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| GENOMICC STUDY PROTOCOL v5  23 October 2024 | | | | | |
| Genetics of Mortality in Critical Care | | | | | |
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# Aims

To identify host genetic variants associated with susceptibility to, and mortality from, life-threatening infection and sterile injury.

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, and outcome from, severe infection and life-threatening systemic injury.

## Recruitment from critical care

We will obtain samples from patients with critical illness caused by infection, specific outbreaks and exposures of public health interest, and quantifiable sterile injury.

Participants group may be recruited prospectively during their illness, or retrospectively following discharge from hospital.

## Other recruitment

We will also recruit the following additional groups, but only when deemed necessary for specific analyses planned by the Chief Investigator in consultation with the study steering committee:

* Parents of patients: we will obtain DNA from parents of patients – in collaboration with research sites where necessary – in the following circumstances:
  + Where the patient’s presentation suggests an extreme susceptibility to eligible syndromes (e.g., those under 40 and free from significant comorbidity)
  + Where the patient is affected by an illness, syndrome or condition of public health concern
* Control groups and volunteers: we will obtain DNA samples, where possible, from appropriate comparison or control groups including volunteers from within the community

Recruitment of these groups will be co-ordinated and communicated to recruiting sites directly by the GenOMICC central management team.

## Data management objectives

* Combine existing DNA resources in a virtual collaborative network to enable rapid testing of disease-associated 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)
* Support international collaborators, including the transfer of data and material into the UK from other countries where appropriate, subject to necessary agreements and regulatory approvals

# 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 syndromes in critical illness such as sepsis, acute respiratory distress syndrome (ARDS), multi-organ dysfunction syndrome, and bronchopulmonary dysplasia. This is also 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 organ failure is often immune in origin (Angus and Poll 2013), and earlier results from this study provide clear evidence that immune dysfunction is a key driver of organ damage in Covid-19 (Pairo-Castineira et al, 2020; Kousathanas et al, 2022; Pairo-Castineira et al, 2023). Hence, we can make predictions from the extensive knowledge of other immune conditions. Furthermore, autoimmune and infectious diseases share a great deal of similarity in genetic predispositions, cell types and mechanisms of pathogenesis. It is therefore very likely that propensity to survive critical illness 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 critical illness.

# Study design and implementation

## Clinical Conditions (Phenotypes) of interest

This study aims to identify genetic predisposition to specific syndromes of critical illness and outbreaks or exposures of public health interest. This includes susceptibility to life-threatening infections, and susceptibility to adverse outcomes, including mortality, following the onset of organ failure due to sepsis or sterile injury.

## Prospective recruitment

Consenting patients meeting the entry criteria will be asked to provide a single DNA sample.

## Laboratory sampling

In some cases, with consent, samples from residual material will be obtained from clinical samples. This will be done on a case-by-case basis by direct negotiation with hospital laboratory teams in participating sites, for example to investigate outbreaks or other public health threats.

## GenOMICC Acute sub-study

### Rationale for GenOMICC Acute

GenOMICC Acute extends the GenOMICC study to include deep biological characterisation of a sub-set of patients, enabling:

1. Identification, early diagnosis, and genetic confirmation, of mechanistically distinct subgroups of patients within broad critical illness syndromes such as sepsis and ARDS
2. Discovery of specific genetic variants with strong influence on quantitative measures (quantitative trait loci, QTLs), such as gene expression, DNA methylation, chromatin marks, or release of nucleotides into the plasma from specific cell types or pathogens
3. Early diagnosis of organ injury, identification of pathogens and quantification of pathogen load using advanced diagnostics to refine diagnoses for host genetic study, provide covariates for outcome studies, identify and characterise new pathogens, and develop diagnostic tests

### Eligibility criteria

All GenOMICC patients are eligible for the Acute sub-study if:

1. the patient’s estimated or measured body weight is more than 20kg
2. samples can be obtained within 48 hours of admission to critical care

### Recruitment procedures for GenOMICC Acute

Recruitment of participants to the GenOMICC Acute sub-study will take place in approved research locations following separate discussion with the central study team. Not all sites are expected to take part in this sub-study.

## 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 that patients we attempt to contact will 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 may be contacted in the first instance by telephone or in writing, depending on the recruitment strategy and preference of the recruiting site. Letters may be personalised from the supplied template based on the local site knowledge of the patient if appropriate.

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

Any person living in a region in which GenOMICC is recruiting critically ill patients will be eligible to volunteer to take part in the study. 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.

