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GenOMICC Study Protocol V4.0

8th November 2023

Genetics Of Mortality In Critical CareA close up of a sign

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# Aims

1. To identify host genetic variants associated with susceptibility to, and mortality from, life-threatening infection and sterile injury.
2. To prioritise therapeutic targets with which to modulate the host response to injury and infection in patients with life-threatening disease.

# Objectives

We will work within the International Severe Acute Respiratory Infection Consortium (ISARIC) and International Forum of Acute Care Trialists (InFACT), two global initiatives, to establish a prospective DNA resource for hypothesis-testing and genome-wide discovery of host genetic variants underlying susceptibility to severe infection, and outcome from life-threatening systemic injury. We will:

Obtain a single DNA sample from patients with:

1. Susceptibility to severe disease;
2. Susceptibility to specific outbreaks and exposures of public health interest;
3. Susceptibility to death following onset of severe illness due to specific syndromes, and;
4. Susceptibility to death from quantifiable sterile injury.

Obtain DNA from the parents of patients with extreme susceptibility to eligible syndromes (those under 40 and free from significant comorbidity).

Obtain DNA samples, where possible, from appropriate comparison or control groups.

Combine existing DNA resources in a virtual collaborative network to enable rapid hypothesis-testing of candidate variants.

Establish and continually replenish a small cohort of individuals with known profound susceptibility to specific pathogens, who will be invited to provide repeat samples for *in vitro* studies of cellular responses to relevant stimuli.

Where appropriate and implementable, allow return of clinically relevant information to the NHS (or appropriate healthcare provider) regarding participants.

Allow lifetime linkage (and beyond) to healthcare and other relevant data (including registries, healthcare records, research datasets, and lifestyle and other data).

# Background

Susceptibility to infection is profoundly heritable (Sorensen et al. 1988). Patients who develop life-threatening illness following infection with usually innocuous pathogens, such as influenza (Miller et al. 2010), are genetically different from the rest of the population (Albright et al. 2008). Understanding the genetic mechanisms of susceptibility may yield new therapeutic targets (Baillie 2014) that can be used to make susceptible patients more like individuals who are resistant to, or tolerant of, specific pathogens.

The genetic mechanisms of susceptibility to infection are likely to be highly pathogen-specific, and may even have opposing roles in different infections (as for CCR5 variants in HIV (Huang et al. 1996) and WNV (Glass et al. 2006) infection). Pathogen-specific interventions (e.g. small molecules to inhibit an enzyme or receptor that is dysfunctional in resistant individuals) would therefore be protective to the host in a similar way to antibiotics, with the advantage that it is conceptually more difficult for any one pathogen to evolve resistance to such a therapy.

A second, more challenging problem arises in patients who become critically ill following infection. The patterns of immune-mediated organ dysfunction, immunoparesis, and death are very similar in severe infections and sterile systemic injuries (such as burns, haemorrhage, pancreatitis and trauma). Ultimately, death is a consequence of the host response to injury (Angus and Poll 2013), through final common pathways of organ failure that are clinically and biochemically evident, and unrelated to the original precipitant.

Broadly, the severity of critical illness follows directly from the severity and duration of the initial insult. In bacterial sepsis, early antibiotics are the mainstay of therapy; in influenza, early antivirals; in haemorrhage, early resuscitation; in trauma, urgent action to prevent secondary injury. We have no therapies with which to modulate the host response to systemic injury.

There is a lack of direct evidence of heritability for outcomes of critical illness, due in part to difficulties in defining and quantifying the heterogeneous multi-organ dysfunction syndrome (MODS), and in part due to the rapid pace of change in critical care medicine, making it impossible to tackle this question in long term outcome studies. However, clinical and biological evidence support the hypothesis that the pathogenesis of MODS is immune in origin (Angus and Poll 2013). Hence, we can make predictions from the extensive knowledge of other immune conditions. Whether we consider MODS to be an autoimmune or infectious condition is moot: these conditions share a great deal of similarity in genetic predispositions, cell types and mechanisms of pathogenesis. It is therefore very likely that propensity to survive MODS has a heritable component, and there is some direct evidence in support of this hypothesis (Rautanen et al. 2015). If this is the case, then the identity of the specific variants that contribute to outcome could potentially be utilised to design therapies to promote survival after the onset of MODS.

# Study design and implementation

## Phenotypes of interest

This study aims to identify genetic predisposition to specific syndromes of critical illness and outbreaks or exposures of public health interest. Specifically, susceptibility to life-threatening infections caused by an identified pathogen, and susceptibility to death following the onset of organ failure due to sepsis or sterile injury. To maximise the probability of identifying host genetic loci associated with susceptibility, we will restrict some analyses to younger individuals in good general health and lacking in known predisposing factors.

