over recent decades. The commonest cause of SARI is influenza which is responsible for periodic pandemics. Between pandemics, SARI is still one of the leading causes of death worldwide and places a major financial burden on health systems, given the substantial hospitalization requirements for affected patients. There is a lack of information about the epidemiology and management of SARI patients globally, and a stated need from international bodies to establish the research infrastructure to gather this information rapidly during a time of acute need, or in an emergency such as the emergence of a new cause of SARI with epidemic potential.

Recent outbreaks of pandemic and zoonotic influenza viruses, SARS-CoV, and MERS-CoV have 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. By creating pre-existing tools, identifying and overcoming barriers to such projects and establishing networks for global observational data collection for SARI we hope, through SPRINT-SARI, to be better prepared for the next outbreak, informing clinicians and decision-makers around the world.

SPRINT-SARI is an ambitious international collaborative project aimed at characterizing SARI patients as a global problem to better inform management strategies and ultimately to improve the ability of health care systems to rapidly respond to emerging infectious causes of SARI.

BACKGROUND & RATIONALE

Clinical & biological rationale

SARI AS A COMMON EMERGING INFECTIOUS DISEASE

Infectious diseases rank high among the greatest threats to human well-being and prosperity. Societal trends such as globalisation, migration, tourism, intensive farming and changing climate enhance the likelihood of emergence or re-emergence of outbreaks of infectious disease. The movement of people, animals, and goods is accelerating and exposed individuals can travel anywhere in the world in less time than the incubation period of the most dangerous pathogens. Infectious disease outbreaks usually emerge unexpectedly and can, in the absence of timely containment, develop into epidemics or even pandemics, characterised by a rapid and sharp increase of the number of infected symptomatic patients. Multiple outbreaks of SARI caused by novel influenza A viruses or coronavirus infections have occurred in the last 10 years, each of which has represented a substantial threat to public health, as witnessed with H7N9, H5N1, SARS-CoV and MERS-CoV outbreaks (6-8). Worldwide, WHO estimates that there are between 3-5 million cases of severe illness and 290,000-650,000 deaths annually as a result of sessional influenza (9, 10). The emergence of a transmissible novel influenza A virus caused the 2009 H1N1 pandemic, and resulted in an estimated >200,000 respiratory and >80,000 cardiovascular deaths globally (2, 3). H1N1pdm09 virus now circulates as a seasonal influenza A virus, continuing to cause severe morbidity and mortality and impacting public health worldwide.

DEFINITION OF SARI

SARI is defined by the WHO as an acute respiratory infection of recent onset (within 10 days) requiring overnight hospitalisation, with fever ($\geq 38^0$C) or a history of fever, and cough (4, 11, 12). The operational characteristics of this definition are not well understood and have undergone numerous revisions over recent years. Alternative case definitions could potentially have important implications on accurate hospital/ICU admission rates and treatment. A 2012 surveillance study highlighted that the WHO and the European Centre for Disease Prevention and Control (WHO/ECDC) SARI case definition in 2009 captured only 55% of H1N1pdm09 positive hospital admissions and 75% of H1N1pdm09 positive ICU admissions (13). A population based cohort study conducted in Auckland has indicated that the requirement for documented fever and the 10 day time window often excludes patients who have an illness caused by an acute lower respiratory tract infection (McArthur, unpublished data). Further work is required to develop an optimal case definition and to understand the operational characteristics of alternative definitions.

AETIOLOGICAL AGENTS OF SARI

SARI may be caused by a wide array of pathogens, including viral and bacterial causes. These include classic pathogens such as seasonal influenza viruses and *S. pneumoniae*, emerging pathogens such as MERS-CoV, highly difficult to treat organisms such as methicillin resistant staph. aureus (MRSA) and carbapenem-resistant enterobacteraceae (CRE), and novel influenza virus strains. Furthermore, co-infections or super-infections with greater than one pathogen are commonplace. The microbiologic diagnosis is often dependent upon the availability and capabilities of the local laboratory. In routine clinical practice, a confirmed pathogen is identified in only a minority of cases, in part because of incomplete microbiological assessment as well as low sensitivity of some microbiological tests (4, 14, 15). Furthermore, SARI, both of bacterial and viral aetiology, is a major cause of antibiotic prescription and over-use of antibiotics is a major driver of increasing antimicrobial resistance.

MANAGEMENT OF SARI

The quality of evidence that is available to guide therapy for patients with SARI is generally low. As a consequence, controversy continues to surround the best treatments for SARI. It is clear that clinicians make decisions regarding multiple aspects of treatment in the absence of evidence regarding the superiority of alternative treatment options to improve patient-centred end-points, such as mortality (14, 16-20). As a consequence of the limited evidence base for the management of SARI there is substantial variation in care (14, 18, 21). Specific treatments for SARI are limited to antibiotics for bacterial infections and antivirals for influenza, as well as organ-specific management strategies for severe disease, such as respiratory or cardiovascular support. Furthermore, some current treatments may result in harm. Moreover, and in part as a consequence of this variation in care, there is evidence of variation in outcome.

