TITLE OF THE PROTOCOL:

Barts BioResource

Short title/Acronym: Barts BioResource (BBR)

Sponsor: Barts Health NHS Trust

Representative of the Sponsor:

Dr Mays Jawad
Research and development Governance Operations Manager
Services & Business Development,
Joint Research Management Office,
5 Walden Street,
London. E1 2EF

Phone: 020 7882 7260
Email: research.governance@qmul.ac.uk

REC reference: 14 / EE / 0007
REC reference: 21 / EE / 0284

ReDA reference: 009265 BLT

BHT Tissue Bank reference: 12199

Protocol Version: **11.0**

Date: **1st January 2022**

AMENDMENTS:

1. 23-May-2014	2. 1st January 2015	3. 26th October 2015	4.26th March 2017
5. 08th April 2020	6. 1st January 2022	7.	8.

STUDY PERSONNEL

Chief Investigator

Steffen E. Petersen, MSc MPH MD DPHIL SFHEA FRCP FSCMR FEACVI FACC FESC
Professor of Cardiovascular Medicine,
Honorary Consultant Cardiologist,
Centre Lead for Advanced Cardiovascular Imaging,
William Harvey Research Institute,
Barts Health NHS Trust, NIHR Biomedical Research Centre at Barts,
Barts Heart Centre, St Bartholomew's Hospital
West Smithfield,
London, EC1A 7BE.

Email: s.e.petersen@qmul.ac.uk
Phone external: +44-207-882-7188 (centre administrator Jane Batchelor)

CLINICAL SOURCE CENTRES

St Bartholomew's Hospital,
Barts Health NHS Trust,
West Smithfield,
London. EC1A 7BE

The Royal London Hospital,
Barts Health NHS Trust,
Whitechapel Road,
Whitechapel,
London. E1 1BB

Whipps Cross University Hospital,
Barts Health NHS Trust,
Whipps Cross Road,
Leytonstone,
London. E11 1NR

Newham University Hospital,
Barts Health NHS Trust,
Glen Road,
Plaistow,
London. E13 8SL

Mile End Hospital,
Barts Health NHS Trust,
Bancroft Road,
London. E1 4DG

NHS Nightingale Hospital
Royal Victoria Dock,
1 Western Gateway,
Royal Docks,
London E16 1XL

NRES recognised RESEARCH ETHICS COMMITTEE

Primary Ethical review:
NRES Committee – East of England
Health Research Authority,
The Old Chapel,
Royal Standard Court,
Nottingham. NG1 6FS.

Site Specific Assessment:
Barts Health NHS Trust.

EMERGENCY CONTACTS

Maudrian Burton
Barts BioResource Senior Research Nurse Manager
Barts Heart Centre, St Bartholomew's Hospital
West Smithfield,
London, EC1A 7BE.
Maudrian.burton1@nhs.net
Telephone: 02078826903

IN THE CASE OF AN EMERGENCY: SERIOUS ADVERSE EVENTS WILL BE REPORTED TO THE PRINCIPAL INVESTIGATOR AND THE SPONSOR WITHIN 24 HOURS OF INITIAL REPORT.

Chief Investigator Agreement Page

The clinical study as detailed within this research protocol Protocol Barts BioResource Version 11.0; 1st April 2022 or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Prof Steffen E Petersen

Chief Investigator Site: Barts Health NHS Trust

Signature and Date:

Statistician Agreement Page

The clinical study as detailed within this research protocol **(**Protocol Barts BioResource Version 11.0; 1st April 2022, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Statistician Name: Not applicable

Site:

Signature and Date:

Principal / Co-Investigators Agreement Page

The clinical study as detailed within this research protocol Protocol Barts BioResource Version 11.0; 1st April 2022, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Prof Steffen E Petersen

Chief Investigator Site: Barts Health NHS Trust

Signature and Date:

Co- Investigator Name: Prof Art Tucker

Investigator Site: Barts Health NHS Trust / Queen Mary University of London

Signature and Date:

Co- Investigator Name: Prof Anthony Mathur

Investigator Site: Barts Health NHS Trust

Signature and Date:

Co- Investigator Name: Prof Richard Schilling

Investigator Site: Barts Health NHS Trust

Signature and Date:

Co- Investigator Name: Prof Adam Timmis

Investigator Site: Barts Health NHS Trust

Signature and Date:

Co- Investigator Name: Dr Saidi Mohiddin
Investigator Site: Barts Health NHS Trust

Signature and Date:

Co- Investigator Name: Dr Andrew Wragg
Investigator Site: Barts Health NHS Trust

Signature and Date:

Co- Investigator Name: Prof Andrew Tinker
Investigator Site: Barts Health NHS Trust

Signature and Date:

Co- Investigator Name: Dr Francesca Pugliese
Investigator Site: Barts Health NHS Trust

Signature and Date:

Co- Investigator Name: Professor Tim Warner
Investigator Site: Queen Mary University of London

Signature and Date:

Co- Investigator Name: Professor Patricia Munroe
Investigator Site: Queen Mary University of London

Signature and Date:

Co- Investigator Name: Professor Michael Barnes
Investigator Site: Queen Mary University of London

Signature and Date:

Co- Investigator Name: Professor Mark Caulfield
Investigator Site: Queen Mary University of London

Signature and Date:

Co- Investigator Name: Dr Malcolm Finlay
Investigator Site: Queen Mary University of London

Signature and Date:

STUDY SUMMARY/SYNOPSIS

TITLE	**Barts BioResource**
SHORT TITLE	**Barts BioResource- BBR**
Protocol Version Number and Date	**Protocol Barts BioResource Version 11.0; 1st April 2022**
Sponsor	Barts Health NHS Trust
Methodology	Establishing, validating and maintaining a clinical and research registry; developing a human tissue bank; collection and analysis of clinical information and non-invasive Monitoring Technology evaluations.
Study Duration	Indefinitely with long-term follow-up via NHS Registries (any kind of health, healthcare and related data available and accessible) and subject to regulatory approvals.
Study Centre	Barts Health NHS Trust
Objectives & Design	The Barts BioResource resource objective is to establish a database of patients to registry participation and the donation of tissues including blood, saliva, throat, buccal and/or nasopharyngeal swabs, urine, faeces and soft/solid tissue samples for the purpose of developing a bio-repository of donated samples which will be used for clinical health and disease-related research opportunities. Research opportunities are envisaged to translate into improving any aspect(s) of health care. The Barts BioResource aligns with the strategic aims of the NIHR Barts Biomedical Research Centre and its associated delivery partners. The **Barts BioResource** further supports the NIHR BioResource REC references 17 / EE / 025 and 21 / EE / 0284 in the collection of clinical data and tissue samples.
Number of Subjects/Patients	The long-term vision of the study is to expand as practicable to ALL clinical speciality patients managed by Barts Health NHS Trust, provided sufficient financial and human resources are available.
Main Inclusion Criteria	ALL patients who are referred to and/or managed in the Barts Health NHS Trust are eligible for participation. Being part of other research studies is NOT an exclusion criterion for participation in the BBR and vice versa.
Statistical Methodology and Analysis	The data derived from the Barts BioResource will not be analysed in isolation, but will form a core resource for teaching, research and any associated healthcare or related service development activities. As such a formal statistical plan is not appropriate or required.

Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
BRC	Biomedical Research Centre
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DPA	Data Protection Act (1998)
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GPRD	General Data Protection Regulation (2018)
HQIP	Healthcare Quality Improvement Partnership
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
MA	Marketing Authorisation
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
NICOR	National Institute for Cardiovascular Outcomes Research
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

The term “Tissues” where relating to tissue samples including blood, saliva, throat, buccal and/or nasopharyngeal swabs, urine, faeces and soft/solid tissue samples.

Table of Contents

EXECUTIVE SUMMARY

Barts Health NHS Trust is an NHS Trust based in London, England. Established in 2012, it currently runs six hospitals throughout the City of London and East London and is one of the largest NHS Trusts in England.

The Trust serves a population of over 2.6 million people, in an area characterised by significant diversity and health inequalities. It is one of the largest NHS Trusts in England, and accounts for 1.5% of all hospital activity in England. It provides district general hospital services to the London Boroughs of Tower Hamlets, Waltham Forest and Newham, and also provides some specialist services to a wider area, including some on a national basis. It runs the largest cardiovascular centre in the United Kingdom, the second largest cancer centre in London, and leading stroke and renal units. The Trust also runs a number of other facilities, including two birthing centres and some dental and primary care services.

In addition to its long term five hospitals, The Board of Barts Health NHS Trust agreed to a request from NHS London that they host the new hospital built for Covid-19 patients at the ExCeL exhibition centre in Newham.

This means the Trust has taken on formal legal responsibility for the operation and governance of the NHS Nightingale Hospital London, working closely with NHS London and the project team that is setting it up with help from NHS colleagues across the capital.

The facility is now officially opened to care exclusively for Covid-19 patients from across the capital and could have a capacity of several thousand beds by the anticipated peak of the coronavirus pandemic.

The purpose of the Barts BioResource is to establish, validate and maintain a repository of generic consented patients clinically managed by Barts Health NHS Trust. In addition to this the consent may include the donation of samples such as human blood, saliva, throat, buccal and/or nasopharyngeal swabs, urine, faeces and soft/solid tissue samples for the purpose of establishing a biobank of for use in health and associated disease research.

The programme will also be used to develop, assess and validate the PowerTrials™ management system for research (Appendices 10-13).

Commencing in February 2014, the now completed study piloted for a period of approximately 3 months for patients attending the cardiovascular magnetic resonance (CMR) unit at the London Chest Hospital. This pilot phase was critical to test feasibility and timings of the study procedures (e.g. acceptability of nurse consenting to patients, enrolment rates, timing and feasibility of blood sample processing, blood sample transportation and blood sample retrieval). Following this successful pilot phase, the registry extended to other areas across the Barts Health NHS Trust to enrol patients with other cardiovascular disease following guidance of the Operational Group depending on available resources and scientific prioritisation.

1.0 INTRODUCTION

1.1 BACKGROUND TO SOURCE DATA FOR REGISTRY

Barts Health NHS Trust: Strengths and track record in translation into patient benefit.

Our clinical and academic partnership combines internationally renowned strengths in basic and clinical cardiovascular (CV) pharmacology within the William Harvey Research Institute (WHRI) at Queen Mary's with cardiovascular clinical research within Barts Health NHS Trust.

In the 2008 Research Assessment Exercise 65% of our research was rated as World Leading or Internationally Excellent. We will benefit from the UK's newest Heart Hospital at Barts (opens 2014) creating the translational Cardiovascular hub for 2.5m people across East London with approximately 30-40% of our population being South Asian with an unusual and clinically relevant phenotype including early coronary disease, type 2 diabetes, renal failure and left ventricular (LV) hypertrophy.

In 2008 the NIHR awarded a Cardiovascular Biomedical Research Unit to Barts Health NHS Trust (NIHR CVBRU at Barts) from which we have transformed our CV research. The focus of NIHR CVBRU at Barts was establishment of the NIHR Imaging Faculty and Centre where we are evaluating risk stratification with MRI and optimising CT angiography for coronary disease diagnosis in renal patients. From April 2017 the NIHR CVBRU at Barts is called the NIHR Biomedical Research Centre (BRC) at Barts.

Our next step change will harness the translational potential of our patient base across East London.