Volunteers may be contacted occasionally to share ethically approved information or updates about the study. Further, we may contact this group to ask if there would be interest in patient and public involvement (PPI) in research. PPI involvement of any kind is completely voluntary. Communication will be primarily electronically by email. Paper copies will be provided if requested.

## 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.

## Study eligibility

### Inclusion criteria

Patients will be recruited who:

* Are deemed, in the view of the treating clinician, to require continuous cardiovascular or respiratory monitoring or any organ support,
* AND provide appropriate consent or assent,
* AND whose primary reason for admission is one of the following primary diagnoses:
  + Critical illness caused by any confirmed or suspected infection

OR

* + Common non-infectious critical illness syndromes:
    - Pancreatitis of any aetiology
    - Full thickness burns covering >20% of body surface area
  + Rare non-infectious critical illness syndromes:
    - Haemophagocytic syndrome
    - Still’s disease
    - Heat stroke
    - Radiation poisoning
    - Suspected reactions to therapeutic agents:
      * This includes cell therapies, gene therapy, CAR T-cell therapy, investigational drugs or vaccines in the view of the treating clinician. For example:
        + Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), or SJS-TEN overlap to any therapeutic agent
        + Cell therapy associated reaction
        + Acute hepatitis associated with gene therapy in any age group
    - Confirmed or suspected presence of an emerging critical illness syndrome, such as:
      * unexplained or idiosyncratic presentations of acute organ injury in the view of the treating clinician
      * confirmed or suspected exposures of public health interest in the view of the study leadership in consultation with public health agencies. An updated description of these syndromes will be maintained by the central study team on the public website at <https://genomicc.org/investigators/emerging_syndromes>
  + Non-infectious critical illness syndromes in children or babies:
* Preterm birth (babies born <32 weeks postmenstrual age)
* Acute seronegative or 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

#### Organ support

Examples of eligible organ support include, but are not limited to:

* Respiratory: High flow nasal oxygen (HFNO), Continuous positive airway pressure (CPAP), Non-invasive ventilation (NIV), Invasive mechanical ventilation (including following intubation for airway protection)
* Cardiovascular: any vasopressors or inotropes that are given by continuous infusion, extracorporeal membrane oxygenation (ECMO)
* Renal: continuous or intermittent haemofiltration/dialysis/diafiltration where it is used to treat acute disease in a patient who is not normally in receipt of renal support

### Emerging Infections and exposures

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, and exposure to chemical, radiological or other agents. All samples must be handled according to the relevant guidance from the Health and Safety Executive.

### Exclusion criteria

The following participants are not eligible for participation in any part of the GenOMICC study:

* Bone marrow transplant recipients

### 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/investigators/participating_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
* Parents of eligible patients
* Volunteers from the general population will be eligible to act as controls

### Number of participants

The global GenOMICC study aims to ultimately recruit a total of 200,000 cases, of whom 100,000 are expected to be recruited in the UK.

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

As the study proceeds and our understanding of the genetic mechanisms of critical illness improves, the discovery yield from recruiting particular groups of patients is expected to decrease. We will update the inclusion criteria to remove these groups of patients as necessary, in order to focus resources on remaining unanswered research questions.

### 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.

All patients will have clinical information collected either directly or from available medical notes. Information will be recorded in the case report form. The following data will be collected from each patient:

* at recruitment, an initial case report form will be completed
* 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)
* at least 60 days after the patient became eligible, a follow-up case report form will be completed detailing the patient’s survival status.

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

### Sample volumes

A maximum of 1ml/kg (<1.5% estimated blood volume) will be obtained during a single sample during acute illness.

#### GenOMICC DNA analysis

One of the following sample types should be obtained:

* Whole blood in EDT A (full blood count tube) – preferred option in all cases:
  + >10kg: 4mls (0.4ml/kg)
  + 4–10kg: 2mls (0.5ml/kg)
  + 0.5-4kg: 0.5mls (1ml/kg)
  + Umbilical cord blood: 1ml
* Dried blood spots:
* >0.5kg: 4 spots (0.5ml, 1ml/kg)
* Saliva:
  + Using saliva collection kit or assisted saliva collection kit as necessary

#### GenOMICC Acute Samples

Within 48h of admission to intensive care, in patients weighing > 20kg:

1. 4ml blood in EDTA for DNA (taken for all GenOMICC participants, as above)
2. 3ml blood for RNA (tube must be shaken immediately)
3. 10ml blood for cell free RNA (cfRNA) (tube must be inverted immediately)

The GenOMICC central management team will supply 24-hour return postage paid, biologically approved specimen kits, fully assembled with all sampling tubes required for GenOMICC Acute sample collection.