The same principle was used to determine an upper age limit for inclusion for some analyses. With advancing age, there is an increase in undiagnosed comorbidity, frailty, and susceptibility to serious complications of infection or critical injury. There is therefore an increase in the probability of susceptibility to, and mortality from, critical illness that is consequent upon non-genetic factors.

## Prospective recruitment

Patients meeting the entry criteria will be asked to provide informed consent, and a single DNA sample.

## Recruitment of survivors

The group of critical illness survivors eligible for recruitment for this study are generally healthy individuals who have suffered critical illness. We know from extensive epidemiological research that, after recovery from critical illness, mortality returns to close to the baseline for the population (Lone et al. 2016). We have therefore assessed that there is a very low risk of contracting patients who have died since discharge from hospital; hence the recruitment strategy we will use will be comparable to primary care studies in the general population, rather than the more burdensome approaches that are used in studies of patients at a high risk of death. Specifically, we will not contact family doctors to confirm that a patient is still alive before approaching the patient.

Patients will be identified from hospital records by clinical or research staff in the critical care unit that provided treatment to each patient. The patient will be contacted by telephone or post by a member of the clinical team, who could reasonably be expected to have access to the patient’s medical details. This may include a research nurse affiliated to the intensive care unit in which the patient was treated.

Patients who cannot be contacted by phone and do not respond after a period of four weeks from an initial letter, will be sent a second letter in case the first letter was lost in the post. If a patient does not respond to this second letter, the study team will assume that this patient does not want to participate.

Patients in this category may also volunteer to take part in the study by registering their interest in the study online (see ‘Recruitment of a comparison (control) group’).

## Recruitment of A COMPARISON (CONTROL) GROUP

Patients who have evidence of exposure to a relevant pathogen (see Inclusion Criteria, below) but who have experienced only mild or no symptoms, will be able to volunteer to take part in the study. They may also be put forward through other studies, e.g. seroprevalence or screening. Volunteers will be able to provide their contact details on the study website and join the study either using conventional paper-based consent procedures or supplemented, where appropriate, with an online consent tool on the study website.

We may wish to contact all control volunteers periodically to share ethically approved communications. Further, we may contact this group to ask if there would be interest in patient and public involvement (PPI) opportunities. PPI involvement of any kind is completely voluntary and will not relate to study participation in any way.

## OBTAINING SAMPLES FROM PARTICIPANTS IN THE COMMUNITY

Participants will be offered multiple routes to participate in the study. Consent will be obtained and recorded (see below). Participants will be sent a record of their consent and a sample collection kit. The kit will contain a copy of the information sheet, a pre-labelled EDTA blood collection tube and UN3373-compliant sample transport packaging. Venepuncture will then be performed by a qualified healthcare provider or phlebotomist in a location that meets the needs of the participant, subject to availability. These may include: a district nurse, a research nurse operating in an outpatient clinic or clinical research facility, a research nurse in the patient’s home, or an otherwise appropriately-qualified practitioner in an appropriate location, subject to local risk assessments and standard operating procedures. In the event that a blood sample cannot be obtained, patients will be sent a saliva collection kit by post.

## Repeat sampling of survivors

Following recovery from acute illness, a subset of critical illness survivors will be invited to provide additional blood samples for further investigation at specific centres.

## Entry criteria

### Inclusion criteria

Inclusion criteria are stratified to facilitate recruitment under conditions in which resources are limited (Dunning et al. 2014). Lower tiers include syndromes with a high probability of genetic susceptibility and will be prioritised in resource-limited settings. Higher tiers describe less-specific syndromes with a focus on mortality.

**Critical illness.** patients will be recruited who:

* Are deemed, in the view of the treating physician, to require continuous cardiovascular or respiratory monitoring or invasive mechanical ventilation,
* AND provide appropriate consent or assent,
* AND present with one of the following primary diagnoses:

*Group 1: specific infectious syndromes in highly-selected patients*

* + **COVID-19.** Confirmed or suspected COVID-19.
  + **Influenza.** Confirmed or suspected infection with influenza virus.
  + **Secondary pneumonia.** Acute pneumonia complicating confirmed infection with influenza virus.
  + **Dengue.** Confirmed or suspected infection with dengue virus.
  + **RSV.** Confirmed infection with respiratory syncytial virus.
  + **Emerging infections.** Confirmed or suspected infection with an emerging infection (see below).
* *Group 2: specific non-infectious critical illness syndromes*
  + **Burns.** Full thickness burns covering of body surface area.
  + **Emerging critical illness syndromes.** Confirmed or suspected presence of an emerging critical illness syndrome. These are unexplained or idiosyncratic presentations of acute organ injury, or suspected reactions to therapeutic agents, including:
    - confirmed or suspected multisystem inflammatory syndrome temporally associated with COVID-19
    - acute disease associated with inhalation of noxious substances or vapours, such as "vaping"
    - acute disease associated with CAR T-cell therapy
* *Group 3: extreme critical illness*
  + **Extra-corporeal life support.** Requirement for continuous veno-venous extra-corporeal support for respiratory failure of any aetiology.
* *Group 4: common/nonspecific critical illness syndromes*
  + **Cellulitis.** Soft tissue infections causing systemic sepsis.
  + **Pneumonia.** Primary pneumonia of any aetiology, with radiographic changes at presentation to critical care. Pneumonia is defined as: symptoms and signs consistent with an acute lower respiratory tract infection associated with new radiographic shadowing for which there is no other explanation (eg, not pulmonary oedema or infarction). Where this illness is the primary reason for hospital admission and is managed as pneumonia, the patient is eligible for inclusion.(Harris et al, 2011) No microbiology information is required to meet this entry criterion.
  + **Pancreatitis.** Pancreatitis of any aetiology.