The creation of the Barts BioResource allowed the identification and validation of teaching and research activities. The first step was to implement patient consent (this unique ethics application and programme of work) to capture rich cross-sectional phenotyping, venous blood, saliva, urine, faeces and soft/solid tissue (e.g. atrial appendage and pulmonary vein tissue) at the time of recruitment, and to obtain robust follow-up clinical data that includes both clinically indicated future patient contact and patient contact specifically for the purposes of research.

This helps our BRC and wider research teams and collaborative partners to maximise trial participation and create a multi-ethnic bar-coded bio-repository (plasma, serum, DNA, RNA and tissue (for example human atrial and atherectomies) to prime translational pull-through.

This integrated approach accelerates candidate selection and Pharma/Biotech/MedTech partnerships for discoveries to be made here. This approach is advocated within the Academy of Medical Sciences (AMS) review, which resulted in the formation of the national Health Research Agency in 2011 (1).

1.1 PATIENT PATHWAYS FOR STUDY RECRUITMENT

This protocol version will expand the remit of the Barts BioResource (BBR) from cardiovascular patients and research to cover all patients/specialties and more

encompassing of health, disease and healthcare related research delivered by Barts Health NHS Trust.

To date the current BBR has recruited over 23,400 cardiovascular patients at a recruitment rate in excess of 80% approval. Further, approximately 2,500 patients have been re-consented illustrating an ongoing commitment to inform and retain patient participation. Further, during this time we have encountered 5 complaints, each of which was resolved transparently and with patient engagement.

is reasonable to expect that cardiovascular patients and those of other specialties would have similar expectations regarding their involvement in healthcare related research opportunities hence the proposal for non-cardiovascular patients to be eligible for enrolment into the BBR. Further, the metrics achieved to date by the BBR clearly illustrate the infrastructure, experience and capability of the BBR team, Standard Operating Procedures, and governance to support such a move.

The expanded scope of research will enable a much broader application of the patient information and donated tissues in areas where the clinical question is not purely cardiovascular but overlaps or is placed solely with(in) other specialties.

The expanded study will include currently identified pathways in all clinical services, with extension to additional clinical services being considered by the Operational group where appropriate.

The prioritisation of how to scale enrolment into the Barts BioResource will be guided by the suggestions and direction of the Operational group. The Operational group will take into account lessons learnt by the BBR regarding feasibility, duration of study procedures, resource (human and financial) availability and will make scientific prioritisation for best use of the resources.

The expansion of the clinical bioinformatics register has enabled the rapid determination of 'local' feasibility for clinical research at an institutional, regional, national and international level. This assists in compliance with the requirements of the National Health Research Agency and will enable the development of research capacity within the Barts Health NHS Trust.

We are currently approved to add a maximum of 10 minutes at the end of clinical assessments such as clinical MRI acquisition, ultrasound, echocardiogram, electroencephalogram or similar monitoring/measuring modalities, but **not** to investigations using radiation (e.g. CT). The main purpose is to test and/or develop new imaging techniques and sequences that may improve our clinical service in the future. The additional scanning is not associated with radiation and will not cause harm to participants.

Future Technology Evaluations will be restricted to **non-invasive** monitoring systems that are NOT used for diagnostics or therapeutic planning. The aim of such activities is to provide the necessary scientific confirmations and data with which to prepare full stand-alone research programmes, where appropriate. This approach formally addresses a known gap in the existing regulatory structures and to test and identify new techniques that may improve our clinical service in the future.

PATIENT PATHWAY FOR PILOT STUDY (Now completed)

The Cardiac Magnetic Resonance (CMR) unit was the ideal pilot centre:

The CMR unit provides a focus point for interaction with patients on the background of established data collection supported by the BRC. This meant that the pathway of patients referred for CMR was ideal to run an approximately 3-month pilot of this project: patients are elective, there was little out of hours work, all patients were sent information prior to the visit anyway and PIS and consent forms could be readily added with consenting taking place during the normal waiting time before the scan. This pilot provided information which was critical to plan and execute the project with its vision of ultimately enrolling all patients referred to and managed within Cardiovascular Services at Barts Health NHS Trust. Relevant outcomes of this now completed pilot phase included but were not limited to recruitment rates, staff time needed for consenting, taking and, preparing and storing blood samples, retrieval of blood samples.

1.3 CLINICAL DATA

The 'Key' element of the initial pilot and extended study protocol was that the development of a clinical health and disease data repository, blood and tissue sample biobank, and technology evaluation activities **would not** alter patient management in any way.

1.4 RATIONALE AND RISKS/BENEFITS

Rationale, risks and benefits are similar for initial pilot and extended study.

Rationale: The development of the Barts BioResource will facilitate a highly valuable clinical and data repository and access point for the purpose of research into disease. In addition, teaching, education, and audits for care quality (through consent to access and use of routine medical and other health-related records) will significantly benefit from the Barts BioResource.

Risks: The risks to patients are minimal, as clinical management is not altered in any way.

The amount of blood to be sampled in the study (up to 50 ml where applicable) is not considered to be significant in adult subjects.

Data will be handled confidentially and securely (see details below) and risk is thus minimal. Appropriate governance structures are in place to approve and monitor study procedures (see Appendix 11).

The application of Future Technology Evaluation activities will be restricted to **non-invasive** monitoring systems. As such these systems will not be utilised to diagnose or alter patient care. Appropriate governance structures are in place to approve and monitor study procedures (see Appendix 11). Examples of devices include activity

monitors such as Fitbit®, heart rate monitors, novel and evolving systems for recording circulatory dynamics. Where required, full regulatory approvals will be ensured, such as Medicines and Healthcare products Regulatory Agency (MHRA) letters of "Non-Objection". All relevant internal Barts Health Policies will be followed such as electrical safety and devices management. The aim of such activities is to provide the necessary scientific confirmations and data with which to prepare full stand-alone research programmes, where appropriate.

The Barts BioResource Ethics and Operational Groups will review, manage and approve all information released in relation to Future Technology Evaluations via Standard Operating Procedures. Specific review and approval will be gained from the linked Public and Patient Advisory Group.

Benefits: The Barts BioResource will facilitate health-related benefits for the population of patients suffering from diseases assessed and managed at Barts Health NHS Trust and as such is likely to increase the reputation of Barts Health NHS Trust and Queen Mary's School of Medicine and Dentistry.

a) Consent to access and use of routine medical and other health-related records for:

   i. *For Teaching / Educational purposes*
   ii. *For Research purposes*
   iii. *To facilitate audit for care quality*
   iv. *For academic or commercial collaboration*

- Consent for the **Barts BioResource** will be attempted after the patients have been screened for eligibility for entry into ongoing hypothesis driven trials if appropriate. Ideally patients will be eligible for both.
- Participation in ongoing clinical research studies does not preclude participation in the BBR as it would have no increased risk to the patient or scientific validity of either project unless said studies specifically preclude entry into observational studies such as the BBR.
- Participation in the BBR programme would not preclude participation in additional clinical research studies as it would have no increased risk to the patient or scientific validity of either project.
- Barts Health NHS Trust is a leading teaching hospital; and there is a reasonable, equitable and appropriate requirement of use of fairly and lawfully processed medical information for benefit of the individual and population in general.
- Research may be either prospective or retrospective in nature.
- Clinical Audit is defined as "a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change" and is a requirement of all NHS Institutions (2).

- Patients who receive care within and are managed by the Barts Health NHS Trust and their families have an "*expectation*" and therefore tacit approval for such activities to occur in a regulated professional environment.
- Further to legally enable, Non-Medical entities to transfer health and lifestyle data from their systems into the Barts BioResource; such as Fitbit®, Apple Health Applications and patient managed systems.

b) Permission to enter and retain patient clinical details on database(s) and to allow future unsolicited contact. To integrate and maintain the Barts BioResource with parallel clinical information resources.

i. For follow up contact and outcome tracing.

ii. For clinical trial site-capability assessments.

iii. For future approaches to patients for potential research participation.

iv. Anonymous data sharing.

- The Barts BioResource will provide access to patient data that protects individual interests and allows approved research and development activities to proceed effectively and efficiently and ethically (1).
- The Barts BioResource will link data derived from a range of related healthcare resources within the Barts Health NHS Trust and external resources within the NHS and national surveillance systems. Approval for access to these external systems will be sought following Research Ethics approval.
- Establishment and management of a healthcare related data '*Safe haven*' to allow access to data for approved research.
- Clinical Research Registries are now widespread and can be of invaluable assistance to clinicians and researchers by providing a repository of information that could assist in understanding the patients they are serving, equitable utilisation of health care services, and the design and implementation of research studies to improve patient care.
- Health service evaluations, increasing research into effectiveness of individual- and service-level interventions, and analysis of pharmaco-epidemiological data, are integral to the government's "*Connecting for Health Research Capability Programme*" (3)
- Accredited investigators and research team members will be "legally considered part of a clinical care team to enable identifying patients eligible for approved studies". The study management team will maintain a list of accredited staff centrally.
- Information with regards to study patients will be kept confidential and managed in accordance with the principals of the Data Protection Act and General Data Protection Regulation (2018), NHS Caldicott Guardian provisions, The Research Governance Framework for Health and Social Care (Second Edition 2005),

NRES Research Ethics Committee Approval and the regulations of the Barts Health NHS Trust.

- Personal data will not be transferred to a country or territory outside the European Economic Area, unless the receiving country or territory ensures an adequate level of protection for the rights and freedoms of data subjects in relation to the processing of personal data.
- A standardised Material Transfer Agreement has been approved by the Joint Research Management Office of Barts Health NHS Trust and is an absolute requirement prior to the release and transfer of any data or human tissue outside the institution.
- To enable the Barts BioResource comply with the UK Data Protection Act 2018 and the UK General Data Protection Regulation (GDPR).
- The Barts BioResource is sponsored by Barts Health NHS Trust and falls under the Trust governance approval. In addition, the Barts BioResource has complimentary governance policies which support its particular activities and have submitted a satisfactory Data Security and Protection Toolkit for 2018/19, 2019/20 and 2020/21 as a Hosted Secondary Use Organisation.

c) Consent to retain residual clinical biological samples to be processed and stored for future research into healthcare and related disease.

d) Permission to collect up to 50ml of venous blood samples, saliva, throat, buccal and/or nasopharyngeal swabs, urine, faeces and soft/solid tissue samples (as appropriate, reasonable and able to be collected) to be processed and stored for future research into healthcare and related disease. The impact on patients will be minimised as subsequent repeat samples will be of lower volumes as far as possible. Typically, blood will be obtained at the time of routine clinical venesection wherever possible. The samples may be prospectively collected with the patients permission during their attendance at Barts Health NHS Trust, but also some samples may be self-collected and transferred to Barts BioResource teams. Such samples could be saliva, urine or faeces. Well established systems exist so that these can be easily collected by the patient remotely and posted back to the Barts BioResource minimising patient inconvenience.

- The proposed method of informed consent, tissue collection and subsequent analysis is fully compliant with the Human Tissue Act 2004 and project-specific Research Ethics Approvals.
- Barts BioResource is fully compliant with Barts Health NHS Trust Tissue Bank.
- Such materials may be accessed within the Barts BioResource, in conjunction with partner institutions and in commercial collaboration. However, no samples will be sold for commercial gain in any circumstances. Further, no samples will be used for medical treatment of a third party or utilised for cloning experimentation.
- Significant parts of this proposal are a reflection of the UK Biobank protocol (4)

and similar safeguards will be applied.

e) Under the initial consent patients will be asked to consent to having blood, saliva, throat, buccal and/or nasopharyngeal swabs, urine, faeces and other tissue samples taken at future appointments. They are under no obligation to provide future samples and can withdraw their consent at any time.