PANDEMIC RESEARCH RESPONSIVENESS

A major lesson from the 2009 H1N1 pandemic was that real-time clinical research and data collection are a vital component of an effective public health response. Such research can only occur effectively if the logistic aspects are planned in advance, that the necessary research infrastructure exists, and that the proposed research has all ethical, administrative, and regulatory approvals that are necessary for it to commence (22). The readily available results of pandemic research are necessary for optimal public health interventions as well as clinical management. Some examples of critical research questions include (23):

- How severe is the pandemic? What is the case-fatality proportion? What is whole-of-population incidence of critical illness? What is the reproduction number (R0) of the infection? Which sub groups are at risk of severe infection?
- What are the components of the host–pathogen interaction that determine susceptibility to severe disease and severity? What are the dynamics of viral quantification and shedding? How is viral shedding influenced by administration of antiviral medications?
- What is the microbiology and antimicrobial susceptibility of secondary bacterial infections? Is virulence or antiviral resistance of the virus changing during the pandemic due to viral evolution?
- Is the case definition valid? What are the clinical features, complications and pathways to critical illness? What are the risk factors for critical illness? Can valid triage or severity scoring systems to predict critical illness be developed? Are there biomarkers that can assist in stratifying risk, and prognosis? How specific and sensitive are the diagnostic tests? What are the optimal clinical specimens to yield a diagnosis?
- Are infection control measures in hospitalized patients effective?
- What was the effect on non-outbreak related health care systems and operations? What was the impact on the patient and care setting? What, if anything, did the responders have to do differently?
- What treatments or treatment strategies, including supportive care, are effective for patients with critical illness? What treatments are effective at preventing progression from earlier stages of disease to critical illness? What are the pharmacokinetic/pharmacodynamic (PK/PD) relationships for commonly used antimicrobials for the pandemic infection? Is vaccination (once it becomes available) effective at preventing critical illness? Were there essential elements or treatments needed that were not available?

Several organisations, with overlapping membership, have been established that have the mission of being better prepared to conduct time-critical clinical research during future epidemics and pandemics.

International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC)

The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) was formed in 2011, in response to global recognition of the unmet need for timely and effective clinical research during outbreaks of emerging infectious disease with epidemic or pandemic potential. ISARIC represents a new paradigm for effective, coordinated, and timely collaborative clinical research during rapidly emerging threats to public health. It is collaboration among clinicians, clinical researchers, epidemiologists, ethicists, statisticians, laboratory based clinicians, basic scientists, and public health experts. The mission of ISARIC is to develop operational readiness and to co-ordinate the conduct of essential clinical research to characterise and respond to new epidemic or pandemic infectious disease threats, thereby informing and guiding evidence-based optimal management.

ISARIC is facilitating the coordination of SPRINT-SARI. The study supports ISARIC's goal of improving the effectiveness of clinical researching globally during a pandemic by:

- Establishing protocols, with standardised definitions and study methods, for conducting time-critical research during outbreaks of emerging infectious diseases;
- Coordinating a large number of globally diversified hospital and / or ICU-based networks with pre-existing ethics, administrative, regulatory and logistics in place, sufficient to implement study protocols, especially including regions where this type of clinical research has traditionally not been performed;

- Identifying and solving EARL barriers to pandemic research, including those identified in SPRINT-SARI;
- Studying SARI globally, providing evidence on SARI microbiology, treatment and outcome in both resource-rich and resource-poor settings;
- Allowing ISARIC to evaluate its research capacity and capabilities; and
- Assisting ISARIC to maintain network stakeholders during inter-pandemic periods.

The International Forum of Acute Care Trialists (InFACT)

InFACT is an umbrella organization of approximately 25 research consortia whose members conduct investigator-led research into the optimal care of acutely ill patients. InFACT member groups come from all continents, and include long-established and highly successful organizations such as the ANZICS Clinical Trials Group and the Canadian Critical Care Trials Group, as well as emerging consortia in China, Latin America, Asia, and Sub-Saharan Africa; they also include established academic consortia such as the George Institute, ICNARC in the UK, and the University of Pittsburgh. Member groups have published many of the most impactful trials in critical care, including more than 40 in the New England Journal of Medicine.

InFACT's global reach facilitates broad engagement in studies like SPRINT-SARI. During the H1N1 pandemic, for example, InFACT led an initiative to pool data across 5 regional registries of patients with severe H1N1 infection, providing an unprecedented opportunity to describe the disease in more than 5000 patients from around the world. Beyond this, InFACT has been actively involved in promoting and mentoring emerging trials groups in Latin America and Asia, providing scientific and logistical assistance as they launch their initial efforts in observational research.