**Outbreaks or exposures of public health interest.** Patients from the groups specified below may be recruited even if they are not admitted to critical care.

* + **Potentially life-threatening complications of vaccines against SARS-CoV-2**. Note that since these complications are all potentially life-threatening, patients will be eligible even if they are not admitted to a continuous monitoring/critical care area. This will include confirmed or suspected:
    - Cerebral venous sinus thrombosis
    - Deep vein thrombosis/pulmonary embolism
    - Other thrombotic events, with or without thrombocytopaenia
    - Neuroinflammatory disorders including Guillain-Barre syndrome
    - Anaphylaxis
    - Vasculitis
    - Other potentially life-threatening suspected complications of vaccine
  + **Unexplained hepatitis in children.** Patients under the age of 16 with elevated liver transaminase (ALT > 500 iU/L or AST > 500 iU/L), not due to other diagnoses such as hepatitis viruses A-E, autoimmune hepatitis, or poisoning.

### Emerging Infections

Emerging infections are by their nature unpredictable and present a significant challenge to the international research community. In order to ensure research preparedness, in accordance with the principles laid out by the International Severe Acute and Emerging Infection Consortium (ISARIC)(Dunning et al. 2014), patients will be recruited to this study if they have confirmed or suspected infection with a novel pathogen, a new strain of an existing pathogen, or a re-emerging known pathogen, that causes life-threatening illness. This will include the Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), highly pathogenic strains of influenza, Ebola virus disease and other epidemics of viral haemorrhagic fever.

### Exclusion criteria

There are no exclusions to recruitment and no age restrictions.

All consenting patients meeting the inclusion criteria will be included.

### Additional groups

The following additional groups of people will be eligible for recruitment:

* **Patients recruited into participating ethically-approved clinical studies** (listed here: <https://genomicc.org/uk/trials>) will be recruited to GenOMICC. This route of inclusion in GenOMICC will be available to research studies of conditions related to the above inclusion criteria, including, but not limited to, the ACCORD-2 and RECOVERY-PK studies of therapy for COVID-19.
* **Parents of eligible patients.**
* **Control groups.** Although some comparison groups can be obtained from population genetic studies and from within the critically-ill population, additional controls may increase discovery power in this study for variants determining *susceptibility* to severe disease. Volunteers from the general population will be eligible to act as controls if they have no prior history of critical illness.

### NUMBER OF PARTICIPANTS

The global GenOMICC collaboration aims to ultimately recruit a total of 100,000 participants, of whom around 40,000 may be recruited in the UK.

### Modification of sampling and data collection during the study

Due to the focus of this study on narrowly-defined and hence rare critical illness phenotypes, it will be necessary to conduct recruitment across a wide geographical area. Recruitment costs are expected to be high. We will therefore initially limit recruitment initially to selected phenotypes, and subsequently extend recruitment to the additional phenotypes defined in this protocol as further funds become available.

### Standard of care for PROSPECTIVELY RECRUITED patients

All patients will be treated according to clinical requirements regardless of their participation in the study. Provision of care will vary by site and by treating physician. It is not possible to define a single standard of care and therefore to define what samples will be taken as a part of medical management and when. Participants in this study will have samples taken in addition to what is required for medical management. The results of tests performed on research samples are unlikely to benefit the health of the participants.

## Sampling and Data Collection procedures

### Sample and Data Collection Schedules

A single DNA sample will be obtained at recruitment, comprising an appropriate volume for the weight of the patient of either:

1. a sample of blood in EDTA, or;
2. a sample of saliva in an appropriate collection kit.

All patients will have clinical information collected either directly through examination including a review of medical, contact and travel history, or from available medical notes. Information will be recorded in the case report form. The following data will be collected from each patient:

1. at recruitment, an initial case report form will be completed;
2. a supplemental case report form will be completed at least 3 days after the patient became eligible (this may be concurrent with recruitment in some cases); and,
3. at least 60 days after the patient became eligible, a follow-up case report form will be completed.

Control volunteers will self-complete a short online case report form.