In summary, the rationale, benefits, approval and monitoring requirements are proportionate to risk.

1.5 ETHICAL CONSIDERATIONS

This protocol is a combination of planned actions related to routine clinical management of patients, audit, service development, education and clinical research. As such, there is a range of ethical considerations, which overlap these various activities.

Some aspects of the protocol are outside the jurisdiction of GafREC 2.0 but are included in the formal ethics application for completeness.

The protocol (and sub-protocols and linked studies) will be conducted in accordance with the principles of the Declaration of Helsinki 1996 (Recommendations guiding Biomedical Research Involving Human Subjects).

This protocol will be conducted in accordance with the requirements of the UK Data Protection Act 2018 and UK GDPR. The GDPR requires that a Data Protection Impact Assessment (DPIA) be performed for all high-risk processing and, for each DPIA, the advice of the Barts Health NHS Trust Data Protection Officer (DPO) be sought. The processing of participant healthcare data requires a lawful basis under each of Article 6 and Article 9 of the GDPR. Consent as defined in this document is considered “ethical consent” from a governance perspective and may/may not necessarily be a lawful basis for a specific set of data processing operations. The Barts BioResource DPIAs specify the appropriate lawful bases applicable to specific data processing operations and are subject to DPO review and advice and, consequently, are not specified in this Protocol. The Barts BioResource Core DPIA covers most overarching processing operations and is publicly available on the Barts BioResource website.

Data will only be collected and utilised for projects which have ethical, scientific and information governance endorsement. All data will be protected within the requirements of the Barts Health NHS Trust and Connecting for Health.

The protocol will be conducted in accordance with the regulations relating to the Human Tissue Act 2004 and relevant institutional standards of conduct relating to Human Tissue. The residual clinical biological samples to be retained are a by-product of the planned clinical procedures and would otherwise be discarded and incinerated. The prospective collections of up to 50ml of venous blood, saliva, throat, buccal and/or nasopharyngeal swabs, urine, faeces and soft/solid tissue tissue, have minimal ethical concerns or issues.

Follow up and contact tracing are routine activities for clinical care within the NHS. However, access to routine medical and other health-related records will be confined to specific members of the research group/clinical care team, but all future patient contact related to potential participation in clinical research will be related to projects which have a specific and project specific Research Ethics approval. Such a system will undoubtedly reduce the incidence of contact with families of deceased patients which is an on-going problem within the NHS, and which causes considerable distress.

The best interests (clinical, physical, mental and personal) of the patient will always take precedence over the conduct and continuance of this and linked protocols.

A communication plan to inform the whole Barts Health Trust community (service users, carers, clinicians and other Trust staff) is planned to be established regarding the existence, potential benefits and proposed uses of the expanded Barts BioResource.

Envisaged stakeholder participation will facilitate regular consultation on the ethical, societal and practical issues of the project.

1.5.1. PATIENTS COMPETENT TO CONSENT

All competent patients will be clearly informed that their consent will be **optional**.

Specific ethical considerations:

- The patient informed consent is voluntary.
- Each component of the consent is optional.
- Patients will be free to withdraw at any time and without giving a reason.
- Their non-participation or dropping out of the study will not affect their planned or future treatment and care in any way.
- The consent for the Barts BioResource does not affect or influence their rights to decline future approaches or contacts related to participation in clinical research.
- Significant efforts will be made to prevent "*intrusive*" approaches to patient volunteers.
- Any re-contact with the patients will be co-ordinated and approved by the Barts BioResource teams.
- If patient donated biological material remains in an accessible and identifiable form they can request that it is destroyed should they wish. However, should it have been processed into a de-identified form, the

research custodians will not have the capacity or resources to enable destruction.

- Further, should patient biological material, images or data be processed and analysed within a cohort of patients for education, audit, service development or research purposes then the research custodians will not have the capacity or resources to enable destruction or removal from the summated data.
- Should the Barts BioResource identify any clinically relevant findings we will inform patients according to our duty of care. However, analysis of biological samples and tissue may occur with a significant time delay from consenting.

1.5.2 PATIENTS INCOMPETENT TO CONSENT

Generally, and with reference to the Covid-19 pandemic, Barts Health NHS Trust manage a number of patients who are intubated on ventilators and therein lack capacity.

This is especially relevant to patients in the London NHS Nightingale hospital. It is in the national interest, and also potentially in the interest of the patient's welfare, that their clinical information and biological samples are collected and made available to research teams.

This section of the protocol seeks to recruit any patients lacking capacity (including but not limited to such as those on ventilators, severe trauma, cardiogenic shock and similar) to the BBR programme. The following are the required considerations to achieve this in an ethical and legal framework:

Some patients may have an Advanced Directive in place, if this is established in a timely manner then we will conduct their care and potential BBR participation in accordance with their wishes.

We acknowledge the HRA guidance on research without consent, that it can be justified if the gravity of the rights infringement is minor and outweighed by the expected social value of the research and obtaining consent is impractical. We propose that this test is clearly met with reference to:

http://www.hra-decisiontools.org.uk/consent/principles-ALC-EnglandandWales.html

We further note and refer to the Medical Research Council's guidance of the **Key principles when considering the participation of adults who lack capacity in research:**

- *The interests of the individual must always outweigh those of science and society.*

- *The research must relate to a condition or impairment that affects the individual or the treatment of this condition.*
- *It must not be possible to conduct equally effective research with adults who have the capacity to consent.*
- *The potential benefits of the project should outweigh the risks: the level of acceptable risk depends partly on the possible benefit to the individual.*
- *Views of those close to the participant should always be sought, unless this is not possible due to particular circumstances.*
- *A participant who lacks capacity should only be included in a study when*
- *there are no indications that he or she objects to this.*

Wherever possible, Next-of-Kin will be consulted in relation to their understanding of the wishes and intentions of the patient, this will be supplemented with the opinion of the nominated clinician (Consultee) not involved in any BBR research present or in future on the data/samples.

As Next-of-Kin [NOK] will generally not be physically present during the current pandemic, the pathway will be by a nominated clinician (Consultee) not involved in any BBR research present or in future on the data/samples; followed by informing the NOK (their wishes to be observed) as soon as is reasonable practicable and appropriate, and finally informed written consent with the patient should they hopefully recover.

The Consultees are not asked to give consent on behalf of the adult, but rather to provide an opinion on the views and feelings of the potential participant. Further, the consultee will be

[a] Told that they are being asked to advise on the views and feelings they believe the adult would have towards participation in the BBR study.

[b] Told that they are free to decide whether they wish to provide this advice or not and

[c] Given sufficient information, in an understandable form, about the BBR study to ensure that they provide you with informed advice.

To this end, we are working directly with the Safeguarding Leads at each individual hospital site to ensure compliance and transparency of the BBR activities and clearly document such activities.

The BBR will develop a robust, transparent and auditable withdrawal system prior to recruitment of these patients and will regularly review such.

Further, we note the principles, provisions and requirements of the Mental Capacity Act 2005 and our teams are experienced in this area.

Risk Analysis: The participation of any patient in the BBR does not convey any significant risk of physical or mental harm. The BBR seeks to collect clinical data and

biological materials such as blood, urine, saliva, swabs and residual samples from clinically relevant procedures.

The application of this amendment will be continuously reviewed by Barts Health NHS Trust governance systems.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 STUDY OBJECTIVES

The Barts BioResource objective is to establish a database of patients who consent to registry participation and the donation of blood, saliva, throat, buccal and/or nasopharyngeal swabs, urine, faeces and soft/solid tissue samples for the purpose of developing a bio repository of donated samples, which will be used for health and related disease based research opportunities. Research opportunities will translate into improving health care. The Barts BioResource aligns with the strategic aims of the NIHR Barts Biomedical Research Centre and its associated delivery organisations.

The now completed pilot phase (approximately 3 months) tested the feasibility and scalability to achieve the extended or main phase's objectives. Specific aims included, but were not limited to assessing recruitment rates, percentage of patients agreeing to enrolment, determining durations of consenting, development and validation of the PowerTrials™ management system, taking of blood samples, processing of blood samples, testing logistics around blood sample transportation to sample storage sites, test of retrieving blood samples from storage sites.

To date the current BBR has recruited >23,400 cardiovascular patients at a primary recruitment rate in excess of 80% approval. Approximately 50 patients have withdrawn their consent. Further, approximately 2,500 patients have been re-consented illustrating an ongoing commitment to inform and retain patient participation (this is recorded as 100% wishing to re-affirm their informed consent). Finally, during this time we have encountered 5 complaints, each of which was resolved transparently and with patient engagement.

2.2 STUDY DESIGN

PILOT: Patients referred for a CMR scan were recruited for the registry due to the elective nature of scans which will facilitate the successful piloting. Also, only a small group of patients (about 5%) who have been scheduled to undergo a CMR scan without contrast agents would need a venepuncture to draw the blood sample. In all other patients the blood sample can be drawn from the intravenous cannula placed for the purpose of administering CMR contrast agent. The pilot phase focused initially on the consenting process, then add the taking of blood samples with necessary processing of blood samples and shipping of blood samples. As anticipated the objectives of the pilot phase were achieved and completed within 3 months and allowed a smooth transition to the extended study guided by the Operational Group.

PILOT AND EXTENDED STUDY:
Prospective, longitudinal cohort study as part of routine clinical care of all patients clinically referred to clinical services within Barts Health NHS Trust. Cross-sectional data will be analysed for prevalence, associations of imaging biomarkers and demographics, clinical findings and blood biomarkers. The long-term follow-up of our patients will allow assessment of the prognostic value of biomarkers.

3.0 SUBJECT SELECTION

Patients will be recruited by attending clinical research staff (at the time of formal consent to Investigation **or** Treatment at The Barts Health NHS Trust as approved by a National Research Ethics Service (NRES) approved Research Ethics Committee.

Patients with capacity will be provided with a full explanation of the nature, purpose and requirements of the study including a concise Information Sheet.

In relation to patients who are incapacitated at their time of recruitment, their Next of Kin (NOK) will be provided with a full explanation of the nature, purpose and requirements of the study including a concise Information Sheet at the earliest suitable opportunity. Further, the process of the Consultee will be fully described and explored with them.

3.1 NUMBER OF SUBJECTS AND SUBJECT SELECTION

PILOT:
We estimated to enrol 600-1000 patients during the 3-month pilot period in our CMR unit. This was mainly the consent for data access and re-contact in the future and only a small proportion of patients were asked to donate a blood sample at this stage, solely for feasibility purposes and not driven by scientific rationale, which will be the case for the extended study.

EXTENDED STUDY:
The proportion of patients enrolled annually will depend on available resources, consent rates and other factors.

The Barts BioResource is unique in many aspects, most importantly the ethnic representation, e.g. in our acute coronary artery disease patients with 58% Caucasians, 12% Bangladeshi, 8% Indian, 7% Pakistani, 7% other Asian, 1.5% Black British, 1.5% Caribbean and 5% others.

This ethnic representation will allow scientifically appropriate extrapolation of our findings world-wide.

Human and financial resources available will guide the total number recruited per year. The operational group will advise on which pathways will be prioritised based on scientific merit, feasibility and resources available.

