

Joint Research Management Office (JRMO) Research Protocol for Research Studies

Full Title: Prospective observational study investigating genomic determinants of outcome from cardiogenic shock (GOIDILOCS)

Short Title: Genomic determinants of outcome in cardiogenic shock

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2. Glossary


ACS	Acute Coronary Syndrome
AE	Adverse Event
CPR	Cardiopulmonary Resuscitation
CS	Cardiogenic Shock
ECMO	Extracorporeal Membranous Oxygenation
eQTL	Expression Quantitative Trait Loci
GCP	Good Clinical Practice
ICU	Intensive Care Unit
MCS	Mechanical Circulatory Support
MTA	Material Transfer Agreement
NRES	National Research Ethics Service
N-STEMI	Non ST elevation myocardial infarction
PCI	Percutaneous Coronary Intervention
OHCA	Out of Hospital Cardiac Arrest
QMUL	Queen Mary University of London
QoL	Quality of Life
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
STEMI	ST elevation myocardial infarction
WHRI	William Harvey Research Institute

3. Signature page

CI Agreement

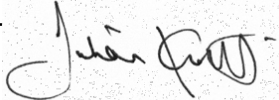
The study, as detailed within this Research Protocol, will be conducted in accordance with the principles of Good Clinical Practice (GCP), the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I agree to take responsibility for the statistical analysis and oversight of this study.

CI Name: Dr Alastair Proudfoot

Signature: _____  _____

Date: 19/12/2023

Statistician Name: Prof Julian Knight

Signature: _____  _____

Date: 19/12/2023

4. Summary and synopsis

Short title	Genomic determinants of outcome in cardiogenic shock
Methodology	Prospective Observational Study
Objectives / aims	The aim is to identify biological or immunological sub-phenotypes associated with differential outcomes from cardiogenic shock
Number of participants	300 patients over 3 years
Inclusion and exclusion criteria	<p>Inclusion criteria:</p> <p><u>AMI with CS</u></p> <ul style="list-style-type: none"> • Presentation of CS within 24 hours of onset of ACS symptoms • CS can only be secondary to ACS (Type 1 MI STEMI or N-STEMI) • Planned or completed revascularisation of culprit coronary artery <p><u>AMI Without CS</u></p> <ul style="list-style-type: none"> • Presentation within 24 hours of onset of ACS symptoms without CS • Evidence of left anterior descending coronary artery disease at angiography • Planned or completed revascularisation of culprit coronary artery <p><u>Non-Ischemic CS</u></p> <ul style="list-style-type: none"> • Patients presenting with non-ischaemic aetiologies of CS. i.e. inflammatory acute cardiomyopathy/ septic cardiomyopathy /myocarditis <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Age <18 and ≥80 years • Unwilling to provide informed consent or appropriate consent from a nominated consultee or personal consultee • Significant systemic illness resulting in life expectancy < 12 months • Known dementia of any severity • Comorbidity with life expectancy <12 months • Out-of-hospital cardiac arrest (OHCA) and any of the following: No ROSC/pH <7/ without bystander CPR within 10 mins of collapse • Patients with a Haemoglobin level of <8g/dl at enrolment • Co-enrolment in any study that may impact upon gene expression <p><u>CS Arms</u></p> <ul style="list-style-type: none"> • Echocardiographic evidence of mechanical cause for CS: e.g., ventricular septal defect,

	<p>LV-free wall rupture, ischaemic mitral regurgitation</p> <ul style="list-style-type: none"> • Shock from predominantly from another cause (e.g. refractory septic vasoplegia, septic shock, haemorrhagic/hypovolaemic shock, anaphylaxis and obstructive shock) • Arterial lactate level of <2.0 mmol/L
Statistical methodology and analysis (if applicable)	<p>No sample size justification has been calculated because of the nature of the proposed study. Conventional statistics (e.g. unsupervised principal component analysis and hierarchical clustering) as well as machine-learning methods (e.g. neural networks, random forests, support vector machines) will be used for prioritizing biologic candidates both for prediction as well as biological inference</p>
Study duration	<ul style="list-style-type: none"> • Recruitment: 36 months • Data collection: 6 months • Data analysis: 3 months • Write-up and reporting: 3 months

5. Introduction

Every year across Europe more than 50000 patients are diagnosed with cardiogenic shock (CS) ¹. CS is a complex and haemodynamically diverse state of end-organ hypoperfusion due to ventricular failure which can be either acute or acute on chronic. Despite several trials, of variable quality, assessing the impact of novel interventions including mechanical circulatory support (MCS), no new evidence-based therapeutic interventions have been introduced since a trial of early revascularisation in CS 20 years ago ¹⁻³. Furthermore, 30% of survivors of CS develop the sequelae of critical illness (e.g. ICU acquired weakness) or chronic heart failure with associated socioeconomic implications, high morbidity and poor quality of life ^{4,5}.