### Sampling procedure for patients or volunteers in the community

Patients or control volunteers who agree to participate will be invited to provide a sample by one of three methods:

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

### Sample handling

Where necessary for specific tests, samples or materials derived from samples may be sent abroad 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.

There is no sample processing required by site research staff or community health care professionals. All samples in the GenOMICC and GenOMICC Acute sub-study are stable at ambient temperature for several days. They should be posted back in the approved specimen kits supplied by GenOMICC as soon as possible after sampling.

### Potentially hazardous samples

**If samples are obtained from patients with potentially hazardous pathogens, the GenOMICC team (genomicc@roslin.ed.ac.uk) should be contacted for advice on how and where to send them.**

Examples of potentially hazardous (HG 3/4, see below) pathogens include, but are not limited to: Dengue virus, Mpox virus, highly pathogenic avian influenza virus (eg H5Nx, H7N7, H7N9), Marburg virus, Ebolavirus, Lassa fever virus, Crimean-Congo Haemorrhagic Fever orthonairovirus, Hendra henipavirus, Nipah henipavirus, Variola virus (major and minor), Bacillus anthracis, Coxiella burnetti, Rickettsia spp, Yersinia pestis, West Nile fever virus, Yellow fever virus, Rift Valley fever virus. A list of hazard group 3 and 4 pathogens can be found on the UK Health and Safety Executive Advisory Committee on Dangerous Pathogens (ACDP) approved list of biological agents (<https://www.hse.gov.uk>).

In dealing with pathogens where little is known about transmissibility and/or virulence, great care must be taken to ensure the safety of hospital staff and patients. All recruiting sites must comply with their local COSHH (Control of Substances Hazardous to Health) and Health & Safety guidelines when collecting samples. The receiving study laboratory, a containment level 2 (CL2) laboratory can only receive samples classified by the Health & Safety Executive as Hazard Group 1 (HG1) and Hazard Group 2 (HG2) samples. SARS-CoV-2, while a Hazard Group 3 pathogen (HG3) can be received, as it has a special exemption in the UK for the safe handling in CL2 laboratories and are permitted with the appropriate risk assessments and safety measures in place.

### 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, nearest relative, legal representative, or an appropriate nominated 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 or other legal or nominated representative) 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.

In England, Wales and Northern Ireland, professional consent from a nominated consultee is an option. Whilst nominated consultees (e.g., professionals not connected to GenOMICC) are permitted to provide an opinion in some areas (not Scotland, where only a welfare guardian or welfare attorney can give advice in the absence of a next of kin), this should only be used if every effort to contact a next of kin or close person has been unsuccessful. Nominated consultee opinions should not be used if the patient has close family or another close person who is willing to act as a personal consultee.

If professional consent is used as an initial means of consent, research staff will subsequently seek an opinion from the participant’s next of kin or other close person where possible, even if the participant is expected to regain capacity to consent for themselves.

Individuals who are normally prisoners but in hospital as patients may be recruited in their capacity as a patient prospectively only.

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. Clinical samples 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 clinical samples. Wherever practical, 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 participants who survive critical illness and regain capacity, and who were included in the study following consent or assent from another party (such as a nearest relative or consultee) because of temporary incapacity. This is expected to occur in-person during the index hospitalisation. In some cases, if consent has not been obtained before discharge or transfer to another hospital, attempts to re-consent directly will be made by other means.

### Attempts to re-consent following discharge

Attempts to contact discharged participants should be made as soon as reasonably possible after discharge to initiate the consent process, if patient capacity allows. Research and clinical teams should be enabled to contact discharged patients by any reasonable means, such as email (if available), telephone or a letter by post. Although the full consent process will be carried out either by telephone or post, the initial means of contacting the patient may take several attempts, especially considering working age people who may not have the same means of communicating during normal working hours or people who may not answer calls from unknown numbers.

Initial contact may be personalised where possible based on knowledge of the participant. Any contact method named above may be attempted twice, with a period of 4 weeks between each contact, before a final letter is issued by post. If there are means to do so, the participant’s GP may be contacted via secure means and asked to pass on our regained capacity consent letter. All contact efforts should be recorded in the investigator site file with a final consent update added to the clinical database.