InFACT members have played a central role in the design of SPRINT-SARI, and in engaging groups outside Australia and New Zealand in supporting the study. Our goals, and our contribution, will be to ensure that SPRINT-SARI draws upon the broadest sample of acutely ill patients to maximize its generalizability, and to provide the necessary methodologic critique to assist in maximizing the scientific rigour of the project.

Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE)

PREPARE is a European clinical research framework, harmonising large-scale clinical research studies on infectious diseases, prepared to rapidly respond to any severe infectious disease outbreak, providing real time evidence for clinical management of patients and informing public health responses. PREPARE will establish a common European clinical research infrastructure covering over 600 primary care sites and over 300 hospital sites in 27 EU member States and other European countries. It will implement 'inter-epidemic' large-scale clinical studies and patient-oriented pathogenesis studies and develop novel near-patient diagnostics. In addition, it will develop and test pre-emptive solutions to ethical, administrative, regulatory, logistical and clinical bottlenecks that prevent rapid clinical research responses in the face of new threats and implement education and training programmes for the members of the clinical network and external opinion leaders, funders and policy makers, strengthening collective capacity and streamlining future response. The peacetime studies will train PREPARE in mounting a rapid, coordinated deployment of Europe's elite clinical investigators, within 48 hours of a severe outbreak. PREPARE is funded by the European Commission's FP7 Programme grant.

PREPARE Workpackage 2 PRIME: clinical PRotocols and guidelines for Infectious disease Management in Europe. This study supports the PRIME goals of describing the current health-service utilisation, clinical management and clinical outcome of patients in Europe with SARI, developing harmonised clinical case definitions and case management guidelines, and developing pre-approved protocols for large multi-site clinical studies in Europe in response to severe SARI outbreaks.

Significance

Due to the severity and communicable nature of SARI - as demonstrated though the 2009 H1N1 pandemic, compounded with annual incidence of SARI during seasonal influenza epidemics - it is clear that investigation of

SARI can provide large scale benefits to improve public health. Rapidly obtaining accurate information on the epidemiology of SARI and providing information on how these patients are currently diagnosed and treated is essential. This study will provide valuable information to improve knowledge of the factors associated with 'how' and 'why' acute respiratory infections progress to the most severe forms of critical illness and death. Extended benefits include shorter hospitalisation stays, reduced financial costs associated with treatment, prevention of the escalation of SARI and complications, which overall will allow clinicians and researchers to serve patients/public with greater knowledge and reassurance. Furthermore, establishing research infrastructure and creating a cadre of individuals skilled in data collection will ensure the sustainability of research in various regions.

OBJECTIVES

Aim

The primary aim of this study is to establish a research response capability for a future epidemic and pandemic through a global SARI observational study. Through this primary aim, we hope to:

- Obtain and maintain ethical approval for this study so that is can be rapidly activated in the event of a future outbreak of SARI in as many locations as possible;
- Generate research capacity in regions and hospitals traditionally under-served by clinical research, including formal mentoring and education initiatives;
- Assist ISARIC in developing an operational plan for a future pandemic; and
- Identify potential topics and patient populations for multidisciplinary studies ranging from interventional clinical trials to investigations of fundamental mechanisms of disease in SARI;

The secondary aim of this study is to investigate the clinical epidemiology and microbiology profiles of patients with SARI. Through this secondary aim, we hope to:

- 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
- Evaluate the impact on incidence of alternative case-definitions of SARI
- Explore the feasibility of extrapolating results obtained at participating sites to population levels.

Tertiary aims

- To assess the Ethics, Administrative, Regulatory and Logistic (EARL) barriers to conducting pandemic research on a global level.

STUDY OUTCOME MEASURES

Primary Outcome:

To test the feasibility of conducting a global study of SARI

1. The number of sites able to participate and submit data for central analysis
2. The completeness of submitted data

Secondary Outcomes:

1. Incidence of SARI
2. Disease severity and risk factors for severe disease due to SARI
3. Case Fatality Proportion of SARI
4. Duration of ICU/hospital stay due to SARI

5. Microbiology of SARI, including variability in testing
6. Treatments received during hospitalization for SARI
7. Evaluate impact on incidence of alternative case-definitions of SARI
8. Evaluate the operational characteristics of this study, including CRF, Completion Guidelines, and entry criteria to provide information by which iterative improvement in study design can be implemented
9. Explore the feasibility of extrapolating results obtained at participating sites to population levels

Tertiary Outcomes

1. Determine the requirement of ethical approval at each site
2. Determine the time required to obtain ethical approval
3. Determine additional EARL barriers
4. Identify solutions for future observational and interventional studies
5. Evaluate questionnaires used to determine additional EARL barriers

OVERALL STUDY DESIGN

Study design

This is a multi-centre, prospective, short period incidence observational study of patients in participating hospitals and ICUs with SARI. The study will be conducted at 20 to 40 hospital networks globally and will aim to recruit more than 1,000 patients per study period. The aim is to recruit all eligible patients at each study location and there is no maximum number of patients that can be recruited from any one site. The study period will occur over a 5 to 7 day study period during which patients meeting a SARI case-definition who are admitted to the in-patient unit of interest will be recruited into the study. Participating hospitals will, prospectively, opt for a period of recruitment of 5, 6, or 7 days, with the presumption being that hospitals will base this choice on their research infrastructure. The planned start dates will be pre-determined by individual sites, within an 8-week window set by the management committee for each study season. 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. The intention is that the 5 to 7 day SPRINT-SARI data collection period will be repeated annually. We encourage networks and sites to participate each year but an alternative, and equally acceptable option, is for sites to rotate on a year-by-year basis. If networks do rotate sites this serves to broaden, as much as possible, the number of sites with ethical approval that would be available in the event of an outbreak.