5.1. Background

Current supportive therapies for CS such as inotropes, diuretics and MCS are targeted to restoration of hemodynamic and biochemical variables such as mean arterial pressure, left atrial pressure, cardiac output and lactate ^{6,7} but they are unlikely to act at a cellular or molecular level and there is significant heterogeneity in the individual response to these supportive measures. Hence, the magnitude of shock and the severity of the associated biological/immune response differ considerably between patients, and also within the same individual over time, despite similar anatomical coronary lesions. This heterogeneity in the host response to CS and supportive therapies complicates the identification of patients at high risk of mortality as well as those who might (or might not) benefit from the introduction of resource intensive, interventional support modalities such as MCS. The challenge of MCS use is further magnified in the UK health system where access to medium- and long- term durable MCS is not centrally funded and the majority of patients are, by necessity, supported as a “bridge to recovery”.

Clinical classification systems such as the ORBI ⁸, SAVE ⁹, ENCOURAGE ¹⁰ scores have been devised to predict outcome from CS including those supported with MCS. However, these scores are imprecise, do not predict benefit from MCS and do not allow for an individualised approach to decision-making and therapies. A more granular and precise understanding of the biological cascades and genomic associations characterizing both CS and recovery from CS as well as the heterogeneity of the response to supportive therapies, including MCS is therefore an unmet need.

Similar to septic shock, a dysregulated immune response seems to be an important determinant of morbidity and mortality in many individuals with CS. Some of the drivers of these responses may be conserved across critical illness syndromes, suggesting common “host” responses to various acute insults. One promising approach to exploring the molecular mechanisms underpinning disease phenotypes, as well as potentially increasing the precision of therapeutic decision-making is analysis of genome wide gene expression. Further, when coupled with genome wide genotyping this approach can reveal inherited DNA sequence variations that regulate gene expression (so-called expression quantitative trait loci – eQTL). Such an approach has identified transcriptomic sub-phenotypes (or endotypes) associated with differential outcomes and responses to therapeutic interventions in sepsis, as well as a significant number of context specific eQTLs, suggesting that some of the observed

individual heterogeneity may be driven by genetic variation (Davenport, Burnham, Sicluna, Antcliffe). In one such study global gene expression profiling of circulating leukocytes was able to identify two endotypes of patients with community-acquired pneumonia. Patients with a type 1 sepsis response signature (SRS) were characterised by an immunosuppressed phenotype, with features of endotoxin tolerance, T-cell exhaustion, and HLA class II downregulation, and a higher 14-day mortality than patients with the SRS2 profile ¹¹. Recently, transcriptomic analysis of an international cohort of patients with sepsis admitted to ICU identified four biological endotypes, with distinct host response signatures, ranging from immunosuppression to hyper-inflammation (MARS 1-4) ¹². Three of these endotypes were associated with similar outcomes, but 28-day mortality was significantly greater in the MARS1 (similar to SRS1) cohort ¹². Finally, genome wide gene expression profiling has identified endotypes in whom mortality is increased when prescribed corticosteroids in both children and adults ¹³. Unpublished data (Knight group) suggests that analysis of proteomic signatures can also identify similar sepsis endotypes. These data support the notion that phenotyping critically ill patients using an “omic” approach holds promise as a means of identifying biological pathways that contribute to outcome differences, as well as potentially guiding individually targeted therapeutic interventions (“personalised” or “precision” medicine).

5.2. Rationale

We propose that, as with other critical illness syndromes (e.g. sepsis, ARDS) the host response to the clinically defined syndrome of CS may be heterogeneous, with two or more biological endotypes associated with differential outcomes (in both the short and longer term) and treatment responses. Thus, identification of biological markers of susceptibility to, and outcome from CS may identify groups of patients who would either optimally respond to supportive therapies such as MCS; or in whom such expensive and resource consuming interventions may be futile ¹⁴. In addition, an improved understanding of the biological pathways associated with CS susceptibility, severity or outcome may identify novel therapeutic targets for intervention ¹⁴. Finally, identification of subgroups of patients with differential outcomes or responses to MCS may help enrich future clinical trials of current or emerging therapies in CS, facilitating study design and recruitment, which has hitherto been challenging.