### Sample volumes

In patients donating blood, no patient will give more than mls/kg ( estimated blood volume) during acute illness. The following volumes of blood will be drawn from patients in each weight category:

* 10kg: 4mls (0.4mls/kg)
* 410kg: 2mls (0.5mls/kg)
* 14kg: 0.6mls (0.6mls/kg)

### SAMPLING PROCEDURES FOR PATIENTS OR VOLUNTEERS IN THE COMMUNITY

Patients or control volunteers who agree to participate will be invited to:

* Attend a hospital, research facility or a primary care facility for a blood sample; or
* Receive a home visit from an appropriately trained research nurse who will obtain a blood sample; or
* Send a specimen of saliva by post.

### Sample handling

Standard laboratory systems will be used for all research samples, adhering to the principles of Good Laboratory Practice.

Where necessary for specific tests, samples or materials derived from samples will be exported with the permission of the patient/parent/guardian/consultee. Any samples sent to external laboratories will be pseudonymised with unique coded identifiers to protect the identity of the patient at the site level at the point of enrolment. When required, national guidance will be adhered to for the transport of specimens.

### Potentially hazardous samples

In dealing with pathogens where little is known about transmissibility and/or virulence, great care must be exercised to ensure the safety of hospital staff and other patients. Strict adherence to collection protocols, biosafety and adequate personal protective equipment (PPE) are essential. Biosafety procedures will be as per local policy/guidance and will be applied to the collection, storage and laboratory handling of research samples.

In the event that a sample is identified at any time during the course of the study as high-risk for transmission of infection (for example, a patient tests positive for MERS coronavirus, Ebola virus, or highly-pathogenic strains of influenza), then the sample will be either:

1. obtained by staff wearing appropriate personal protective equipment (PPE) under national public health guidance, and processed under laboratory biosafety conditions appropriate to the pathogen, including pathogen inactivation prior to transport (Blow et al. 2004), or
2. safely destroyed.

### Follow up

Prospectively-recruited patients will be followed up by a member of the research team to determine their outcome. For hospital in-patients, this will be done by review of clinical records, or communication with clinical staff, or the patient. For patients discharged from hospital, follow-up will be undertaken by telephone.

### Outcome measures

The outcome of mortality will be measured at 60 days from the first time the patient met the medical criteria for inclusion in the study.

## Enrolment Procedures

### Enrolment procedures for PROSPECTIVELY RECRUITED patients

Critically ill patients will primarily be identified and recruited in hospital during acute illness. Potential participants will be identified through hospital staff upon presentation at recruiting sites. The disease processes under study have a high mortality, so it is desirable to recruit patients as early as possible in the disease process. Participants who can consent for themselves or where the patient cannot consent for themselves a personal consultee will be approached by staff trained in consent procedures that protect the rights of the patient and adhere to the ethical principles within the Declaration of Helsinki and to the Adults with Incapacity Act (2000) Scotland, Mental Capacity Act (2005) England and Wales 2005 or the Mental Capacity Act (Northern Ireland) 2016, depending on the location of recruitment. Staff will explain the details of the study to the participant, their parent/guardian, or nearest relative or an appropriate consultee and allow them time to discuss and ask questions. The staff will review the informed consent form with the person giving consent or the personal consultee and endeavour to ensure understanding of the contents, including study procedures, risks, benefits, and the right to withdraw. Participants who can agree to participate (or where the participant is unable to consent, with the advice of the personal consultee) will be asked to sign and date an informed consent form.

In view of the importance of early sampling, participants or their parent/guardian/nearest relative/consultee will be permitted to consent / advise and begin to participate in the study immediately if they wish to do so. Those who prefer more time to consider participation will be approached again after an agreed time, normally one day, to discuss further.

Patients who meet the entry­­ criteria and who have given informed consent to participate directly, or where agreement is declared by a parent/guardian/nearest relative/consultee, will be enrolled to the study.

Samples and data will be collected according to available resources and the weight of the patient will be measured for children under 12 in order to prevent excessive volume sampling. Samples required for medical management will at all times have priority over samples taken for research tests. Aliquots or samples for research purposes should never compromise the quality or quantity of samples required for medical management. Wherever practical, taking research samples should be timed to coincide with clinical sampling. The research team will be responsible for sharing the sampling protocol with health care workers supporting patient management in order to minimise disruption to routine care and avoid unnecessary procedures.

### procedures for CONSENTING PATIENTS WITH REGAINED CAPACITY

Consent will be sought from patients who were included in the study following consent or assent from another party (such as a nearest relative or consultee) because of temporary incapacity, where such patients survive critical illness and regain capacity to give consent. This is expected to occur during follow-up during the index hospital admission, but in some cases consent may be obtained over the telephone, for example if the patient has been transferred for tertiary or quaternary care to a hospital some distance away. At each of the follow-up sessions, the investigator gathering data will determine whether the patient has regained capacity. In the event that a patient continues to be incapacitated beyond the follow-up period, the local investigator will plan a subsequent capacity check at a specific date, after an interval to be determined by the nature of the incapacity. The planned dates of capacity checks on incapacitated survivors will be stored locally in the site file, together with a record of the outcome of each check. Patients who decline to participate at this stage will be removed from the study. Where the patient cannot be re-contacted despite best endeavours, they will remain in the study.