3.2 INCLUSION CRITERIA

The set of criteria that determines that the patient is eligible to participate in the study is:

1. Aged over 18 years.
2. Patients with INCAPACITY will follow the criteria and pathways of Section 1.5.2

OR

3. If Able to understand and voluntarily sign the written Informed Consent Form.
    a) Agrees specifically access and use of routine medical and other health-related records for:
        i. Teaching
        ii. Audits
        iii. Current research and future research
    b) Agrees specifically to the donation of human soft and hard tissue.
    c) Agrees specifically to the additional collections of up to 50ml of venous blood to be collected, processed and retained for research purposes.
    d) Agrees specifically to the donation of saliva, throat, buccal and/or nasopharyngeal swabs, urine, faeces and soft/solid tissue samples available to be collected, processed and retained for research purposes.
    e) Agrees specifically to the retention of residual biological tissues and samples that remain after all clinical requirements are completed and the samples related by the relevant pathology lead.

3.3 EXCLUSION CRITERIA

The set of criteria that determines that the patient is ineligible to participate in the study:

1. Any pre-existing requirement of the clinical team to retain or analyse the excised tissue for routine clinical purposes, for example Histopathology.

3.4 CRITERIA FOR PREMATURE WITHDRAWAL

Estimates of comprehensive withdrawal are 1 in 500 participants (data derived from UK Biobank study protocol). This model entails approximately 5% of subjects withdrawing almost immediately (within the first year) and a subsequent on-going withdrawal rate of 1.4% per annum. Similar estimates were provided by the proportion

of participants in the Whitehall study of Civil Servants who were willing to be re-assessed after about 20 years.

To date the current BBR has recruited >23,400 cardiovascular patients at a primary recruitment rate in excess of 80% approval. Approximately 50 patients have withdrawn their consent. Further, approximately 2,500 patients have been re-consented illustrating an ongoing commitment to inform at retain patient participation (this is recorded as 100% wishing to re-affirm their informed consent). Finally, during this time we have encountered 5 complaints, each of which was resolved transparently and with patient engagement.

Minimal risk, our experience of both recruitment and retention clearly demonstrates the comprehension and cooperation of the patient population. An approximation of drop-out rate may be illustrated by the ~11,000 participants of the NHSBT BioResource (07/Q0104/14) who were written to/emailed and invited to join the NIHR BioResource (17/EE/025); participants were asked to withdraw if they did not want to continue. The withdrawal rate was approximately 4%, however the cohort dated back over 15yrs.
The best interests of the patient will always take precedence over the conduct and continuance of this protocol.

Subjects will be advised that they are free to withdraw from the study at any time for any reason.

In relation to patients who are incapacitated at their time of recruitment, their Next of Kin (NOK) will be advised that they are free to withdraw their family member from the study at any time for any reason and without having to provide a reason.

If necessary, the investigator may withdraw a subject from the study to protect the subject's health. The investigator may withdraw a subject from the study if it is considered that the scientific, and therefore, ethical standards of the study are compromised. Subjects may also be withdrawn for not complying with study procedures. The reasons for withdrawal will be fully recorded.

If a subject is withdrawn from the study because of an adverse event, treatment discontinuation must be explained on the Adverse Event Form, and this subject will be followed-up to the satisfaction of the Chief Investigator, and a withdrawal visit scheduled where possible and appropriate.

The options for withdrawal will be fully explained:

- ***"No further contact":*** This means that the Barts BioResource team would no longer contact the participant directly, but would still have their permission to use information and samples provided previously and to obtain further information from their health-relevant records.

- ***"No further access":*** This means that the Barts BioResource team would no longer contact the participant or obtain information from their health-relevant records in the future, but would still have their permission to use the information and samples provided previously.

- ***"No further use":*** This means that, in addition to no longer contacting the participant or obtaining further information, Barts BioResource team would aim to destroy all of their information and samples collected previously (although the participant would be told that it may not be possible to trace all distributed sample remnants for destruction). Such a withdrawal would prevent information about them from contributing to further analyses, but it would not be feasible to remove their data from analyses that had already been done.

If, having discussed their concerns and options, a participant (or in relation to patients who are incapacitated at their time of recruitment, their Next of Kin (NOK)) decides to withdraw then the investigators will seek written confirmation of the level of withdrawal from the participant/NOK. The Barts BioResource will need to retain some minimal personal data on such individuals for a number of reasons, which include: ensuring that participants who have withdrawn are not re-contacted; and assessing the determinants of withdrawal and any impact on research findings. Participants who withdraw will be assured that this administrative record will not be part of the main database that is available to others.

The Barts BioResource team will not enrol potential participants who express the view that they would want to withdraw should they lose mental capacity or die, because this would reduce the value of the resource for research. But, if a participant decides sometime after enrolment that he or she would wish to be withdrawn in the event of incapacity or death then this request will still be honoured and their consent modified accordingly.

If a participant loses mental capacity or dies, the Barts BioResource team will be guided by the most recent record of the participant's consent. Family members will not be able to withdraw incapacitated or deceased relatives unless the participant's consent was amended accordingly beforehand. In all events, the Barts Bioresource will safeguard the confidentiality and security of participants' data and samples as long as it holds them, including after a person's death.

4.0 STUDY PROCEDURES

Recruitment through each pathway will vary slightly depending on special circumstances.

<u>Research staff training</u>

Research staff consisting of a team of researchers, research nurses, research assistants and/or health care assistants will receive in-house training to ensure adherence to standard operating procedures (SOP) across all areas of the study including consenting patients to the study and high quality data collection according to standard criteria, and to ensure standardisation of data collection as far as possible. It is the responsibility of the study coordinator to source external training for research field staff as required e.g. venepuncture training. Research staff will complete and maintain the *Training Log* for all training undertaken as part of the study.

4.1 INFORMED CONSENT PROCEDURES

PILOT:
Patients referred for an elective CMR study were sent the patient information sheet (see Appendix 7) and relevant consent form (see Appendix 8, 9, 10) with the routine appointment letter. Patients considering involvement were invited to attend the CMR unit 30 minutes prior to their scheduled CMR scan appointment to meet with the research nurse to discuss the study in more detail and to seek consent for participating in the study. On occasions when an appointment was offered within 24 hours of referral, the opportunity for patients to consider participation in the study over an extended period before consenting did not exist. In these cases, the research nurse/ research assistant approached the patient when they arrive for their appointment to discuss the study with them and invited them to take part after screening for study inclusion criteria. If the potential participant was deemed suitable, the Barts BioResource and its nature, purpose, procedures, risks and benefits of the Barts BioResource were explained to the participant (and witness if required).

The participant was given the opportunity to ask any questions arising about the study or documentation. The patient did not and was not coerced into participating in the study.

The Investigator, or appropriately GCP trained person(s) delegated by the Investigator as documented in the site delegation log obtained written (or validated electronic) informed consent from each subject prior to any participation/study specific procedures. This followed adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.

A research nurse or other suitably qualified person took consent. This consent was deemed to be complete and did not require counter signature. This provision was proportional to the risk of participation in that no therapy or treatment was provided (or withheld) above routine clinical management.

Except where the Principal Investigator's signature is specifically required, it is understood that the term 'Investigator' as used in this Protocol and on any CRFs refers to the Principal Investigator or a designated member of the staff that the Principal Investigator designates to perform specified duties of the Protocol. The Principal Investigator is ultimately responsible for the conduct of all aspects of the study.

If the participant wished to speak to a physician (Sub-Investigator) who was present or contactable via telephone, further information was given to the participant and any questions were answered.

The investigator (or other suitably qualified person) explained to the potential participant that they were free to refuse any involvement within the study or alternatively withdraw their consent at any point during the study and for any reason.

If there was any further safety information which may have resulted in significant changes in the risk/benefit analysis, the PIS (Patient Information Sheet) and Informed Consent Form (ICF) would be reviewed and updated accordingly. All subjects that are

actively enrolled on the study are informed of the updated information and given a revised copy of the PIS/ICF in order to confirm their wish to continue on the study.

The programme was also used to develop, assess and validate the PowerTrials™ management system for research (Appendices 10-13).

EXTENDED STUDY:
Patients will be recruited from a range of sources within the hospital such as emergency patients, in-patients acute, in-patients elective, and out-patients. Irrespective of the details of their individual clinical pathway, every patient will be given ample time to consider giving their consent for the study. Extensions to the study will be carefully planned and will only take place if appropriate resources have been identified to consent consecutive patients.

ELECTRONIC CONSENTING (e-Consenting):
Patients eligible for entry to the Barts BioResource will be directed to the use of electronic platforms either on site or at home using an on-line computer based Patient Information/Consent system.

On site, the Barts BioResource staff will approach the competent participants using an electronic device for the consenting process. The device may be used for adults irrespective of the details of their individual clinical pathway and every patient will be given ample time to consider giving their consent for the study. Web links to the online pathway will be supplied with routine clinical correspondence.

Should the patient prefer then an individual information sharing and paper based consenting process will be followed where it is practicable to do so.

Any patient, irrespective of 'traditional' paper-based or eConsenting will be provided with a clear pathway to seek personal one-to-one support, guidance and opportunities to ask questions to facilitate and inform the Informed Consenting Process.

The BBR recruiter will then generate a BBR number. Good Clinical Practice (GCP) will be followed and patients will be provided with a signed copy of their consent form. The consent form will be converted to a PDF and then either emailed (if consent provided) or printed in the clinic or the patient's address can be collected and a signed copy of the form may be mailed to the participant.

Extensions to the study will be carefully planned and will only take place if appropriate resources have been identified to consent consecutive patients. If participants consent and at a later stage wishes to opt out, they will still be given an opportunity to do so at any point after consenting. E-Consent also has the potential to standardise the informed consent process and make it more accessible to a wider range of participants in terms of education, culture and language.

At the completion of the pilot assessment of e-Consenting; the Barts BioResource Operations team directed an audit of the user interface, data integrity, and Public & Patient experience dimensions. The conclusion was that the system was demonstrated to be legally, ethically and technically 'fit for purpose' and then the Barts BioResource

Operations team staged an implementation plan which was executed across the Barts BioResource.

Key elements of the evaluation of the quality control and assurance of the eConsenting platform will be an ongoing evaluation of the core Informed Consenting Process; such as Is the patient competent to consent? Did they read and understand the information provided? Did they make a fully informed decision to consent? Did they opportunity to seek additional support and information? And do they understand their right to withdrawal consent at any time and that this will not affect the standard or type of treatment they will receive from the hospital or doctors, now or in the future?

Further, the proposed e-Consenting platform will enable the delivery of a range of assessments relating to Patient Reported Outcome Measures (PROMS) and Patient Reported Experience Measures (PREMS). The former are standard healthcare activities, such as Sort Form-36 Health Survey (SF-36), General Health Questionnaire (GHQ) and Depression Patient Health Questionnaire (PHQ-9). These documents are in common usage. The latter form the basis of universal healthcare audit within the NHS.

The Barts BioResource Ethics and Operational Groups will review, manage and approve all information released on the e-Consenting Platform via Standard Operating Procedures. Specific review and approval will be gained from the linked Public and Patient Advisory Group.

The development and application of the Electronic Consenting and Information system will reflect the guidance document of the Office for Human Research Protection, US. Department of Health 2016; which is currently the leading resource.

4.2 SCREENING PROCEDURES

Initial PILOT:
There were no specific screening procedures other than those detailed in the Inclusion/Exclusion criteria.

At the time of clinical appointment, the patients had the nature of the study, the procedures and the risks fully explained both verbally and as part of the PIS (Patient Information Sheet). The patients were invited to sign an optional Informed Consent Form in which they acknowledged that they were willing to be enrolled in the study; that they agreed to provide personal particulars to the investigators and recognise that these may be available to non-medical investigators and may be sighted by the Sponsor.