5.3. Risks / benefits

The risks of this observational study are minimal, with the only invasive procedure being phlebotomy. The risks of this procedure will be managed with a relevant SOP and by employing a professional trained in acquiring the samples. The benefits of the study are that it will add to the body of knowledge regarding the mechanisms determining susceptibility, severity, outcomes and response to treatment in CS, specifically through improved understanding of the heterogeneous host response. Findings may suggest novel therapeutic targets and inform a precision medicine approach to managing CS, as well as the design of clinical trials; the long-term objective being to reduce the persistently high mortality and morbidity associated with this condition.

6. Study objectives

6.1. Primary objective

The primary aim is to identify biological or immunological sub-phenotypes of patients with CS, and their association with outcomes and the response to supportive therapies such as inotropes and MCS

6.2. Secondary objective

- Identify transcriptional and proteomic signatures at presentation that provide information about the pathobiology of CS
- Identify gene expression and proteomic signatures at presentation that may predict survival and functional recovery in both medically managed and mechanically supported patients with CS
- Investigate inter-individual heterogeneity in the transcriptomic and proteomic response to CS and identify context-specific regulatory genetic variants involving gene networks central to the pathogenesis of CS
- Interrogate any added value of combining gene expression data with existing clinical risk prediction scores to assess whether their accuracy can be augmented
- Investigate whether changes in gene expression over time are associated with recovery from CS

6.3. Primary endpoint

The primary outcome is the association between transcriptomic and proteomic signatures and all-cause mortality at hospital discharge.

6.4. Secondary endpoint

Secondary endpoints include associations between 'omic signatures and:

- All-cause mortality at 48 hours, discharge from hospital and 30 days
- Intensive care unit days
- Duration of hospital stay

7. Study population

All patients presenting to recruiting sites who fulfil study inclusion criteria and have no exclusion, will be considered. The majority of patients will be present through the heart attack centres and pathways. Some patients will, however, develop cardiogenic shock (CS) during their admission. These patients will be recruited from the coronary care units, intensive care units or cardiology wards and will be identified by clinicians who will alert research staff.

7.1. Inclusion criteria

AMI with CS

- Presentation within 24 hours of onset of ACS symptoms.
- CS can only be secondary to ACS (Type 1 MI STEMI or N-STEMI)
- Planned or completed revascularisation of culprit coronary artery
- CS will be defined by:
- Systolic blood pressure <90 mmHg for at least 30 minutes or a requirement for a continuous infusion of vasopressor or inotropic therapy to maintain systolic blood pressure > 90 mmHg.
- Clinical signs of pulmonary congestion, or signs of impaired organ perfusion with at least one of the following manifestations:
 - altered mental status.
 - cold and clammy skin and limbs.
 - oliguria with a urine output of less than 30 ml per hour.
 - elevated arterial lactate level of >2.0 mmol per litre.

Samples will also be collected from 2 additional patient cohorts as a control / comparator group:

AMI without CS

- Patients presenting within 24 hours of onset of ACS symptoms but without CS with evidence of left anterior descending coronary artery disease at angiography

Non-Ischemic CS

- Patients presenting with non-ischaemic aetiologies of CS i.e., inflammatory acute cardiomyopathy/ septic cardiomyopathy/ myocarditis (Clinical diagnosis as confirmed by attending clinician based on clinical history, ECG changes, echocardiography, low likelihood of culprit coronary disease/normal coronary arteries, troponin rise, CRP. MRI not required for diagnosis.)

7.2. Exclusion criteria

Any of the inclusion criteria not met and:

- Age <18 and ≥80 years.
- Unwilling to provide informed consent or appropriate consent from a nominated consultee or personal consultee
- Significant systemic illness resulting in life expectancy < 12 months
- Known dementia of any severity
- Comorbidity with life expectancy <12 months.
- Out-of-hospital cardiac arrest (OHCA) **and any** of the following:
 - No return of spontaneous circulation (ongoing resuscitation effort)
 - pH <7
 - Without bystander CPR within 10 minutes of collapse
- Patients with a Haemoglobin level of <8g/dl at enrolment
- Co-enrolment in any study that may impact upon gene expression

CS Arms

- Echocardiographic evidence of mechanical cause for CS: e.g. ventricular septal defect, LV-free wall rupture, ischaemic mitral regurgitation.
- Shock predominantly due to another cause (e.g refractory septic vasoplegia, septic shock, haemorrhagic/hypovolaemic shock, anaphylaxis, and obstructive shock).
- Arterial lactate level of <2.0 mmol per litre.