### PROCEDURES FOR INITIAL APPROACH TO ELIGIBLE PARTICIPANTS

If a participant has expressed willingness to participate directly to the central team (for example, as is commonly the case for participants in the control group) they will be contacted by the central team and samples will be obtained as described in item 2 below. The steps described here apply to all other participants, including cases and eligible parents of cases.

Recruitment procedure for all participants will follow the following steps, in order, stopping when sample is obtained and sent by post to GenOMICC central laboratory. The central team here refers to a team of research staff working on the GenOMICC study who are not connected with the clinical care of the patient.

1. If possible, participant or appropriate representative approached by the clinical or research team caring for case.
   * If possible, blood sample obtained during acute admission;
   * or else, blood sample obtained by appointment with clinical team caring for case.
2. Or else:
   * if possible, agreement to approach participant or appropriate representative granted by the clinical or research team caring for case;
   * or else, agreement to approach participant or appropriate representative granted by special request from public health team in contact with case/family;
     + Approached by central team:
       - if possible, blood sample kit sent by post to participant,
         * blood sampled at home by research nurse;
       - or else, saliva kit sent by post to participant,
         * saliva self-sampling at home.

### Enrolment procedures for PARENTS OF CASES

Parents of cases meeting the eligibility criteria will be recruited according to the procedure for cases, in order, such that the primary aim is for the initial approach to be made directly by the clinical or research team caring for a case. Where this is not possible, the agreement of an existing clinical or public health team will be required before contact is made from the central team. In new outbreaks or exposures of public health interest, such as the outbreak of unexplained hepatitis in children in 2022, parents of cases are well aware of the unusual circumstances and the close involvement of public health.

Research teams at approved research locations are not asked to routinely recruit parents of patients and the central study team will advise on circumstances of special interest.

### ENrolment procedures for patients after death

In some cases, discarded blood samples from routine clinical sampling are stored in hospital laboratories after death. Since these cases are, by definition, the most susceptible to a given disease, they are the most important group to include in a genetic study. In almost all cases, the patient will have been recruited to GenOMICC during life, either by direct consent from the patient or through a representative. However, in rare cases, in which death occurs within hours of presentation to critical care or a patient could not be recruited during life for some other reason, it may be necessary to ask the grieving relatives of a recently-deceased patient for consent to participate in line with the Human Tissue Act 2004 (in England, Wales and Northern Ireland) and the Human Tissue (Scotland) Act 2006.

Where possible this will be done in person. Critical care clinicians and nurses are very accustomed to dealing with distraught relatives, and in all cases the approach will be made by an experienced clinician who will handle the discussion with the utmost sensitivity and care. The patient’s next of kin, or another appropriate person to represent the wishes of the deceased, will be asked to consent on behalf of the patient. In some cases, contact may be made by telephone. If the request is declined, this will be clearly recorded in the local site file in order to ensure that no further contact is attempted.

A subsection of participants already recruited have sadly died. To ensure that the programme is able study the genetic factors that cause people to succumb from COVID-19 despite intensive care as well as those that cause people require intensive care but survive, a submission is being prepared for the Confidentiality Advisory Group to collect and use their data for research purposes.

### Enrolment procedures for RETROSPECTIVELY RECRUITED patients

Where patients have met the inclusion criteria for this study, but have recovered and been discharged, they remain eligible for recruitment to GenOMICC. Such patients may be approached directly by a member of the clinical or research team in the hospital or intensive care unit who cared for them during their primary illness (including affiliated research staff), and hence would reasonably be expected to have knowledge of the patient’s eligibility for the study.

If the patient presents for out-patient care or attends the hospital for any other reason, they may be approached in person.

Otherwise, the patient will be contacted by mail, telephone or email by a member of the clinical team who cared for them (including affiliated research staff). If the patient refuses, this will be clearly recorded in the site file at the recruiting site to ensure that the patient is not contacted again.

### Enrolment procedures for volunteers from the community

Eligible volunteers (including individuals for the control or comparison groups, such as individuals with non-severe COVID-19, or other individuals who meet the entry criteria but have not yet been included in the study) will be identified through advertising to the general population, or through existing research activities such as sero-surveillance studies. Volunteers will be able to provide their contact details on the study website and join the study either using conventional paper-based consent procedures or supplemented, where appropriate, with an online consent tool on the study.

