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2 Aims

1. To systematically identify host genetic variants associated with susceptibility tolife-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.

3 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:

1. Obtain a single DNA sample from patients with:
(a) Susceptibility to severe infection with specific pathogens;
(b) Susceptibility to death following onset of severe illness due to these pathogens, and;
(c) Susceptibility to death from quantifiable sterile injury.

2. Obtain DNA from survivors of critical illness due to eligible infections
3. Combine existing DNA resources in a virtual collaborative network to enable rapid hypothesis-testing of candidate variants
4. 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.

4 Background

Susceptibility to infection is profoundly heritable[12]. Patients who develop life-threatening illness following infection with usually innocuous pathogens, such as influenza[10], are genetically different from the rest of the population[1]. Understanding the genetic mechanisms of susceptibility may yield new therapeutic targets[3] that can be used to make susceptible patients more similar to 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[8] and WNV[7] infection). Pathogen-specific interventions (eg. 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[2], 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[2]. 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[11]. 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.

Since the evolutionary pressures on childhood immunity are different from those affecting adults, and immune responses change considerably with maturation, genetic predisposing factors in children are expected to be different from those in adults[5]. We therefore intend not to exclude children from participation in this research.

5 Study design and implementation

5.1 Phenotypes of interest

This study aims to identify genetic predisposition to specific syndromes of critical illness. 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. In order to maximise the probability of identifying host genetic loci associated with susceptibility, we will restrict participation to individuals in good general health, and lacking in known predisposing factors.

The same principle was used to determine the upper age limit for inclusion. 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.

5.2 Prospective recruitment

Patients meeting the entry criteria (5.5) will be asked to provide informed consent, and a single DNA sample.

5.3 Recruitment of survivors

The group of survivors eligible for recruitment for this study are generally healthy individuals who have suffered critical illness. We know from extensive epidemiological research in that, after recovery from critical illness, mortality returns to close to the baseline for the population[9]. We have therefore assessed that there is a very low risk of contacting patients who have since died; 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 writing to the patient.
Patients will be identified from hospital records by research staff in the critical care unit that provided treatment to each patient. A letter will be sent to the patient from 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 will be invited to contact the study administrators by email, internet, telephone, or mail. Respondents will be sent a postal saliva collection kit, information sheet, consent form, and a return envelope. Consenting patients will return the completed consent form, together with the saliva sample, to the study team.

Patients who do not respond after a period of four weeks will be sent a second letter in order to confirm that the first letter did not get lost in the post. If a patient do not respond to this second letter, the study team will assume that this patient does not want to participate.

5.4 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.

5.5 Entry criteria

This study will recruit previously-well individuals with critical illness due to primary infection with a specific pathogen, or following a quantifiable sterile injury consistent with the subsequent development of organ failure. Recruitment will be expanded or contracted subject to the availability of funds and local disease incidence, according to the groups described here.

5.5.1 Inclusion criteria

Patients will be recruited who:

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

**GROUP 1**

- **Influenza.** Confirmed infection with influenza virus.
- **Secondary pneumonia.** Acute pneumonia complicating confirmed infection with influenza virus.
- **Emerging infections.** Confirmed or suspected infection with an emerging infection (see below).
Group 2

- **Cellulitis.** Soft tissue infections causing systemic sepsis.
- **Burns.** Full thickness burns covering > 20% of body surface area.

Group 3

- **RSV.** Confirmed infection with respiratory syncytial virus.
- **Pneumonia.** Primary pneumonia with radiographic changes at presentation to critical care.

Group 4

- **Pancreatitis.** Pancreatitis of any aetiology.

5.5.2 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)[6], 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.

5.6 Exclusion criteria

Patients who are functionally limited by any comorbid illness or have significant immunosuppression will be excluded from this study. Specifically, patients who have any of the conditions listed below will be excluded:

1. demographic criteria:
   (a) age > 70

2. chronic functionally-limiting comorbid illness, including:
   (a) asthma
   (b) chronic obstructive pulmonary disease (COPD)
   (c) bronchiectasis
   (d) heart failure
   (e) alcoholic liver disease
   (f) cirrhosis of the liver (any cause)
3. primary immunosuppressive disease, including:
   (a) acquired immunodeficiency syndrome (AIDS)
   (b) severe combined immunodeficiency

4. therapeutic immunosuppression, including:
   (a) antineoplastic chemotherapy
   (b) long-term (> 7 days) steroid treatment

5. major trauma, including:
   (a) perforated hollow viscus
   (b) aortic rupture
   (c) traumatic brain injury (haemorrhage/DAI/Contusion)

5.7 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.