8. Study design

This is an observational cohort study with patient enrolment occurring in 3/4 centres in England and 2-3 Centres in Germany. The recruitment target is 300 patients. We will focus on patients presenting with acute myocardial infarction and cardiogenic shock who are supported medically), with ECMO and with the Impella Device n=160 total. We will also enrol patients who present with either a heart attack and no evidence of CS (n=50) or CS due to other reasons e.g., acute inflammation of the heart (n=50) and CS due to decompensation of known or newly diagnosed non-ischemic heart failure (n=40 St. Bartholomew's only).

Blood collection

We will collect blood samples (up to 20ml per time-point) at research-specific time points

Serum and plasma will be extracted from spun blood in appropriate blood collection tubes, aliquoted and stored at -80°C.

DNA will be extracted from the Buffy Layer of spun whole human blood using a commercial kit. The buffy layer containing cellular DNA will then be taken from the spun sample using a pipette and placed into cryotubes and stored at -80°C in 3x3mL cryotubes. DNA will be extracted according using the Maxwell 16 DNA purification kit (Promega, WI, USA).

RNA from human whole blood will be collected into a Tempus tube. Samples will be collected and processed according to the manufacturer's instructions. Following processing whole blood RNA will be stored at -80°C and then shipped for batch analysis.

All samples will be labelled with a cryogenic freeze resistant labels and marked with a barcode unique to that sample and patient.

Clinical data

Patient study data will be captured in an electronic case report form (eCRF). We will use the REDCap (Research Electronic Data capture) electronic data capture platform. This will be hosted at Queen Mary University London and all patient data will be pseudo-anonymised. Patient numbers consist of a 3- or 5-digit site code and a 4-digit patient number. Local investigators should be assigned patient numbers sequentially for each site beginning with 0001

9. Study procedures

Study Intervention	Day 0	24 hrs	Day 5	Death or discharge
Screening	x			
Consent	x	x		
Enrolment	x			
Blood collection	x	x	x	
CRF completion	x	x	x	x

Screening and participant identification will take place on arrival by a member of the patient's existing clinical care team and as soon as the diagnosis of CS is made. All patients presenting with the protocol definition of CS will be considered for this study.

Participants will remain in the study for the duration of their hospital stay or until the end of collection of new data for the CRF. If at any time consent/declaration (by patient or relatives) is withdrawn then only data to that point will be used for the trial. Patients enrolled in the AMI without CS arm do not require day 5 bloods.

10. Statistical considerations

10.1. Sample size

A sample size of 300 patients will enable cluster discovery with an individual endotype comparator subgroup of 50 having >80% power to show a difference in expression with >2.5% genes prognostic and a >1.5-fold change in gene expression (average read counts 20, dispersion 0.2) with FDR <0.05. The sample size of 300 will have >80% power to detect eQTL where the SNP has an effect size explaining >5% of variance (significance threshold of 1×10^{-5}).

10.2. Method of analysis

Inter-individual heterogeneity in whole blood (leucocyte) transcriptome will be interrogated using unsupervised hierarchical cluster analysis for the 10% most variable probes. Correlation analysis of continuous data will be done using Spearman's rank correlation coefficient. Survival analysis will be done by Kaplan-Meier estimation (log-rank test) and Cox proportional hazards regression will be implemented in the survival method (R package, version 2.37). Hazard ratios (HRs) and 95% CIs will be calculated for each endotype discovered with reference to other endotypes. We will map gene expression and protein abundance as quantitative traits using linear mixed model including CS status as an interaction term.

11. Ethics

This study has been granted approval by the National Research Ethics Service (IRAS Project ID: 290406) HRA and Health and Care Research Wales (HCRW) Approval for the study in England and Wales.

Site specific ethics will be sought from German centres according to relevant national guidance; data sharing and material transfer agreements will be established between German and UK sites (Barts and Oxford).

The CI will require a copy of the approval documentation before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Informed Consent

One important aspect for consideration in CS patients is informed consent. Many patients (up to 80%) will not be able to provide informed consent due to intubation,

mechanical ventilation, and sedation, and some with impaired peripheral and central perfusion induced by the CS itself, will be only partially able to provide full informed consent. In the real world, only some patients will thus be able to give full informed consent in the acute setting. As the majority of patients with CS are unable to consent, a personal or nominated consultee process will be used:

If a patient is not able to provide Informed Consent, then 2 options will be considered:

1. Consent from a personal consultee (next of kin or relative)
2. Consent from a nominated consultee (an independent physician unrelated to the trial). The local PI or designated person will also countersign.