Drawing on relevant guidance of good practice, the online consent tool to be used is aligned with the key principles in the sponsor guidance, HRA and MHRA statements on consent by electronic methods and advice of other relevant stakeholders. The online consent tool for submitting participants allows for a secure onward despatch to a secure database. Access to this database and data will be closely monitored with limited users. Joining of the participant will require a minimum amount of information allowing unambiguous identification of the participant: name, date of birth, postcode and standard drop-down lists for symptoms and ethnicity. Should further identification of the participant be required, this can be undertaken by the healthcare professional responsible for blood sampling. Linkage with the NHS allowing access to medical records will allow further verification of the participant’s medical history. Depending on personal preference, the participant can then receive a printed or digital copy of the consent form.

## Repeat sampling after recovery from critical illness

A small sub-study will focus on the function of isolated and cultured immune cells exposed to inflammatory and other stimuli. Putative cellular functions of disease-associated genes will be investigated and compared to healthy individuals who do not have the susceptibility genotype. Immune cells, including monocytes, monocyte-derived macrophages, neutrophils and lymphocytes will be isolated from peripheral blood and studied immediately or following culture. Gene expression, protein synthesis and degradation, cytokine release and other functional studies will be measured in immune cells from cases and age- and sex- matched controls.

Patients who participated, with appropriate consent, in this study or in a previous study of host genetic determinants of outcome of infection or injury, may be invited to provide additional samples. In these cases, a research nurse will send the patient a formal letter requesting further participation. Patients will be invited to contact the study administrators by mail, telephone, or email, after which a patient information sheet and consent form will be sent to each respondent by post. Respondents will be invited to attend for blood sampling.

In order to monitor the potential distress caused by attempting to contact patients when it is inappropriate to do so, for example in the event that the patient has died since discharge from hospital, a log of inappropriate contact attempts will be kept.

All blood samples will be obtained by an experienced phlebotomist. Each donation will last for a maximum of 1 hour. Consent will be obtained before each donation, so the patient will be re-recruited at each visit. Patients will not donate blood more often than every 3 months. In the case of patients who have not already explicitly consented to be contacted by the research team, the clinical team in the recruiting hospital (or a research nurse based in the recruiting hospital) will contact the patient’s family doctor to confirm that it is appropriate to approach the patient directly.

Participants presenting for repeat sampling will be fully recovered, otherwise healthy individuals with no contraindications to blood donation, including:

* Infection with any blood borne diseases (e.g. HIV, Hepatitis B or Hepatitis C)
* Previous or current intravenous drug abuse
* Current anaemia
* Blood clotting disorders
* Current anticoagulant (blood thinning) drug therapy
* Under the age of 16, or unable to give informed consent
* History of donations to the blood transfusion service (or any other donation) within the last 12 weeks.

### Repeat sampling volumes

Depending on the participant’s weight, the following maximum volumes of blood will be obtained, with a minimum interval of 3 months between samples:

* 40kg: 240mls (6.0mls/kg)
* 2040kg: 80mls (4.0mls/kg)

Where consent is obtained to do so, each participant’s family doctor will be informed of their participation in this part of the study.

### Recurrent sampling

Each consenting patient will donate a single sample of blood. Every effort will be made to obtain the maximum possible information from this sample. In some cases, it is possible that additional samples may be required to confirm initial findings, replace inadequate samples, or study the cellular effects of genetic variants. Patients who wish to continue to contribute to this part of the study may therefore be given the opportunity to donate further samples, subject to the strict volume and frequency limits specified above ([5.8.1](#repeatsamplevols)). New consent will be obtained before each subsequent donation. Each donation will comply with the strict volume and frequency limits specified above. It is anticipated that most subjects will donate less than 3 times; however, in some cases more donations may be desirable to study unusual genotypes or cellular phenotypes. For this reason, we have not specified an upper limit on the number of times a volunteer can present for repeat sampling. The responsible ethics committee will be informed in the event that any individual patient donates blood for a period of 5 years or more.

## Withdrawal from the study

Participants are freely able to decline participation in this study or to withdraw from participation at any point without suffering any implied or explicit disadvantage. All patients will be treated according to standard practice regardless of whether they participate.

The following options of withdrawal will be made available to participants:

1. Partial withdrawal. Data WILL continue to be updated and used for research, but no further contact will be made with the participant

2. Full withdrawal.

* no further contact will be made with the participant;
* data will not be updated from health records;
* data will not be removed from research that is underway or has already been done, and an audit record will be maintained to confirm participation.

## Statistical analysis

Initial genome-wide and focused gene (using a longlist of immune-regulated genes) analyses will use standard protocols adjusting for any population structure. The models will incorporate clinical and environmental determinants of disease severity.

# Study management

## Data collection

Clinical and laboratory data will be collected throughout the study according to local resources. Clinical data will be collected locally and CRFs completed by study staff. For control volunteers in the community, they will be able to provide their contact details on the study website and join the study either using conventional paper-based consent procedures or supplemented, where appropriate, with an online consent tool on the study website. The data will be linked with national regional and other (e.g. other research studies) data sources, and longitudinal life course data will be collected. Data will be made available to researchers in a de-identified format.