Study population

We plan to recruit as many patients as possible, in as many locations as possible, who meet the inclusion criteria with no-exclusion criteria at the participating sites. It is anticipated that each participating network could contribute between 5 and 50 hospitals. Each site's recruitment will be determined by the incidence of the disease during the study period, and their ability to collect the required data. The specific inclusion criteria may be narrowed in subsequent SPRINT-SARI iterations based upon evaluation of different case definition criteria.

Inclusion criteria

All patients newly admitted at participating hospitals to the in-patient unit of interest of any age, presenting with SARI during the study period, commencing at 0000 or at the start of the chart day and concluding 120 hours (5 days), 144 hours (6 days), or 168 hours (7 days) later. Patients will be eligible for the study if the patient meets the case definition for SARI, as follows (4, 11):

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 feverishness or measured fever of ≥ 38° 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 (24). 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 time window than the WHO definition (14 as opposed to 10 days) and a broader case definition including dyspnoea, tachypnoea to allow partial 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 into SPRINT-SARI. This will allow for a detailed analysis of different SARI case definitions and the associated operational characteristics.

Exclusion criteria

There are no exclusion criteria.

Co-enrolment

This is an observational study. Co-enrolment with other studies including interventional clinical trials is accepted.

PARTICIPATING STUDY SITES

This study aims to recruit as many study sites as possible. Recruitment of participating hospitals will be done through advertising of the study:

- To the hospital and / or ICU based networks currently holding membership with ISARIC, InFACT and PREPARE;
- Through a study specific web site;
- Through advertising at national and international meetings.

It is anticipated that 30 to 40 hospital networks in ISARIC's global hospital network will agree to take part in this study. A potential of >1,000 study sties could be recruited globally, based on the 45 hospital networks who are current members of ISARIC, with no specific restrictions on participation (25).

Mentoring & Development

Given the expansive nature of the study and the aim to capture data from SARI patients in all regions worldwide, the study will include a significant training and educational component. Local research capacity will be assessed via a brief email survey, including information on research staff, access to electronic Case Report Form (eCRF) technology, and experience with clinical research, and linked with site codes. Upon expression of interest to participate, the management committee and network leads will target local junior and emerging investigators to spearhead local collection of data. These local champions will participate in teleconferences and webinars on clinical research and have access to educational materials relating to study design and clinical research. A small educational package will be distributed upon participation with relevant materials. Local research infrastructure will be an explicit target of performing the study, incorporating knowledge translation in all aspects of study completion. Ongoing data collection about comfort with clinical research and other components of research infrastructure will be embedded within ongoing monitoring procedures during the multi-year course of the study.

ETHICS

Guiding Principles

The Principal Investigator and study management team are responsible for ensuring the study is performed in accordance with the protocol. This study is to be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964, most recently amended in October 2013), and the most recent, relevant ethical conduct of research guidelines published in the country of the participating site.

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 their countries research guidelines (26).

Comply with all local requirements

National or regional Co-ordinators in their defined location will be responsible for clarifying the requirements for ethics approval. It is the responsibility of the site Principal Investigator and Research Co-ordinator to ensure ethics approval has been granted prior to commencing the study and all local requirements are addressed. Each participating site will require ethics approval for this protocol and all data collection tiers (0-3, discussed in Data Collection Methods below) of the WHO and ISARIC Severe Acute Respiratory Natural History and Biological Sampling CRF (RAPID, CORE, SUPPLEMENTARY TO CORE, DAILY and EPIDEMIOLOGY) and any other study documents. Ethics approval for all data collection tiers will ensure that pandemic preparedness is achieved. As a result, in the event of a respiratory epidemic or pandemic, participating hospitals will have the ability to immediately conduct clinical research using any of the CRFs included depending on their own objectives for epidemic/pandemic research and their research capacity. Ethical approval should be obtained to participate in SPRINT-SARI on an up to annual basis for as long a period allowed by the local ethical approval process and then maintained by renewal. Ethical approval should include the capacity to activate the study protocol, for an indefinite period, in the event of an outbreak.