Before any research bloods are drawn patient wishes will be sought from a relative or friend acting as consultee or documented by a nominated consultee. If any patient regains capacity at any point in the study then they will be approached and asked for consent for permission to remain in the study. If at any time consent (by patient or relatives) is withdrawn then only data to that point will be used for the study. Consent will be obtained by one of the research team trained in the process of obtaining consent. The right of the participants' next of kin to refuse to participate without giving reasons will be respected. All participants are free to withdraw at any time from the study without giving reasons and without prejudicing further treatment.

Risks to Participants

Participants may have blood drawn more often than is required for standard care. Phlebotomy can be associated with pain at the draw site and rarely with infection. Discomfort will be minimized by having expert staff obtain blood samples, and by combining research sampling with routine clinical sampling, where possible, which normally occurs daily in acutely unwell patients in hospital.

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 generally 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.

Benefits to Patients

There will be no direct benefit to research participants. The study may include biological sampling in addition to sampling required for medical management. The results of the tests done on these samples may not contribute to improving the participant's health. The results of this study will not be available in time to contribute to the participant's care. Where possible, test results with potential relevance to patient care will be informed to the participant and/or treating doctor. The feasibility of this will depend on local resources. Some assays cannot immediately benefit the patient because data will need to be pooled with others, or because the assays take time.

11.1. Annual Safety Reporting

All adverse events will be reported. Depending on the nature of the event the reporting procedures previously stated within the document (risks and benefits subsection) should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance. The CI and PI will send an annual progress report to the REC and the sponsor using the HRA template on the anniversary of the REC “favourable opinion”.

12. Public involvement

Patient and public engagement plans for the study will follow NIHR/INVOLVE guidance. Using existing infrastructure the BHC patient representatives will be involved throughout the study, including 1) providing insight into the acceptability of the research plans, 2) involvement in designing the informed consent process, 3) ensuring patients have a positive experience of participating in this research by providing insight into the methods and data collection and 4) developing the patient and public dissemination. In addition, we will engage patients and public by contributing to newsletters, engaging associated patient organisations eg. pumping marvellous and by presenting talks at the local (William Harvey Research Institute and Barts Heart Centre) and national patient forums. Depending on the impact of the results, we will collaborate with the Barts Charity Communications department to disseminate results in the national media.

13. Data handling and record keeping

13.1. Data management

All data will be handled and stored in compliance with General Data Protection Regulation 2016 (GDPR) and national Data Protection Act 2018 Regulations. Throughout, utilising appropriate security, protection against unauthorised access and protection against data loss in accordance with data protection regulations will be guaranteed. We will work with the Barts Data Protection officer regarding the need for a Data Protection Impact Assessments (DPIA) given that we are collecting and storing large volumes of patient data, including genetic data, to demonstrate compliance with existing data protection legislation. Data storage at Barts will conform to the standard operating procedures of the Joint Research Management Office at Barts Health (<http://www.jrmo.org.uk/performing-research/conducting-research-in-the-nhs/data-protection-and-gdpr/>).

13.2. Source Data

Source documents will be stored safely in confidential conditions in accordance with GDPR. On all trial-specific documents, other than the signed consent form, the participant will be referred to by the trial participant number/code, not by name. Data collection will commence on enrollment to the study and discontinued on completion of blood-sampling and completion of the case report form dataset.

13.3. Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under General Data Protection Regulation for health and care research (GDPR), NHS Caldicott Principles, the UK Policy Framework for Health and Social Care Research, and the conditions of Research Ethics Committee favourable opinion. 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, study protocol, 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 unauthorized third party.

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, but all data will be pseudo-anonymised before transfer by eCRF. Site specific contracts will establish outlining what they can and cannot do with the data, including restrictions on passing data to other third parties. Access to data will be restricted to members of the research team with password permitted access, representatives from the sponsor, host institution, and any regulatory authorities to permit trial-related monitoring, audits and inspections when necessary

Plasma, DNA and RNA samples will be stored in two monitored -80°C freezers as a precautionary measure in accordance with the lab standard operating procedure. The samples will be labelled via a cryogenic vial label marker and specific freeze resistant labels and marked with a unique patient identifier. Samples will be batch shipped to Oxford for analysis. Unused plasma and RNA will be stored locally and may be used for future analysis. The Patient Information Sheet (PIS) is drafted such that the patients' next of kin are aware that they are consenting for this also.