During the screening evaluation the following procedures will be conducted and recorded for all Patients:

- Informed Consent (Section 4.1; Section 8.6.3)
- Evaluation of compliance with inclusion and exclusion criteria (Sections 3.2 and 3.3)

- Access to the result of relevant existing or planned laboratory tests; including clinical imaging, haematology and biochemistry.

Patients who satisfy all of the inclusion and exclusion criteria, who signed the Consent Form, and who agree to the conditions of the study, were eligible to enter the study.

EXTENDED STUDY:
The procedures are the same as described for the pilot study the exception is for Incapacitated patients.

Generally, and with reference to the COVID19 pandemic, Barts Health NHS Trust have a number of patients who are intubated on ventilators or for other clinical management, and therein lack capacity.

This is specifically relevant to all patients in the NHS Nightingale hospital and in the Barts Health NHS Trust Intensive Care Units. It is in the National Interest, and also potentially in the interest of the patient's welfare, that their clinical information and biological samples are collected and made available to research teams.

This section of the protocol seeks to recruit patients lacking capacity (such as those on ventilators, severe trauma, cardiogenic shock and similar) to the BBR programme. The following are the required considerations to achieve this in an ethical and legal framework:

Some patients may have an Advanced Directive in place, if this is established in a timely manner then we will conduct their care and potential BBR participation in accordance with their wishes.

We acknowledge the HRA guidance on research without consent, that it can be justified if the gravity of the rights infringement is minor and outweighed by the expected social value of the research and obtaining consent is impractical. We propose that this test is clearly met with reference to:

http://www.hra-decisiontools.org.uk/consent/principles-ALC-EnglandandWales.html

We further note and refer to the Medical Research Council's guidance of the **Key principles when considering the participation of adults who lack capacity in research**

- *The interests of the individual must always outweigh those of science and society.*
- *The research must relate to a condition or impairment that affects the individual or the treatment of this condition.*
- *It must not be possible to conduct equally effective research with adults who have the capacity to consent.*

- *The potential benefits of the project should outweigh the risks: the level of acceptable risk depends partly on the possible benefit to the individual.*
- *Views of those close to the participant should always be sought, unless this is not possible due to circumstances.*
- *A participant who lacks capacity should only be included in a study when there are no indications that he or she objects to this.*

Wherever possible, Next-of-Kin will be consulted as "Consultee" in relation to their understanding of the wishes and intentions of the patient, this will be supplemented with the opinion of the nominated clinician (Nominated Consultee) not involved in any Barts BioResource research present or in future on the data/samples.

As Next-of-Kin [NOK] will generally not be physically present during the current pandemic, the pathway will be by a nominated clinician (Nominated Consultee), not involved in any Barts BioResource research present or in future on the data/samples; followed by informing the NOK (their wishes to be observed) as soon as is reasonably practicable and appropriate, and finally informed written consent with the patient should they hopefully recover.

Should participants regain capacity we will involve them in the on-going consent process at the earliest appropriate opportunity. In most cases it is appropriate to ask them to give their own consent when and if they are able. Both the Consultees and the Nominated Consultees will be informed of this intention at the outset. We have prepared an appropriate Participant Information Sheet and consent form for the participants themselves that explains what has happened so far, and what you are seeking their consent for.

The Consultees are not asked to give consent on behalf of the adult, but rather to provide an opinion on the views and feelings of the potential participant. Further, the consultee will be

[a] Told that they are being asked to advise on the views and feelings they believe the adult would have towards participation in the BBR study.

[b] Told that they are free to decide whether they wish to provide this advice or not and

[c] Given sufficient information, in an understandable form, about the BBR study to ensure that they provide you with informed advice.

To this end, we are working directly with the Safeguarding Leads at each individual hospital site to ensure compliance and transparency of the BBR activities and clearly document such activities.

During the COVID-19 restriction of travel, a consent form may be sent electronically to participants who have expressed interest in volunteering to the Barts BioResource.

The participant would, if possible print, sign and then scan and return the completed consent form electronically, keeping the original, or they could sign the consent form electronically and return it electronically.

Telephone/electronic means support by Barts BioResource staff would be available to ensure any queries are answered and the participant provides informed consent. An offer to record the conversation could be made if the volunteer wishes and is feasible (and securely stored until full consent is received), but no recording will be done without asking the volunteer first and the volunteer explicitly consenting to recording the conversation.

For Incapacitated hospitalised patients, where necessary verbal consent from a Consultee will be sought in the first instance via telephone/ electronic means conversation. This verbal consent will be documented (or recorded, with the Consultee's explicit consent to record the conversation) and sent electronically to the Consultee, alongside the full consent form for signature and return to the study team.

The same approach will be applied to the Next of Kin as soon as is reasonably practicable and appropriate.

The BBR will develop a robust, transparent and auditable withdrawal system prior to recruitment of these patients and will regularly review such.

Further, we note the principles, provisions and requirements of the Mental Capacity Act 2005 and our teams are experienced in this area.

4.3 RANDOMISATION PROCEDURES

Not applicable.

4.4 SCHEDULE OF TREATMENT FOR EACH VISIT

Initial PILOT:
Current clinical practice:
All patients referred for CMR scans were sent information sheets explaining the scan procedure and a questionnaire asking questions relevant to safety using MRI.

On the day of the appointment, they were seen by a clinician/ radiographer authorised for MRI and the 'Safety Questionnaire' verified for eligibility to MRI scanning, administration of gadolinium contrast and in cases of perfusion imaging to adenosine, a pharmacological stressor agent.

Almost all patients (95%) needed one intravenous cannula inserted to enable delivery of contrast ± stressor agent during the scan. The current scan time varied from 30 to 45 minutes depending upon the clinical question and thus the type of image sequences performed.

Subsequent Approved changes:
All competent patients will continue to receive information as before with the addition of the information sheet inviting participation for the any of each of the following:

- Opportunity to (re-) review the patient information sheet and to meet the research nurse to have any remaining related questions answered (up to 15 mins)
- Consenting to this research study (3-5 mins)
- Blood sampling (in majority of the cases via the intravenous cannula as is clinical practice, thus in almost all cases no additional needle insertion necessary, 3-5 mins)

It is always highlighted that their participation is solely voluntary for each of the above (may consent to participate in one or more) and by no means will it affect their proposed clinical management.

This section applies to **both the Initial Pilot and the Extended study protocol**:

- No additional visits or treatments are required by this protocol.
- Patients who agree to donations of up to 50ml venous blood sample(s) per occasion will have the blood collected at the time of routine clinical venepuncture. An additional venepuncture will be necessary if no clinical venepuncture is scheduled to be performed on the patient attendance.
- The donation of saliva, throat, buccal and/or nasopharyngeal swabs, urine, faeces and soft/solid tissue samples that will be collected, processed and retained are for research purposes as defined by the BBR protocol.
- Consented patients who are undergoing surgery will have tissue samples harvested by the appropriate clinical professional.

4.5 FOLLOW UP PROCEDURES

This section applies to **both the Initial Pilot and the Extended study protocol**:

- Certain sub-studies may require follow-up via phone if patients agreed to be contacted in the future (separate ethics approval will be sought).
- Review routine medical and other health-related records both within the hospital and externally as required.

- Information via Central Registries and Data Controllers (such as hosted by NHS Digital, HQIP/NICOR and others including primary care data, Hospital episodes statistics (HES), and death registry formerly via Office for National Statistics, ONS).
- Information from GPs or their central registries if available.

4.6 LABORATORY ASSESSMENTS

- Samples will be stored under the Human Tissue Act license and will be stored at Barts Health NHS Trust temporarily before being shipped to Charterhouse Square (Queen Mary University of London) and Biocentre South for more permanent storage.
- The amount of blood to be sampled in the study (up to 50 ml where applicable) is not considered significant in adult subjects.

Location of sample analysis is not determined and will vary from project to project. Appropriate material transfer agreements will be in place prior to transferring material for analysis to approved laboratories.

The purpose of this consenting project (the now completed pilot and the current extended study) is to gain consent to allow researchers, educationalists and clinicians preparing audits to rightfully access clinical data, to allow future contact for follow-up or recruitment into new research studies, taking and storing biological material (blood, saliva, throat, buccal and/or nasopharyngeal swabs, urine, faeces and any other biological samples available plus relevant human soft/solid tissue samples and to allow more detailed analysis of existing clinical data (e.g. MRI, ultrasound, echocardiogram, electroencephalogram or similar monitoring/measuring modalities).

At this time, outside the routine clinical pathology indicated for each patient, no specific laboratory assessments have been planned. Blood, saliva, throat, buccal and/or nasopharyngeal swabs, urine, faeces and any other biological samples available, plus human soft/solid tissue samples, donated for this research project can be analysed in the future without repeat consent similar to the approach taken in UK Biobank (www.ukbiobank.ac.uk) and the NIHR BioResource. As described in the ethical issues section above, clinically relevant findings made by these laboratory tests will be fed back to the patients according to the duty of care to our patients.

Development of this protocol for the collection of biological samples was led by a number of key principles. In particular, the aim should be to collect samples that would allow the widest possible range of assays that could plausibly be envisaged for the future, and to avoid collection, processing or storage approaches that would inherently preclude such assays (i.e. “future proof” the collection as far as possible given current knowledge and available resources).

The coordinating centre laboratories Standard Operating Procedures will detail the samples to be collected, the preliminary processing and storage temperatures, the

transport of samples to a central processing facility, and the processing, aliquoting and storage of each sample (including barcoding).

4.7 END OF STUDY DEFINITION

Initial Pilot:
The 3- month pilot study informed the logistics required to extend the study. We moved stepwise to the extended study as resources could be identified based on the information provided by the initial pilot study, adding additional patient pathways for recruitment. If changes to the protocol were required, an amendment would be submitted to the ethics committee. If no changes to the protocol were required, Barts Health R&D (Operational group) would sign off any extension to additional patient pathways, if feasibility is likely, i.e. sufficient human and financial resources are available to perform the study and if of sufficient scientific priority.

Extended study:
The current intention of the study is to recruit patients for 10 years (if extended we will apply for major amendment). Samples will be stored for a minimum of 10 years. The end of the study is thus after 20 years; although subject to revision with regulatory approvals.

4.8 PROCEDURES FOR UNBLINDING

Not applicable.

4.9 SUBJECT WITHDRAWAL

Subjects will be withdrawn from the **Barts BioResource** if the subject withdraws consent. Withdrawal procedures reflect the types of withdrawal outlined in Section 3.4.

4.10 DATA COLLECTION AND FOLLOW UP FOR WITHDRAWN SUBJECTS

See Section 4.9

The options for withdrawal will be fully explained:

"No further contact": This means that **Barts BioResource** team would no longer contact the participant directly, but would still have their permission to use information and samples provided previously and to obtain further information from their health-relevant records.

"No further access": This means that **Barts BioResource** team would no longer contact the participant or obtain information from their health-relevant records in the future, but would still have their permission to use the information and samples provided previously.

"**No further use**": This means that, in addition to no longer contacting the participant or obtaining further information, **Barts BioResource** team would aim to destroy all of their information and samples collected previously (although the participant would be told that it may not be possible to trace all distributed sample remnants for destruction). Such a withdrawal would prevent information about them from contributing to further analyses, but it would not be feasible to remove their data from analyses that had already been done.