If required, it is the responsibility of each site Principal Investigator and Research Coordinator to obtain ethics approval at their site. Study sites will not be permitted to record data unless ethics approval of the protocol and related documents is in place. When possible, each participating study site will be supported by the University of Oxford, Project Manager with their application. During the study, any amendment or modification to the study protocol will be notified to the independent Ethics Committee by the Principal Investigator and approved by the independent Ethics Committee before implementation. The Principal Investigator will produce progress reports, and any other required documentation for the local independent Ethics Committee in accordance with their guidelines. It is the responsibility of the Principal Investigator at each participating hospital to keep an up to date record of all correspondence and applicable documentation with the local Independent Ethics Committee. We will be collecting data on the requirements and the time frame for approvals in each participating network region.

Confidentiality of patient data

No identifying data will be entered into the central database. Participants' names will not be collected, and confidentiality of information in medical records will be preserved. The confidentiality of the participant will be maintained unless disclosure is required by regulations. To adhere to international ethical review board requirements and facilitate global SPRINT-SARI data polling/sharing the Data Management System will convert all dates entered (DD/MM/YYYY) into the eCRF into a de-identifiable format (D1, D2) at a system level. The original entered data (DD/MM/YYYY) will only be accessible by the site Research Co-ordinator and the site Principal Investigator using their unique database account details.

Rule of Transfer

It is proposed that if a patient is transferred from a facility participating in SPRINT-SARI 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.

All sites participating in SPRINT-SARI will be asked to include a SPRINT-SARI study information sheet in the patients transferring documents, notifying the new hospital of the patient's inclusion in SPRINT-SARI, the patients de-identified participation number, the contact details of the Principle Investigator of SPRINT-SARI in

the country and the SPRINT-SARI coordinating centre. If you are unsure if a patient has previously been enrolled in SPRINT-SARI please check to see if the patients transferring hospital and ward/unit are included in the participating sites list on the SPRINT-SARI website (https://isaric.tghn.org/sprint-sari/). Please use the patients existing SPRINT-SARI participant number at the new hospital when entering data into the paper and/or eCRF.

Sites will not have access to any data collected outside their hospital; 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 attended.

Informed consent

It is expected that this study will not require individual patient consent. This study is in effect a large-scale clinical audit, as all data is already recorded as part of routine clinical care, therefore justifying participant enrolment using a waiver of consent. Waiver of consent may be available for studies that submit only de-identified information and where involvement in the research carries no more than low risk. Any location that deems individual consent necessary will not be able to participate in SPRINT-SARI at this stage.

DATA MANAGEMENT

Data collection methods

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 and ISARIC Severe Acute Respiratory Natural History and Biological Sampling CRF and eCRF. This CRF comprises three CRFs. The sites research capacity will determine which CRF or combinations of CRFs that are to be completed, at the site's discretion. The CRF was assembled by ISARIC members on the basis of the WHO natural history protocol, INFINITE (ANZICS), MOSAIC and others (27, 28). The CRF was assembled to be a basic CRF with the aims of avoiding data duplication, and with the intention of being user friendly and applicable in all settings, regardless of the resources available (29). The CRF has previously been used in Singapore, New Zealand, Saudi Arabia, Vietnam, and North America and adapted by a working group for the purposes of this study with ISARIC approval to all changes made). The CRF will be available on the SPRINT-SARI website (https://isaric.tghn.org/sprint-sari/).

To account for the varying capacity, resources and infrastructure of sites, the CRF is comprised of four tiers:

Tier	Site Resource Level	CRFs completed for each patient
Tier 0	Sites that do not have the resources to collect Tier 1	• Rapid CRF
Tier 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 2	Sites with available resources to complete forms	• Core CRF;
		• Daily CRF, day 1 & 2:
		  ○ hospital admission; and
		  ○ Daily CRF, day 1 & 2 of ICU admission (if applicable).

Tier 3	Optional additional CRFs, sites can choose to complete Tier 3 CRFs according to their scientific interests	• Epidemiology CRF.

The CRF will be made available at all participating sites as a paper CRF. The translation of the paper and electronic CRFs from English into the required language will be the responsibility of the national lead investigators and checked for consistency by an appropriate investigator in the relevant country. All data will be collected by trained staff at each study site and these individuals will enter all required 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 Research Coordinator or 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.

Data collection

Data will be entered into an online eCRF database managed by ISARIC, United Kingdom. In Countries unable to upload data on a centralised database the right to retain a local database on a national server is available with aggregated completely anonymised data exported centrally for analysis. Each site will be identified via a 3 digit network code, 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 in SPRINT-SARI. The site-code will be specified as to whether it is an ICU, hospital ward, or other facility. The site code is obtained by contacting the SPRINT-SARI project management. 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 A001 onwards, in-patient ward will assign B001 onwards). The full patient identification number will therefore be a 10 digit number, with the format of the following: network code - site code – individual patient code [_][_][_]-[_][_][_]-[_][_][_][_](eg. 001-012-0001). The register of patient names and study numbers will not leave the participating hospital.

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 Research Coordinators or 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 is maintained locally and is not to be transferred to any other location.

The Research Coordinator 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 study number only. The enrolment log and study data will be kept separately.