If the reserve samples are not required, we may choose to collaborate with academic or industrial partners by sharing the samples so that additional analyses can be performed, in order to derive maximum scientific value from the experimental effort. These partners may be within or outside the European Union and the PIS will be drafted so that the patient is aware that they are also consenting to this process.

13.4. Record retention and archiving

In accordance with the UK policy Health and Social Care Research, we will keep all samples for 5 years after the project has completed. Due to the research containing Barts Health NHS trust patients and being carried out by Barts Health NHS Trust staff the approved repository for long-term storage of local records is the Trust Corporate Records Centre. All documentation will be stored physically as paper copies in a file folder and electronically on an encrypted database, utilizing the trust hospital system and archived as per the trust policies.

14. Laboratories

14.1. Central and local laboratories

Mr Giuseppe Scozzafava, Wellcome Centre for Human Genetics, Nuffield
Department of Medicine, University of Oxford, OX3 7BN

14.2. Sample preparation and collection

Samples will be collected and processed as per section 8 of the protocol and in accordance with the sample collection, processing, and transportation SOP.

14.3. Laboratory procedures

Sample	Aliquots	Ultimate Use
Blood (Cytodelics)	: freeze at -80°C	Flow/ Mass cytometry
Blood (EDTA)	Supernatant: freeze at -80°C	Plasma proteomics
	Supernatant: freeze at -80°C	Mediators/proteomics other assays
	Supernatant: freeze at -80°C	Future exploratory analysis
	Cell Pellet: freeze at -80°C	eQTL analysis
Blood (RNA tube)	freeze at -80°C*	Gene expression analysis and/or RNA seq analysis

14.4. Sample storage and transfer

All samples will be processed and stored locally and shipped then analysed in batches. All samples will be fully anonymized and packaged and shipped by a recognised provider that complies with institutional policy. SOPs for processing, labelling, storage and shipping will be provided for each site. Each site will have local ethical approval and a Material Transfer Agreement (MTA) in place for shipment of samples.

15. Safety reporting

All non-serious adverse events, whether expected or not which are thought to be related to participation in the study will be recorded.

An SAE form will be completed and emailed to the Chief Investigator within 24 hours. However, relapse and death due or hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs. Post-operative complications that are not thought to be related to the taking of blood samples do not need to be reported. All SAEs will be reported to the local Research Ethics Committee where in the opinion of the Chief Investigator and sponsor, the event was:

'Related', resulted from the administration of the research procedures; and 'Unexpected', an event that is not listed in the protocol as an expected occurrence. Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. SAEs will also be reported to the sponsor. Local investigators should report any SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.

16. Monitoring and auditing

The Sponsor or delegate retains the right to audit any study, study site or central facility. In addition, any part of the study may be audited by the funders where applicable. In addition, the funders may audit any part of the study where applicable. The study may be subject to inspection and audit by representative of the Sponsor under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research. Monitoring will include source data verification.

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

- A detailed data dictionary will define the data to be collected on the case report form
- Quality checks will be built into the data management system and there will be quality checks of critical data points entered into the CRFs to ensure standardization and validity of the data collected

Data queries may be generated. Any information that is not available for the investigator will be considered as missing. No assumptions will be made for missing data.

17. Study committees

Throughout, we will adhere to the UK Policy Framework for Health and Social Care Research.

Study progress will be continuously monitored by the study management group comprising; Alastair Proudfoot, Charles Hinds, Julian Knight, Mervyn Andiapen, and Emma Davenport. The study management group will meet (by teleconference) at least quarterly to review milestones and deliverables, safety reporting and agree how best to manage the dissemination of results (e.g. content, objectives and timing of scientific publication).

18. Finance and funding

This study is funded by a Barts Charity large project grant, Grant Reference Number: MGU0535, amount £274,062 and Medical Research Council Clinical Academic Research Partnership Award: Grant Ref: MR/W03011X/1, amount £218,391.

19. Insurance and indemnity

NHS indemnity scheme will apply. It provides cover for the design, management, and conduct of the study. The NHS indemnity scheme will apply for samples collected within the UK. Local / national regulations will cover indemnity for samples collected at German centres. NHS indemnity provides cover for the design, management, and conduct of the study in the UK

20. Dissemination of research findings

We expect to publish the research results in high quality, peer reviewed journals and present our findings at national and international scientific meetings. With regards to the patient and public, we will contribute to newsletters and attend talks at the local and national patient forums.

21. References

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