These patients will be removed from any data registry relating to the **Barts BioResource** and any donated samples stored in house will be destroyed in accordance with our Standard Operating Procedures.}

In relation to patients who are incapacitated at their time of recruitment, their Next of Kin (NOK) may also direct the "No further use" option which will be respected and acted on in accordance with our Standard Operating Procedures.
Donated samples stored at the long term sample storage supplier will be destroyed in accordance with the SOP.

5.0 LABORATORIES

See also Section 4.6

5.1 CENTRAL/LOCAL LABORATORIES

Associated BBR delivery organisation laboratories used for the short-term storage of tissue and biological samples will be subject to Standard Operating Procedures and the HTA licence held by Barts Health NHS Trust.

Laboratories used for the long-term storage of tissue and biological samples will be subject to the supplier's Standard Operating Procedures and HTA licence.

Type and location of sample analysis is not determined for the Barts BioResource . As per access procedures specific research projects will determine the most cost-effective and appropriate laboratory for analysis and samples will not be released until the Barts Health NHS Trust approved Material Transfer Agreement has been signed by all parties.

5.2 SAMPLE COLLECTION/LABELLING/LOGGING

Collection of Blood Samples

Barts BioResource personnel will follow detailed Standard Operating Procedures for processing, logging and storage of samples, including adverse event standard procedure and reporting. A blood sample (up to 50 ml) will be obtained from all consented individuals by a nurse/ technician trained in cannulation and venepuncture. A summary of the blood processing procedure is provided in Figure 2 below.

Up to 50mls of blood will be collected into aliquots. These will include 2x 4.5ml EDTA, 1x 5ml PST, 2x 5.0ml STT/gel, up to 2x 2.5ml PAXgene for RNA and a 20 ml “floating” sample. The floating sample will be available and processed for specific projects in accord with access applications approved by the Barts Heart Centre peer review committee. Blood will undergo on−site processing and samples will be aliquoted into bar coded cryovials as follows: EDTA (plasma) to 9 cryovials, EDTA (white cells) to 2 cryovials, LH (PST) up to 4 cryovials, SST up to 8 cryovials, PAXgene RNA to up to 10 cryovials (Figure 2).

Each cryovial will be individually logged into the Barts BioResource database (LIMS) by research staff using a bar-code reader and then stored in a secure location on-site in an appropriate freezer aligned to the appropriate management of the samples obtained (e.g. -20ºC, -40ºC or -80ºC freezers). Samples will be collected on an approximately monthly basis by secure courier and transported on dry ice for long term storage with a 3rd party supplier where they will be stored at an appropriate temperature until they are retrieved for analysis, which may be up to 20 years after sampling.

Samples will be stored with the National Biosample Centre (‘biocentre’) under contract with the Sponsor and/or its delivery partners to access the logistical requirements before a long-term solution is confirmed (Figure 3).

Residual tissue will be collected on a case-by-case basis according to routine pathology practice.

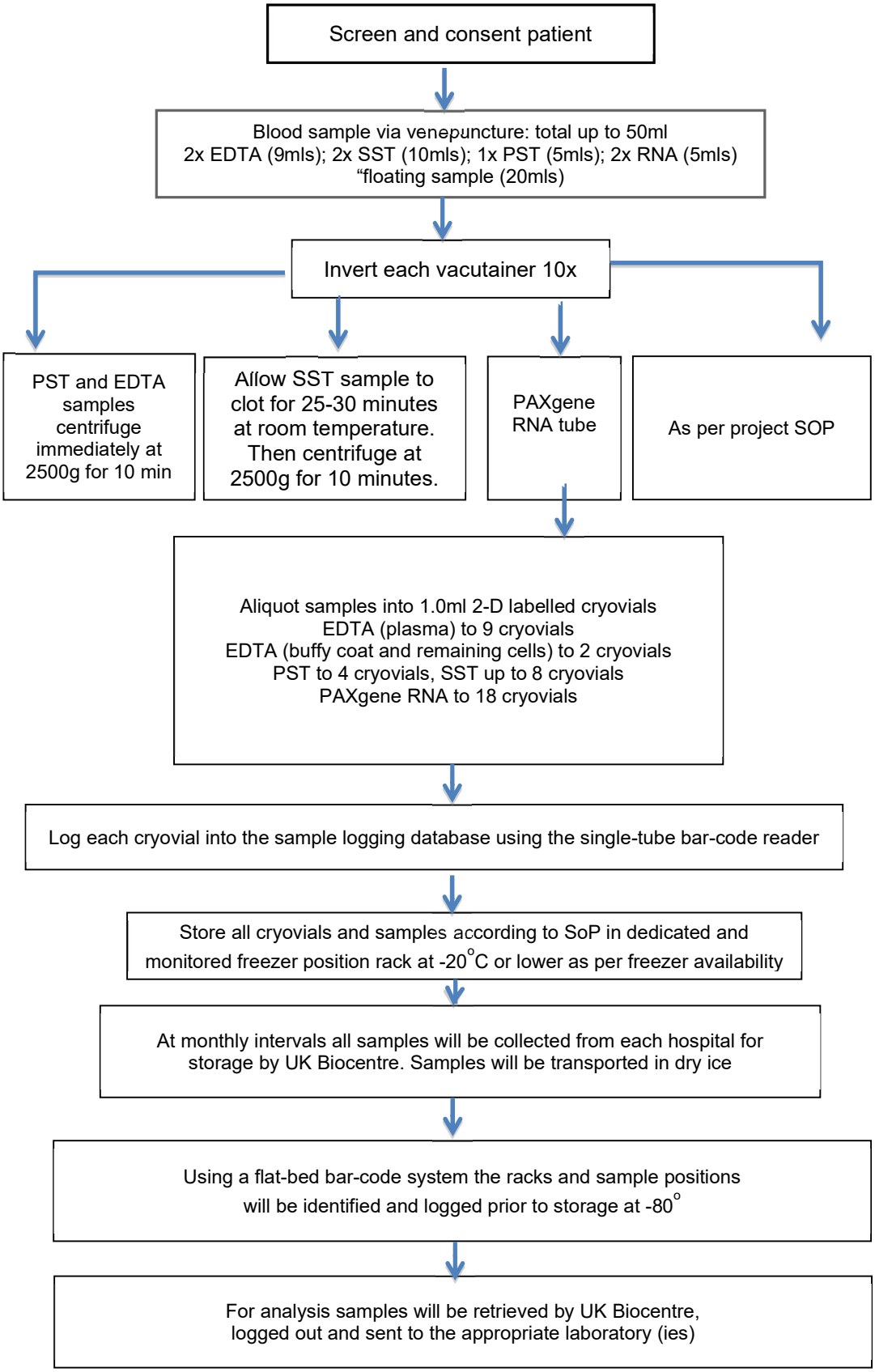


Figure 1: Summary of an Example Standard Operating Procedure (SOP) for Business As Usual processing and on-site short term storage of research biological samples (blood, saliva, throat, buccal and/or nasopharyngeal swabs, urine, faeces, soft/hard tissues and any other biological samples available).

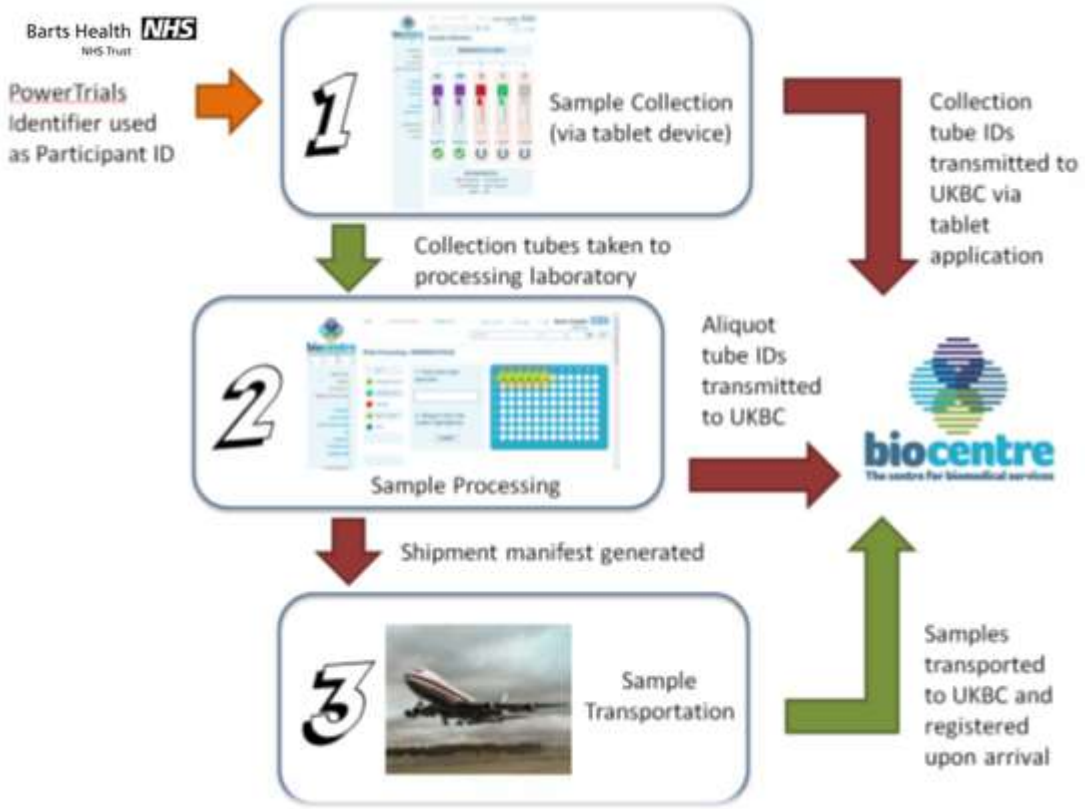


Figure 2: Summary of logistics pathway for sample storage and transfer.

Labelling of all study biological materials:

- Subject Number
- Date of Collection
- Sampling Time (nominal)
- Protocol No.

All samples collected within this protocol will be recorded on a Laboratory Management Information System, which will further record subsequent patient consent, tracking and tracing of samples, temperature control of samples and locations

Short–term sample storage facilities will be within associated Barts BioResource delivery organisations *and samples will be stored until collection by long-term storage supplier.*

Long-term storage and management of biological samples

Samples will be appropriately sent to the party or parties contracted to handle the samples for extraction of biological material e.g. extraction of RNA or analysis e.g. for

circulating biomarkers at the appropriate time and will be carried out in accordance with the analytical plan agreed with the Chief Investigator.

5.3 SAMPLE RECEIPT/CHAIN OF CUSTODY/ACCOUNTABILITY

For both short-term and long-term sample storage handling of the samples upon arrival at the laboratory will to be documented. Upon receipt of the samples, the laboratory should ensure that the physical integrity of these samples have not been compromised in transit. If any damage has occurred or the samples have been compromised in any way it is important that the study team, as well as the Sponsor, are informed of this immediately. Upon receipt of samples laboratory staff should ensure that all samples are accounted as per the labelling. All samples received should be logged in an accountability log.

5.4 TISSUE MANAGEMENT AND ANALYSIS

UK Biobank's sample handling studies have demonstrated that maintaining whole blood samples at 4°C for at least 36 hours prior to processing and cryopreservation allows a very wide range of assays to be performed.

All tissue donated and collected for the protocol will be accessed only for the purposed outlined in this protocol and linked protocols as approved by Research Ethics Committees.

Samples will be tested until completely utilised, however, any residual derivative materials (such as cell culture and histological samples) will be discarded following completion of the various assays and where this is no further scientific value in their continued storage

Storage of the samples will be undertaken within the reference and definition of the Human Tissue Act 2004.