Screening log

No screening log will be maintained.

Data quality

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

1. An online start-up meeting for all research coordinators prior to study commencement will be held to ensure consistency in procedures;
2. A detailed data dictionary will define the data to be collected on the case report form;
3. 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;

An achievable data set will be fundamental to the success of the study. We have identified the key data points whilst not discouraging centres from participating through an excessive burden of data collection. 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.

Data variables collected

The number and type of data variables collected varies between the three tiers. All tiers include all data points collected in tier 0 (RAPID CRF). Appendix: Data Schedule of Events (page 31-34) provides a summary and time schedule of the data to be collected for each tier.

Data management

Data entry and data management will be coordinated by ISARIC, including programming and data management support. On behalf of the management committee and ISARIC, ISARIC will act as custodian of the data. The management committee of the study will take responsibility for the content and integrity of any data. There will be periodic assessments of data burden to ensure that the infrastructure is organized to handle large amounts of incoming data in small time periods.

SPRINT-SARI will adhere to the research and data sharing policies of ISARIC, Sample and Data Sharing Policy, Version 4, 21 July 2014 (30). 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 it. Networks will retain the right to request raw data for all sites included in their network for research purposes, provided that the research proposal has been reviewed and approved by the management committee and ISARIC following publication of the primary manuscript.

All analysis of pooled data will be undertaken with the explicit agreement of each site who contributed. 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.

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.

STATISTICAL CONSIDERATIONS

The data to be collected are all collected as part of routine clinical care. Categorical variables will be described as proportions and will be compared using chi-square or Fisher's exact test. Continuous variable will be described as mean and standard deviation if normally distributed or median and inter-quartile range if not normally distributed. Comparisons of continuous variables will be performed using one-way ANOVA or Mann-Whitney test as appropriate. A logistic regression model will be performed to assess independent association between prognostic factors and outcomes, taking into account the hierarchical nature of the data. Significance will be set at $p<0.05$.

Power calculations and sample size

The study will utilise a convenience sample of, subject to ethical approval, consecutive patients at participating sites. The main analyses are descriptive and, as a consequence, somewhat less dependent on sample size. Analyses of factors associated with outcome will be performed subject to there being sufficient recruitment to justify these analyses being conducted.

ANCILLARY STUDIES

SPRINT-SARI encourages participating sites and networks to conduct ancillary studies. Ancillary studies must submit a formal proposal to the Management Committees and ISARIC and include one SPRINT-SARI

Management Committee member as an investigator on the ancillary study. Ancillary studies must not publish their findings until after the publication of the SPRINT-SARI primary manuscript. All ancillary study publications must adhere to ISARIC Publication Policy (Version 2, 21 July 2014) and Data and Sample Sharing Policy (Version 4, 21 July 2014) (30, 31).

Ancillary study proposals must include:

- If independent funding will be sought;
- Background and study rationale;
- Hypothesis and research question;
- Methods and a detailed description of the statistical analysis to be performed;
- Study significance; and
- Description of ethical requirements specific to the ancillary study, if necessary

STUDY GOVERNANCE

Management Committee

SPRINT-SARI will be coordinated by University of Oxford and supported by additional regional coordination if required. A management committee comprising the named investigators and the project manager will take responsibility for the conduct and management of the study. The duties of this team will include administration of all project tasks, communication between project partners (including funders, management committee members, national and local co-ordinators, etc.), data collation and management. The management committee is responsible for the scientific conduct and consistency of the project. The management committee will ensure communication between the funder(s), study management team and co-ordinators as necessary.

RESPONSIBILITIES OF THE INVESTIGATOR AND COORDINATING CENTRE

Responsibilities of the National co-ordinators

The management committee will liaise with each participating network to identify an individual who will lead the project for that network. The national/network co-ordinator is responsible for identifying the investigator at participating sites, ensuring distribution of study materials (as required), researching the country's ethical regulatory requirements and ensuring each site is adhering to ethical requirements, communicating with sites within their nation, communicating with the management committee, ISARIC and University of Oxford. The national/network co-ordinators will be the primary contact for each site within the country and/or network. In addition, the national co-ordinator will be responsible for collating the EARL data in the region

Responsibilities of the Site Investigator

The Site Investigator agrees to perform the study in accordance with this protocol, ICH guidelines for GCP and the applicable regulatory requirements. The Investigator is required to ensure compliance with all procedures required by the protocol and with all study procedures provided by ISARIC and University of Oxford.

The Investigator agrees to provide reliable data and all information requested by the study protocol in an accurate and legible manner according to the instructions provided.

Responsibilities of the Coordinating Centre

The University of Oxford Project Manager and representatives of ISARIC will take all reasonable steps to ensure the proper conduct of the study protocol.

Prior to initiation of the study at each participating site, University of Oxford and ISARIC will ensure that each National/network Co-ordinator, site Principal Investigator and study personnel understand all aspects of the study protocol and procedures and the use of the CRF and other study materials.