Participants who decline to participate at this stage will be removed from the study following our established withdrawal procedures. Data that has already been used in research cannot be removed from the study.

Where the participant cannot be re-contacted despite best endeavours, they will remain in the study based on the advice from the patient’s next of kin, legal representative, or consultee at the time of enrolment. This does not affect the rights of any participant to withdraw from the study at any future date.

In the situation where a participant does not survive or will not regain mental capacity, they will remain in the study based on the advice from the patient’s next of kin, legal representative, or consultee at the time of enrolment.

### Capacity assessments

Healthcare professionals in the research or clinical team will assess capacity. If a patient continues to be incapacitated beyond the follow-up period, the local investigator will plan a subsequent capacity check, after an interval to be determined according to 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.

### Procedures for initial approach to consent and sample eligible participants

When a patient is identified as eligible to participate, recruitment procedure for all participants will follow the following steps, in order, stopping when a sample is obtained and sent by post to GenOMICC central laboratory.

1. In England, Wales or Northern Ireland, where safe, appropriate, and feasible given local staff resources, a sample may be obtained and stored pending deferred consent. (See section on [Deferred consent](#_Deferred_consent))
2. The participant, or appropriate representative will be approached by the clinical or research team caring for case to obtain consent:
   * If not already done, a DNA sample should be obtained during the acute admission

OR

* + A DNA sample should be obtained by appointment with the patient, in coordination with the clinical or research team caring for the case

OR

* + In the case of a retrospectively recruited patient who has been discharged from hospital, sampling can be obtained as outlined in step 3 below.

1. If agreement to approach the participant or appropriate representative is granted by a public health team in contact with case/family
   * The participant or representative will be approached by the clinical or research team caring for case or by the central GenOMICC coordinating team to obtain consent:
     + if possible, a blood sample kit will be sent by post to participant
       - a blood sample will be obtained by research nurse in the patient’s home or another appropriate location

OR

* + - a saliva kit will be sent by post to the participant,
      * a saliva sample will be obtained by the participant

1. If a participant has expressed willingness to participate directly to the central GenOMICC coordinating 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 3 above.

### 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 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 aware of the unusual circumstances and the close involvement of public health agencies.

Research teams at approved research locations are not routinely asked to 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.

We may in extraordinary circumstances recruit patients who have died. To ensure that the programme is able study the genetic factors that cause people to succumb from serious and sudden outbreaks such as 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:

1. Infection with any blood borne diseases (e.g., HIV, Hepatitis B or Hepatitis C)
2. Previous or current intravenous drug abuse
3. Current anaemia
4. Blood clotting disorders
5. Current anticoagulant (blood thinning) drug therapy
6. Under the age of 16, or unable to give informed consent
7. 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:

1. >40kg: 240mls (6.0mls/kg)
2. 20–40kg: 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
   * Personal identifiable information and genetic data will be deleted from the GenOMICC study computer records, and the DNA sample will be destroyed
   * De-identified information, and genetic data that is already included in analyses, will persist in the record of those analyses and in the aggregated results

A record of participation in the study will remain with the original records at the NHS research site.

## 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.

Investigator site files and associated paperwork relating to participation in GenOMICC at NHS research sites may be held in paper format or electronically by secure means on an NHS computer.

## 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.

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 activity involves 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 16 and were recruited as a child, an attempt will be made to contact them to request continued consent for data linkage to health records. If consent can’t be obtained, then data linkage will cease at age 16. The GenOMICC central management team will alert research sites to any instance of a child reaching 16 to discuss how best to approach re-consent.

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. 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 or professional 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.

### Deferred consent

In England, Wales and Northern Ireland, a deferred consent process can be applied. In these cases a sample will be taken as described in the sampling details section above on page 13, from any patient meeting the entry criteria. The sample will be held at the recruiting site for up to 7 days pending appropriate consent. No samples will be transferred to the central laboratory for testing, or stored at site beyond 7 days, without consent having first been obtained.

The option of deferred consent is not currently available in Scotland.

### Antenatal consent

It is possible that parents who will have a preterm baby will be identified by hospital staff prior to the birth of the child. Such parents may be given an opportunity to take part and consent to the donation of cord blood, or another sample from the preterm child following birth, prior to the birth of the child.

### 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 or research 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

Although there are no direct benefits to research participants in taking part in this study, there is a very small possibility that clinically relevant information could 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.

As a sample only study, any co-enrolment in GenOMICC with another study or clinical trial does not require any formal written documentation.

## 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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