The *Chief Investigator* and designated deputies will oversee and audit the process of materials transfer and distribution to the recipient groups within the Barts Health NHS Trust and research groups within Queen Mary, University of London (such as The William Harvey Research Institute). Transfer and distribution to partner organisations with the UK, Europe and Worldwide will occur in accordance to documented materials transfer agreements.

5.5 SAMPLE ANALYSIS PROCEDURES

This protocol was led by a number of key principles. The bioresource aims to collect samples allowing the widest possible range of assays that could plausibly be envisaged for the future, and to avoid collection, processing or storage approaches that would inherently preclude such assays (i.e. "future proof" the collection as far as possible given current knowledge and available resources).

Sample Type	Selection Criteria
Blood	• Variety of fractions: plasma, serum, white cells, red cells, peripheral blood lymphocytes • Wide range of biomolecules: DNA, RNA [5' ends], proteins, analytes • Wide physiological coverage: genome, proteome and metabolome, haematological parameters • Suitable for a very wide range of assay technology • Ease and low cost of collection
Saliva, throat, buccal and/or nasopharyngeal swabs	• Wide range of biomolecules: DNA, RNA, proteins, lipids • Wide physiological coverage: genome, proteome • Suitable for microbial/fungal/viral species detection, biomarkers • Suitable for a wide range of assay technology • Ease and low cost of collection
Urine and faeces	• Range of biomolecules: DNA, protein • Physiological coverage: metabolomics, biomarkers, hormones, ions • Suitable for a wide range of assay technology • Ease and low cost of collection
Soft/solid tissue samples	• Biomolecules: DNA, RNA [5' ends], proteins, analytes • Wide physiological coverage: genome, proteome and metabolome • Suitable for a very wide range of assay technology • Research samples will be collected following clinical biopsy (if performed) and only if minimal risk to patient.

5.6 SAMPLE STORAGE PROCEDURES

Samples will be stored according to GCP and the Barts Health NHS Trust Tissue Bank policies.

5.7 DATA RECORDING/REPORTING

All study-related data will be recorded on CRF documents and/or electronically according to GCP standards and Barts Health NHS Trust policies.

The programme will also be used to develop, assess and validate the PowerTrials™ management system for research (Appendices 10-13).

6.0 PHARMACOVIGILANCE

Not applicable to current protocol has no treatment or therapy is a consequence of planned actions.

6.1 GENERAL DEFINITIONS

6.1.1 Adverse Event (AE)

During any clinical study, onset of Adverse Events may occur. An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or intervention and that does not necessarily have a causal relationship with this treatment (where 'treatment' includes also all investigational agents such as comparative agents and placebo). An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease.

All adverse events encountered during the clinical study are to be reported on the Adverse Event Forms contained in the Case Report Form (CRF). For each adverse event which occurs during the clinical study the Principal Investigator will give a judgment on its severity and make a causality assessment of the treatment using one of the four given definitions: certainly related, probably related, possibly related and definitely unrelated. Moreover, the Principal Investigator will indicate the action to be taken for the adverse event that has occurred and its outcome.

In the case of an adverse event, the trained medical personnel will act with appropriate diagnostic and therapeutic measures until the subject has recovered. Adverse events will be classified as 'serious' and 'non serious'. All this information will be recorded for each adverse event on the Adverse Event Form of the CRF. Detailed information on the compilation of the Adverse Event Form is available in Appendix 1.

6.1.2 Serious Adverse Event (SAE)

An SAE fulfils at least one of the following criteria:

- Is fatal – results in death (NOTE: death is an outcome, not an event)
- Is life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is otherwise considered medically significant by the Investigator

Serious adverse events will be reported to the Principal Investigator and the Sponsor (see Section 6) within 24 hours. The 24 hours emergency contact numbers are listed on page iii of this protocol.

Serious adverse events will also be reported to:

- Barts Health NHS Trust, School of Medicine and Dentistry, Joint Research Office.

- National Research Ethics Service (NRES) approved Research Ethics Committee (the responsibility of the investigator) as soon as possible, but in any case, within 72 hours.

All available information will be provided, referring to the Serious Adverse Event paragraph of the Reporting Adverse Events document (Appendix 1). The Investigator will complete the Serious Adverse Event Form by carefully following the relevant instructions (Appendix 1) and will fax it within 24 hours to the Sponsor.

The Investigator, and others responsible for subject care, should institute any supplementary investigations of serious adverse events based on their clinical judgment of the likely causative factors. This may include seeking further opinion from a specialist in the field of the adverse event.

The Sponsor may also request extra tests. Continuation of the trial will be contingent upon approval from an independent safety review Committee.

6.1.3 Non Serious Adverse Events

A non-serious adverse event is one, which does not meet any of the criteria listed in the Section 6.1.3 defining serious adverse events, which is otherwise judged by the Investigators as significant.

If a non-serious adverse event occurs, the Investigator will fill in one Adverse Event Form for each adverse event describing its complete evolution to the outcome. Therefore the assessment of severity, frequency and causality will be given at the event outcome. The completed Adverse Event Form will be sent to the Sponsor.

During a clinical study, an adverse event previously reported as a non-serious event may change becoming, upon the Investigator's clinical judgment, a serious adverse event (i.e. dramatic worsening with hospitalisation etc.). At this moment, the Investigator will follow directions for reporting a serious adverse event.

6.2 INVESTIGATORS ASSESSMENT

6.2.1 Seriousness

The Chief/Principal Investigator responsible for the care of the patient, or in his absence an authorised medic within the research team, is responsible for assessing whether the event is serious according to the definitions given in Section 6.1.2.

6.2.2 Causality

The Investigator must assess the causality of all serious adverse events in relation to the trial treatment according to the definition given

6.2.3 Expectedness

The investigator must assess the expectedness of all SAEs according to the definition given. If the SAE is unexpected and related, then it needs immediate reporting.

6.2.4 Severity

The Investigator must assess the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on patient/event outcome criteria.

Mild: Some discomfort noted but without disruption of daily life

Moderate: Discomfort enough to affect/reduce normal activity

Severe: Complete inability to perform daily activities and lead a normal life

6.3 NOTIFICATION AND REPORTING ADVERSE EVENTS OR REACTIONS

If the AE is not defined as SERIOUS, the AE is recorded in the study file and the participant is followed up by the research team. The AE is documented in the BRC database, participants' medical notes (where appropriate) and the CRF (where appropriate).

6.4 NOTIFICATION AND REPORTING OF SERIOUS ADVERSE EVENTS

6.4.1 Serious Adverse Event (SAEs)

That are considered to be 'related' and 'unexpected' are to be reported to the Sponsor within 24 hours of learning of the event and to the Main REC within 15 days in line with the required timeframe. For further guidance on this matter, please refer to Appendix 2

6.5 URGENT SAFETY MEASURES

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety, in accordance with Regulation 30. The measures should be taken immediately. In this instance, the approval of the Licensing Authority Approval prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the

Sponsor and Main Research Ethics Committee (via telephone) of this event immediately.

The CI has an obligation to inform both the Main Ethics Committee in writing within 3 days, in the form of a substantial amendment. The Sponsor (JRO) must be sent a copy of the correspondence with regards to this matter. For further guidance on this matter, please refer to (Appendix 1).

6.6 ANNUAL PROGRESS AND SAFETY REPORTING

The CI will send the Annual Progress Report to the main REC using the NRES template (the anniversary date is the date on the MREC "favourable opinion" letter from the MREC) and to the Sponsor.

6.7 PROCEDURES FOR REPORTING BLINDED 'UNEXPECTED' AND RELATED' SAES

In the case of a blinded study, it is recommended the treatment code for the patient is broken in the reporting of an 'unexpected and related' SAE. However, the blind should be maintained, where possible and appropriate, for staff that are involved in data analysis and interpretation. It is the allocated responsibility of the CI by the

Sponsor for vigilance management and reporting. In this instance, an allocated unblinded individual (s), with no involvement in data management of the study should be responsible for the unblinding event. The unblinding of single cases by the PI/CI in the course of a clinical trial should only be performed if necessary for the safety of the trial subject.

It is recommended that in the case of a blinded study, the case is assessed for seriousness, expectedness and causal relationship as if it was study procedures that caused the reaction. If the case appears to be an 'unexpected and related' SAE then it should be unblinded and should be reported to the appropriate Main Research Ethics Committee within the required timelines outlined in section. For further guidance on this matter, please refer to Appendix 1.

6.8 OVERVIEW OF THE SAFETY REPORTING PROCESS/VILIGANCE RESPONSIBILITIES

The CI/PI has the overall vigilance oversight responsibility. The CI/PI has a duty to ensure that vigilance monitoring and reporting is conducted in accordance with the Sponsor's requirements.

7.0 STATISTICAL CONSIDERATIONS

The data derived from the BRC Bioinformatics systems will not be analysed in isolation, but will form a core resource for Teaching, Research and Service development activities.

As such as formal statistical plan is not appropriate or required. All of the Investigators are experienced in medical statistics and clinical research.

7.1 PRIMARY ENDPOINT EFFICACY ANALYSIS

See above.

7.2. SECONDARY ENDPOINT EFFICACY ANALYSIS

See above.

7.3 SAFETY ENDPOINTS

Not applicable.

7.4 SAMPLE SIZE

Initial PILOT:
We aimed to approach most patients attending a CMR scan at Barts Health NHS Trust during the three month recruitment period. This was likely to be 600-1000 patients.

EXTENDED STUDY:
We aim to recruit as many patients as possible and as human and related resources allow (for consenting).

7.5 STATISTICAL ANALYSIS

See 7.0

8.0 DATA HANDLING & RECORD KEEPING

The conduct of the study will be monitored by the Investigators, and if required by a representative of the Sponsor in accordance with the GCP Guidelines. The investigator will co-operate fully with any study monitors and auditors.

The organisation, monitoring, and quality assurance of the present clinical study is the responsibility of the Sponsor.

In order to ensure the accuracy of data, direct access to source documents by the representatives of both the Sponsor is mandatory. Anonymity of the subject will be maintained at all times.

8.1 CONFIDENTIALITY

The Investigator has a responsibility to ensure that patient anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. Information with regards to study patients will be kept confidential and managed in accordance with the eight core principals of the Data Protection Act (2018), NHS Caldicott Guardian provisions, The Research Governance Framework for Health and Social Care (Second Edition 2005), NRES Research Ethics Committee Approval and the regulations of the Barts Health NHS Trust.

Subjects will be informed that their data are held on file, that these data may be viewed by Sponsor on behalf of the Sponsor and by external auditors on behalf of either the Sponsor or regulatory agencies. They will similarly be informed that this data and a report of the study will be submitted to the Sponsor and may also be submitted to government agencies and perhaps for publication, but that they will only be identified in such reports by their study identification number, initials and perhaps their gender and age. The investigators undertake to hold all personal information in confidence.

8.2 STUDY DOCUMENTS

- A signed protocol and any subsequent amendments
- Sponsor Self-Monitoring template for the trial team to complete on a regular basis as detailed by the Monitoring section
- Current/superseded Patient Information Sheets (as applicable)
- Current/superseded Consent Forms (as applicable)
- Indemnity documentation from Sponsor
- Conditions of Sponsorship from Sponsor
- Conditional/final R&D Approval
- Signed site agreement
- Ethics submissions/approvals/correspondence
- CVs of CI and site staff
- Delegation logs
- Staff training logs
- Site signature logs
- Patient identification logs

- Screening logs
- Enrolment logs
- Protocol training logs
- Correspondence relating to the study
- Communication Plan between the CI/PI and members of the study team
- SAE reporting plan for the study

8.3 CASE REPORT FORM

Presentation of the CRF
The CRF to be used for the study consists of pages that contain within the header or footer the Protocol number, subject initials, subject number and other relevant information. It is composed of an introductory section for the selection and inclusion of subjects in the study and a section for the treatment period. Contained within the treatment period section are the forms for registration of possible adverse events and for any suspension of the study.