The study site's progress will be monitored by ISARIC and the University of Oxford,Project Manager. During the study, the national co-ordinators will be contacted through emails or telephone calls, to review study progress,

site investigator / patient compliance with study protocol requirements and any problems. Investigators will be assisted to maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

ISARIC will review the CRF based on feedback form participating sites and the research centre at the completion of the study. The SPRINT-SARI investigators will provide suggestions on how, if possible, to improve data quality, adherence to CRF to ISARIC.

FUNDING

Central project coordination is supported by the Wellcome Trust to facilitate the long-term sustainability for central infrastructure of this project. Some aspects of the North American study may be supported by the North American Cooperative for Emergency Preparedness supported by a contract from the Association of Public Health Laboratories with funds from their cooperative agreement with the Centers for Disease Control and Prevention held by Prof. J. Perren Cobb. ISARIC is supported by a variety of sources including the Wellcome Trust and the European Union FP7 framework. PREPARE is funded by a European Union FP7 grant that is led by Prof. Herman Goossens. It is not planned that any per patient payments will be made to support site costs.

PUBLICATION POLICY

The study will be conducted in the name of the SPRINT-SARI Investigators on behalf of University of Oxford and ISARIC. Publications using data collected by SPRINT-SARI will be published on behalf of the SPRINT-SARI Investigators with a writing committee taking responsibility for all manuscripts. All members of the Steering Committee will be given the opportunity to contribute to the work of writing committees and all members of the writing committee who contribute to the writing will be recognised with authorship. All study publications will adhere to ISARIC Publication Policy (Volume 2, 21 July 2014) (31).

RESEARCH TIMELINES

Time frame indicator	Project Milestones
June 2015	Develop study materials, adapt CRF
July 2015	Project EOI distributed to networks
September 2015	Project EOI distributed to sites
November 2015	Site training on study material
Jan –Mar 2016	Northern hemisphere winter 2015/16 recruitment
Jul-Sep 2016	Southern hemisphere winter 2016 recruitment
Jan-Mar 2017	Northern hemisphere winter 2016/17 recruitment
Jul-Sep 2017	Southern hemisphere winter 2017 recruitment
Aug 2017 –Mar 2018	CRF adaptation, database design and migration
Jan-Mar 2018	Northern hemisphere winter 2017/18 recruitment
Jan-Mar 2018	Data analysis of data from season 1 and 2
Mar 2018	Manuscript submission (data from season 1 and 2)
Apr 2018	Data analysis and manuscript submission (Season 3)
May-Jul 2019	Database migration from Monash University to University of Oxford
Jan-Mar 2020	Northern hemisphere winter 2019/20 recruitment

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APPENDIX

STUDY ADMINISTRATION STRUCTURE

ISARICCoordinating Centre

Responsibilities

Responsible for all aspects of study management, including:

- Final protocol
- Management of Study Website
- National Co-ordinator training on protocol and study procedures
- Management of regulatory affairs
- Organisation of investigator meetings
- Liaison with independent data and safety monitoring committee
- Data analysis and collaboration on publications
- Providing support to National Co-ordinators

Data Management Centre

Responsibilities

Responsible for all aspects of the data management, including:

- Case Report Form design and production
- Electronic Case Report Form design and production
- Database development, maintenance and administration
- Data management
- Allocation of network and site numbers

Networks

Responsibilities

Responsible for all aspects of network activities, including:

- Liaise with the project manager and management committee regarding all study issues
- Coordinate the study for their participating sites
- Assist and liaise with interpretation of ethical issues to the local requirements
- Identify and encourage sites to participate in SPRINT-SARI
- Complete the network level component of EARL activities

National Co-ordinators

- Identifying research co-ordinators and principal investigators at each site
- Providing support to all sites within country and/or network

Management Committee

Responsibilities

Responsible for overseeing all aspects of the study management including:

- Liaison with coordinating centre staff, steering committee and ISARIC
- Funding applications, negotiations and communications
- Reports to funding bodies
- Study budget
- Development and approval of final protocol and study materials
- Development and approval of data management systems
- General study management issues

Members

Dr	Kenneth	Baillie	Clinical Lecturer, Critical Care Medicine	University of Edinburgh / The Rosin Institute
Dr	Gail	Carson	Clinical Lead, ISARIC Coordinating Centre	University of Oxford/ISARIC Coordinating Centre
Dr	Michael	Christian	Physician, Critical Care and Infectious Diseases	Mount Sinai Hospital & University Health Network Toronto
Dr	J. Perren	Cobb	Director, Surgical Intensive Care Unit, Massachusetts General Hospital	Associate Professor of Surgery and of Anesthesia, Harvard Medical School
Dr	Jake	Dunning	Senior Clinical Research and Honorary Consultant in Infectious Diseases and General Medicine	Centre for Tropical Medicine and Global Health, University of Oxford
Dr	Robert	Fowler	Sunnybrook Health Sciences Centre Assistant Professor, Department of Medicine and Interdepartmental Division of Critical Care Medicine,	University of Toronto
Professor	Peter	Horby	Professor of Emerging Infectious Disease and Global Health,	Epidemic Disease Research Group Oxford, Oxford University
Dr	John	Marshall	Professor of Surgery / Chair Canadian Critical Care Trials Group / Chair International Forum of Acute Care Trialists	University of Toronto St Michael's Hospital