## Data Management

When available, data collected by staff at each site will be submitted electronically to a secure online database. Data will be entered by study staff where possible, in order to minimise the workload on site clinical staff. Quality checks will be built into the data management system and there will be quality control checks of critical data points entered into the CRFs to ensure standardisation and validity of the data collected. The study will adhere to national and international data protection regulations. Patients’ identities will be protected and their information held securely.

Relevant identifiers, including personal identifiers, will be used to link the additional data sources and to allow robust and safe return of any clinically relevant information back into the NHS. Where whole genome sequencing is performed by Genomics England, data will be added to the National Genome Reference Library and raw and processed data will be shared within the GenOMICC database.

All clinical, genetic and genome sequence data gathered during the course of this study will be hosted on the GenOMICC study database in a secure computing environment hosted on the University of Edinburgh servers. Deidentified and summary-level data will be made available to external investigators both directly and through a data analysis platform.

Deidentified individual level data will only be shared with other organisations that have Access Review Committee approval.

## Medical management and safety reporting

Medical management will be according to standard of care at the treating site and not a part of this research protocol. Research interventions include only collection of clinical information and specimens; hence adverse event reporting is not applicable as there is no intervention.

## Data and materials access committee

The data and materials access committee will control all requests for access to protected samples and data. The committee will comprise one representative from each contributing region, and representatives from the core study team. The committee will meet by teleconference at 6 monthly intervals, and will consider extraordinary requests out of cycle by email where the committee chair deems it appropriate. All requests for materials and protected data must be approved by a majority vote of this committee.

## Protected data and materials

Protected data refers to all genotype-level data from all studies, and clinical data relating to individual patients. All samples acquired in the course of this work will be considered protected materials.

## Materials access

Access to samples for additional analyses will be governed by the data and materials access committee, in collaboration with the individual recruiting sites.

## Data access

Access to data for outside investigators will be reviewed by the data and materials access committee. Linked anonymised data generated during the course of these studies may be shared between investigators. Each local site will hold their own data. Genomics England will act as data controller for any data held in the National Genomic Research Library and access will be granted via an Access Review Committee including patients and the public and researchers who do not work on these data.

## Future use of samples

Samples collected will be used for the purpose of this study as stated in the protocol and stored for future use with consent. The standard consent form will request consent from subjects for sample storage and/or export of samples to collaborating institutions for investigations that cannot be performed locally. Any proposed plans to use samples other than for those investigations detailed in this protocol will be approved by the relevant ethics committees. Data may be used alone or in combination with data from related studies in secondary analyses.

This study will adhere to the research policies of ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium, www.isaric.org). A fundamental principle of this work is that clinical investigators contributing to research efforts, often in extremely difficult circumstances, must be given full recognition for their efforts and the opportunity to access data and samples. Ownership of any data transferred to the centralised database will be retained by the site that contributed it. All analysis of pooled data will be undertaken with the explicit agreement of each site who contributed.

# Ethical considerations

## Informed consent

Where participants lack capacity to consent due to altered mental state, critical illness or coma, a personal consultee will be asked to provide advice for the patient (aged 16 or over) to participate on behalf of the patient, based on the patient’s presumed wishes and feelings according to local laws and guidelines, namely: the Adults with Incapacity Act (2000) Scotland, the Mental Capacity Act 2005 (England and Wales) 2005 and the Mental Capacity Act (Northern Ireland) 2016.

Parents or guardians of children under the age of 16 will give consent for their child. Study staff obtaining consent will consider the ability of the child to understand the basic principles of the study and will discuss the study with the child in age appropriate language. Where appropriate, children will be invited to give assent, which will be recorded on the relevant assent form. The right to withdraw at any time without negative impact will be reinforced with the child and their parent/guardian. Where a young person reaches the age of majority and they were recruited as a child, they will be provided with an opportunity to provide consent, or withdraw from the study themselves.

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

A copy of the informed consent form will be given to the person who gives consent.

### Patients unable to consent for themselves

It is anticipated that, in many cases, illness may be severe and patients may not be able to consent for themselves. This study aims to improve understanding, and ultimately treatment, of life-threatening disease. In order to do this, there is no option but to study patients who are extremely unwell. In the event that an eligible patient (aged 16 or over) is unable to consent for herself/himself we will consult with a personal consultee (in compliance with the Mental Capacity Act 2005 (England and Wales) and the Mental Capacity Act (Northern Ireland) 2016 and the Adults with Incapacity Act (2000) Scotland on the patient’s presumed wishes and feelings) before taking any samples for research.

### Immediate consent / immediate declaration

Potential participants/representatives will be given as long as they require to decide if they wish to take part. For repeat sampling, and where possible for prospective recruitment, patients or representatives will be given at least 24hrs to consider participation. In some cases, it may be necessary to respect the convenience of distressed critically ill patients, or their relatives or representatives, by giving them the option of consenting immediately to participate.