5.7.1 Enrolment procedures for prospectively-recruited patients

Patients will be identified and recruited in hospital during acute illness. Potential participants will be identified through hospital workers 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 or an appropriate parent/guardian/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. Staff will explain the details of the study to the participant or parent/guardian/consultee and allow them time to discuss and ask questions. The staff will review the informed consent form with the person giving consent (or assent) and endeavour to ensure understanding of the contents, including study procedures, risks, benefits, and the right to withdraw. Participants who agree to participate (or their parent/guardian or consultee who declares their wishes to do so) will be asked to sign and date an informed consent form.

In view of the importance of early sampling, participants or their parent/guardian/consultee will be permitted to consent 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 inclusion/exclusion criteria and who have given informed consent to participate directly, or have been consented by a parent/guardian or whose wishes have been declared by a 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.

Consent will be sought from patients who survive critical illness and regain capacity to give consent. 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.

5.7.2 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 extremely unlikely to benefit the health of the participants.

5.7.3 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.

5.7.4 Sample volumes

In patients donating blood, no patient will give more than 0.6mls/kg (> 1% estimated blood volume) during acute illness. The following volumes of blood will be drawn from patients in each weight category:

- >40kg: 9mls (0.225mls/kg)
- 20–40kg: 7mls (0.35mls/kg)
- 10–20kg: 4mls (0.4mls/kg)
- 4–10kg: 2mls (0.5mls/kg)
- 1–4kg: 0.6mls (0.6mls/kg)

5.7.5 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 anonymised 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.

5.7.6 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[4], or

2. safely destroyed.

5.7.7 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.

5.7.8 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.

5.8 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.

5.8.1 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)
- 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.

5.8.2 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). 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.

5.9 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.

Patients enrolled to any component of the study who ask to withdraw, or whose illness is subsequently confirmed to be the result of infection with a pathogen which is not relevant to the objectives of this study will be withdrawn. No further follow-up will be conducted.

5.10 Statistical analysis

Initial genome-wide (for genes with a very large effect) and focussed gene (using a longlist of immune-regulated genes) analyses will use standard protocols adjusting for any population structure using the GenABEL software implemented in R. The models will incorporate clinical and environmental determinants of disease severity.

6 Study management

6.1 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 a study staff. The data will be anonymised at site and a unique alphanumeric study number issued.

6.2 Data Management

When available, data collected by staff at each site will be submitted electronically to a protected online database. Anonymised 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 local data protection regulations. Patients’ identities will be protected and their information held securely.
6.3 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.

6.4 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.

6.5 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.

6.6 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.

6.7 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.

6.8 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.

Electronically-held research data for future use will only identify participants by a unique alphanumeric participant number. Participant names or any other identifying details will not
be included. 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.

7 Ethical considerations

7.1 Informed consent

Where participants lack capacity to consent due to altered mental state, critical illness or coma, an appropriate consultee will be asked to provide consent or assent to participate on behalf of the patient, according to local laws and guidelines.

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 informed consent form. The right to withdraw at any time without negative impact will be reinforced with the child and their parent/guardian.

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.

7.1.1 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 is unable to consent for herself/himself we will obtain assent/consent (as appropriate for the local legal requirements) from a patient representative (nearest relative or friend) before taking any samples for research.
7.1.2 Immediate consent

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.

7.2 Risks to participants

7.2.1 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.

7.2.2 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.

7.2.3 Incidental findings in genetic testing

This study includes genetic testing to identify host genetic variants associated with disease progression or severity. There is a very small chance that these tests may result in the incidental discovery of information that is relevant to the participant’s health. Since the samples will be analysed anonymously in batches, and often in non-clinical laboratories with investigational techniques, we will not attempt to identify and inform participants of any results from genetic tests. If we were to do so, there would be a considerable risk of accidental harm in the form of unnecessary anxiety and distress.

7.2.4 Benefits to participants

There will be no direct benefit to research participants.

7.3 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.

7.4 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. 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 age, sex and ethnicity 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.

Site files will at all times be accessible only to clinical and research staff. Consent will be sought for investigators to access patient data. Local research staff will access personal information/ All data will be anonymised before transfer outwith the recruiting institution.

All samples will be labeled with a unique, non-identifiable subject number. The patient’s name and subject number will be recorded on the consent form. This will preserve the link between anonymous and identifiable data. Data and samples obtained from routine clinical care will be anonymised. The only link to identifiable data will be the consent form. 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.

7.5 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.
GenOMICC study protocol 1.07

References