Dr	Colin	McArthur	Department of Critical Care Medicine at Auckland City Hospital / Chair Australian and New Zealand Intensive Care Society-Clinical Trials Group	Auckland District Health Board
Ms	Laura	Merson	Head of Clinical Trials Unit, Group Head / PI and Member of congregation	University of Oxford Clinical Research Unit, Viet Nam
Dr	Srinivas	Murthy	Assistant Professor, Critical Care and Infectious Diseases	University of British Columbia
Dr	Alistair	Nichol	Professor	University College Dublin
Dr	Rachael	Parke	Nurse Senior Research Fellow	Auckland District Health Board
Dr	Steve	Webb	Clinical Professor and Adjunct Professor	University of Western Australia / ANZIC-RC
Dr	Tim	Uyeki	Chief Medical Officer, Influenza Division/ Associate Clinical Professor of Paediatrics	Centers for Disease Control and Prevention/University of California, San Francisco
Dr	Husna	Begum	Project Manager	ANZIC-RC, Monash University

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MANAGEMENT COMMITTEE AUTHORISATION PAGE

We the management committee have read the attached protocol and authorize it as the official protocol for the study entitled **S**hort **P**e**R**iod **I**ncide**N**ce s**T**udy of **S**evere **A**cute **R**espiratory **I**nfection (SPRINT-SARI)

Chief Investigator **Date** 3rd June 2019
Dr Srinivas Murthy

Management Committee **Date** 3rd June 2019
Dr Kenneth Baillie

Management Committee **Date** 3rd June 2019
Dr Gail Carson

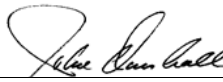
Management Committee **Date** 3rd June 2019
Dr Michael Christian

Management Committee **Date** 3rd June 2019
Dr. J. Perren Cobb

Management Committee **Date** 3rd June 2019
Dr Jake Dunning

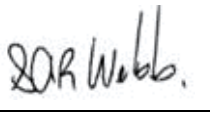
Management Committee **Date** 3rd June 2019
Dr Robert Fowler

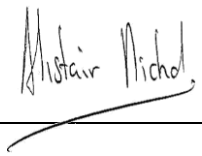
Management Committee Date 3rd June 2019
Professor Peter Horby

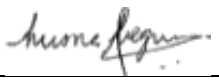
Management Committee  **Date** 3rd June 2019
Professor John Marshall

Management Committee  **Date** 3rd June 2019
Dr Colin McArthur

Management Committee  **Date** 3rd June 2019
Ms Laura Merson

Management Committee  **Date** 3rd June 2019
Professor Steve Webb

Management Committee  **Date** 3rd June 2019
Professor Alistair Nichol

Management Committee  **Date** 3rd June 2019
Dr Husna Begum

Management Committee  **Date** 3rd June 2019
Dr Rachael Parke

Management Committee  **Date** 3rd June 2019
Dr Tim Uyeki

APPENDIX

Data Collection Schedule of Events

Tier 0- Schedule of Events

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. Demographics	X						
2. Onset & Admission	X						
3. ICU or High Dependency Unit Admission				X			
4. Infectious Respiratory Diagnosis							X
5. Treatment							X
6. Outcome							X

Tier 1 – Schedule of Events

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							
1. Demographics	X						
2. Onset and Admission	X						
3. ICU or High Dependency Unit Admission				X			
4. Signs & Symptoms at Hospital Admission	X						
5. Comorbidities	X						
6. Complications							X
7. Infectious respiratory Diagnosis: Diagnosis							X
8. Infectious respiratory Diagnosis: Pathogen Testing							X
9.							
10. Treatment				X			X
11. Outcome							X
Daily CRF							
1. Date of assessment		X			X		
2.							
3. Daily Laboratory Results		X			X		

Tier 2 – Schedule of Events

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							
12. Demographics	X						
13. Onset and Admission	X						
14. ICU or High Dependency Unit Admission				X			
15. Signs & Symptoms at Hospital Admission	X						
16. Co-morbidities	X						
17. Complications							X
18. Infectious respiratory Diagnosis: Diagnosis							X
19. Infectious respiratory Diagnosis: Pathogen Testing							X
20.							
21. Treatment				X			X
22.							
23. Outcome							X

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)
Daily CRF							
4. Date of assessment		X	X		X	X	
5.							
6. Daily Laboratory Results		X	X		X	X	
7.							

Tier 3 – Schedule of Events

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 the previous 14 days	X						
2. Living arrangement	X						
3. Occupation	X						
4. Vaccination History	X						