### Telephone consent / immediate declaration

This study aims to explain, and ultimately to improve treatment of, extreme susceptibility to life-threatening disease. It is therefore essential that the most susceptible, and hence the most unwell, patients are able to participate. Sadly, many of the sickest patients have a precipitous decline in the first 24hrs in critical care, so it is often impractical to discuss recruitment in person with a personal consultee. For this reason, we will offer appropriate individuals the opportunity to provide advice over the telephone to a member of the local clinical team.

Telephone consent or declaration will be guided by a script. Personal consultees will be sent the relevant information sheet by email, post, by direction to the study website, or by having the telephone summary information read over the phone to them. The individual taking advice from the consultee consent will create a paper record of the consultee advice which will also be placed on the electronic case record form.

### ONLINE consent for control volunteers in the community

Completion of a consent form online, on the study website, will allow control volunteers in the community the opportunity to participate without the necessity to attend a study site to provide consent in person. This facility will be restricted to individuals with the capacity to provide consent for themselves. The website will provide the same information contained in the information sheet and volunteers will be prompted to read this and confirm they have understood the content prior to consenting to participate. Volunteers will be able to provide their contact details on the study website and join the study either using conventional paper-based consent procedures or supplemented where appropriate with an online consent tool on the study website. An option will be provided for volunteers to request a telephone call and provide telephone consent if they do not understand the material online or have additional questions.

## Risks to participants

### Inconvenience

Participation in this research study poses a minimal risk of inconvenience through attendance of follow-up visits. Appropriate compensation for travel costs to attend follow-up visits and for time of attending visits will be given according to the standard policies of the sponsor.

### Phlebotomy

Phlebotomy can be associated with pain at the draw site and rarely with infection. Blood draw volumes have been restricted according to weight so that combined clinical and research sampling is within recommended limits. Discomfort will be minimised by having expert staff obtain blood samples, and by combining research sampling with routine clinical sampling where possible.

### CLINICALLY-ACTIONABLE findings in genetic testing

Clinically actionable findings are not expected during the time course of a patient’s illness. It is possible that, in a very small number of participants, the research will identify a genomic finding that explains their severe response and that is relevant to their future medical care e.g., a rare genetic immune deficiency. Where this is the case, and where the NHS Genomic Medicine Service agrees that the finding meets criteria for diagnostic reporting, it will be returned to the participant via their NHS care team.

### Benefits to participants

There is unlikely to be direct benefit to research participants. However, should clinically relevant information be identified, there is a process through which this can be returned via the NHS.

## Participation in other research studies (co-enrolment)

Particularly in the case of emerging infections, it is likely that other research projects, including clinical trials, will also recruit participants in this study. In fact, it is important that they do so, and great effort has been expended to ensure that this study is compatible with, and complementary to, other possible research projects.

## Confidentiality

This study will be conducted by clinical staff and those involved in the study will ensure that each study participant’s privacy and confidentiality is maintained. Participants will not be identified in any published reports of this study. All records will be kept confidential to the extent provided by international and local law. All laboratory specimens, evaluation forms, reports, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorised third party.

Minimal personal data will be entered into the database for analysis. The patient’s identifying personal information will be logged separately and stored securely in paper format at the recruiting site. Where recruitment is performed in the community by an appropriately trained practitioner from a third party organisation, minimal patient identifiers will be passed to the organisation to allow the visit to be scheduled and carried out. The patient might be asked to take part in future research, and therefore their identifiers need to be retained for this purpose. The stored research data is also likely to be of significant value in the future for other studies and so research data that does contain minimal patient identifiers such as name, date of birth, and NHS/CHI number will be stored indefinitely.

Paper and electronic medical records may be accessed during the study to confirm, verify or complete clinical information provided in the case report form.

Identifiable data will be entered into the study database to allow for electronic health record linkage. The data will be pseudonymized to allow for linkage with national regional and other data sources (e.g. other research studies), and the collection of longitudinal life course data.

Data will be pseudonymised prior to access by researchers.

All samples will be labelled with a unique, non-identifiable subject number. The patient’s name and subject number will be recorded on the consent form. This will preserve a link between anonymous and identifiable data. Further research questions, subject to appropriate ethical approval, may be answered in retrospect in the future. Since the samples and data generated by this work may be irreplaceable after an outbreak of infectious disease has passed, it is essential that future work is not impeded by unnecessary data loss. Data will be encrypted before transfer on portable devices. Multiple backups will be maintained on institutional servers. Critical data will be stored in a stable storage format.

It is important that data generated now is not destroyed unnecessarily, since they will be of considerable potential value to future research. Electronic data and electronic copies of paper documents will be stored indefinitely

## Scientific and peer review

The proposed study has undergone extensive peer review in successive iterations including formal review and approval by the ISARIC Executive Committee and the InFACT Executive Committee, three rounds of peer-review during successive applications to the Wellcome Trust, and presentation at national and international conferences.

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