How to use the CRF
All CRFs will be completed using a ball-point pen with black ink. All unused CRFs for drop-outs must be retained.

All requested information must be entered on the CRFs. If an item is not available or is not applicable, this fact should be indicated; there should be no blank spaces. Corrections should be made by striking through the incorrect entry with a single line and by entering the correct information adjacent to it. The correction must be initialled and dated by an Investigator or a designated qualified individual. Each set of completed CRFs must be reviewed, signed and dated by an Investigator. The completed original CRFs are to be returned to the Sponsor as soon as is practicable after completion and review. A photocopy of each completed CRF is to be retained by the Investigator.

8.3 STUDY COMPLETION OR DISCONTINUATION

Upon completion of the study, the following activities, when applicable, must be conducted by the Investigator Investigators, as appropriate:

- Return of all study data to the Barts Health NHS Trust.
- Data clarifications and/or resolutions.
- Review of site study records for completeness.

In addition, Barts Health NHS Trust, Queen Mary, University of London and the Principal *or* Chief Investigator reserve the right to temporarily suspend or prematurely discontinue this study for any reason. If such action is taken, Barts

Health NHS Trust will discuss this with the Investigator (including the reasons for taking such action) at that time.

If the study is terminated for safety reasons, Barts Health NHS Trust / Queen Mary, University of London will promptly inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. The Investigator must inform the Ethics Committee promptly and provide the reason for the suspension or termination. After such a decision, the investigator must call in all participating subjects within a reasonable time period. At this visit all medical files and case report forms must be completed as far as possible.

If the study is prematurely discontinued, all study data must be returned to the Barts Health NHS Trust.

8.5 RECORD RETENTION AND ARCHIVING

During the course of research, all records are the responsibility of the *Chief Investigator* and must be kept in secure conditions. When the research trial is complete, it is a requirement of the Research Governance Framework and Trust Policy that the records are kept for a further 20 years.

For trials involving Barts Health NHS Trust patients, undertaken by Trust staff, or Sponsored by Barts Health NHS Trust or QMUL, the approved repository for long-term storage of local records is the Trust Modern Records Centre which is based at 9 Prescott Street. Site files from other sites must be archived at that external site and cannot be stored at the Modern Records Centre.

8.5 COMPLIANCE

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

8.6 CLINICAL GOVERNANCE ISSUES

8.6.1 Ethical Considerations

A complete assessment of the Rationale and Risks/Benefits may be found in Section 1.4 and a full exploration of the Ethical Issues is presented in Section 1.5.

The study will be conducted in accordance with the principles of the Declaration of Helsinki (Recommendations guiding Medical Doctors in Biomedical Research Involving Human Subjects).

The study will be conducted in accordance with the guidance of the Human Tissue Authority relating to the Human Tissue Act 2004.

The Investigators will take care to minimise any discomfort experienced by subjects during these studies. The only invasive procedure will be blood collection by cannulation. The amount of blood to be sampled in the study (50mL where applicable) is not considered to be significant in adult subjects.

To ensure compliance with the Mental Capacity Act 2005 and HRA guidance in relation to the recruitment of patients lacking capacity, we are working directly with the Safeguarding Leads at each individual hospital site to ensure compliance and transparency of the BBR activities and clearly document such activities.

8.6.2 Ethical Review Committee

The Protocol, core Consent Forms and Subject Information Sheets will be submitted to a National Research Ethics Service (NRES) approved Research Ethics Committee before patients are recruited and subjects are enrolled. The Investigators will receive all the documentation needed for submitting the present Protocol to the Ethics Committee. No study activities will be initiated until the written approval of that Committee is received. A copy of the respective approval letters will be transmitted to the Sponsor before starting the study. The composition of the Ethics Committee will also be provided to the Sponsor. If approval is suspended or terminated by the Ethics Committee, the Investigator will notify the Sponsor immediately.

It is the responsibility of the Investigator to report study progress to the Ethics Committee as required or at intervals not greater than one year.

The Investigator will be responsible for reporting any serious adverse events to the Ethics Committee as soon as possible and in any event within 72 hours.

This protocol and any subsequent amendments, along with any accompanying material provided to the patient in addition to any advertising material will be submitted by the Investigator to an Independent Research Ethics Committee. Written approval from the Committee must be obtained and subsequently submitted to the JRO to obtain Final R&D approval.

8.6.3 Informed consent

Before enrolment into the study, competed subjects will be fully informed of the nature of the study, and all relevant aspects of study procedures. Each prospective candidate will be provided with the Privacy Information and the Information for Patients Sheet.

Consent forms shall be signed and dated by the appropriate parties or appropriately notarised in the case of or validated electronic consenting systems.

A notation that written informed (or validated electronic) consent has been obtained will be made on the subject's database records. Completed Consent Forms will be retained by the Investigator and a copy of this will be provided by the Investigator to the subject.

The Informed Consent Forms are included as part of the submission to the Ethics Committee.

We acknowledge the HRA guidance on research without consent, that it can be justified if the gravity of the rights infringement is minor and outweighed by the expected social value of the research and obtaining consent is impractical. We propose that this test is clearly met with reference to:

http://www.hra-decisiontools.org.uk/consent/principles-ALC-EnglandandWales.html

We further note and refer to the Medical Research Council's guidance of the **Key principles when considering the participation of adults who lack capacity in research:**

- The interests of the individual must always outweigh those of science and society.
- The research must relate to a condition or impairment that affects the individual or the treatment of this condition.
- It must not be possible to conduct equally effective research with adults who have the capacity to consent.
- The potential benefits of the project should outweigh the risks: the level of acceptable risk depends partly on the possible benefit to the individual.
- Views of those close to the participant should always be sought, unless this is not possible due to particular circumstances.
- A participant who lacks capacity should only be included in a study when there are no indications that he or she objects to this.

Wherever possible, Next-of-Kin will be consulted in relation to their understanding of the wishes and intentions of the patient, this will be supplemented with the opinion of the nominated clinician (Consultee) not involved in any BBR research present or in future on the data/samples.

As Next-of-Kin [NOK] will generally not be physically present during the current pandemic, the pathway will be by a nominated clinician (Consultee) not involved in any BBR research present or in future on the data/samples; followed by informing the NOK (their wishes to be observed) as soon as is reasonable practicable and appropriate, and finally informed written consent with the patient should they hopefully recover.

The Consultees are not asked to give consent on behalf of the adult, but rather to provide an opinion on the views and feelings of the potential participant. Further, the consultee will be:

[a] Told that they are being asked to advise on the views and feelings they believe the adult would have towards participation in the BBR study.

[b] Told that they are free to decide whether they wish to provide this advice or not; and

[c] Given sufficient information, in an understandable form, about the BBR study to ensure that they provide you with informed advice.

To this end, we are working directly with the Safeguarding Leads at each individual hospital site to ensure compliance and transparency of the BBR activities and clearly document such activities.

The BBR will develop a robust, transparent and auditable withdrawal system prior to recruitment of these patients and will regularly review such.

Further, we note the principles, provisions and requirements of the Mental Capacity Act 2005 and our teams are experienced in this area.

8.6.4 Subject Reimbursement

There will be no financial reimbursement to the patients for participation.

8.6.5 Emergency Contact with Investigators

The nature of the protocol precludes the requirement for clinical emergency contact. However, the patients may contact the research team for any further information regarding their participation in the study such as withdrawal, data protection issues and outcome feedback of the study.

8.6.6 Notification / Contact of Primary Care Physician

The primary care Physician will not be notified of the patient's study participation, as this information has no relevance to the continued care of the subject. However, subject to patient informed consent, the primary care Physician may be approached for clinical update and confirmation of patient status.

8.6.7 Investigator Indemnification

Indemnity is provided by the Barts Health NHS Trust.

Details of insurance cover have been forwarded to the NRES recognised Ethics Committee for review and to the Joint Research office of The Barts Health NHS Trust/Queen Mary University of London for the NRES Part C Sire-Specific assessment.

The study Sponsor will ensure sufficient insurance is available to enable it to indemnify and hold the investigator(s) and relevant staff as well as any hospital, institution, ethics committee or the like, harmless from any claims for damages for unexpected injuries, including death, that may be caused by the study drug but only to the extent that the claim is not caused by the fault or negligence of the subjects or investigator(s).

8.6.8 Financial Aspects

The conduct of the study is subject to internal and external funding streams which currently supports the BRC and associated delivery organisations; and may in the longer term be supported by research grants, charities, or other industries outside of the latter where research utilising Barts BioResource resources has been approved. The Research & Development department and NRES will be advised following significant alteration of funding provisions.

8.6.9 Confidentiality

The Investigator and other study site personnel will keep confidential any information provided by the Barts Health NHS Trust (including this protocol) related to this study and all data and records generated in the course of conducting the study, and will not use the information, data, or records for any purpose other than conducting the study.

These restrictions do not apply to: information which becomes publicly available through no fault of the investigator or study site personnel; information which it is necessary to disclose in confidence to an Ethics Committee solely for the evaluation of the study; information which it is necessary to disclose in order to provide appropriate medical care to a study subject, or study results which may be published as described in Section 10. If a written contract for the conduct of the study, which includes confidentiality provisions inconsistent with this statement, is executed then that contract's confidentiality provisions shall apply rather than this statement.

8.6.10 Protocol Amendments

Neither the Investigators nor the Barts Health NHS Trust / Queen Mary, University of London will modify the Protocol without first obtaining the concurrence of the other in writing. Protocol modifications that impact on subject safety or the validity of the study will be approved by the Ethics Committee. No changes (amendments) to the Protocol may be implemented without prior approval from the Sponsor and the appropriate Ethics Committee. If a Protocol amendment requires changes in an informed consent form, the revised informed consent form prepared by the Investigator must be approved by the Ethics Committee.

Once the final Protocol has been issued and signed by the Investigator and the authorised signatories, it shall not be informally altered. Protocol amendments are alterations to a legal document and have the same legal status. Therefore, they must pass through appropriate steps before being implemented. In general, any important change which theoretically increases risk to subjects constitutes an amendment. Minor changes of a purely administrative nature need documentation and advice to the committee, but may be implemented without prior approval.

It is the responsibility of the Investigator to submit the amendment to the Ethics Committee for their approval; written approval should be obtained and a copy provided to the Sponsor. The Sponsor is responsible for determining whether or not the local regulatory authority must be notified of the Protocol change. Completed and signed

Protocol amendments will be circulated to all those who were on the circulation list for the original Protocol.

The original signed copy of amendments will be kept in the study file with the original Protocol. It should be noted that where an amendment to the Protocol substantially alters the study design or the potential risks to the subjects, each subject's consent to continue participation should be obtained.

8.6.11 Quality Control and Quality Assurance

The instructions and procedures specified in this Protocol require diligent attention to their execution. Should there be questions or consideration of deviation from the Protocol, clarification will be sought from the *Principal Investigator* and Sponsor. Any subject treated in a manner that deviates from the Protocol, or who is admitted into the study but is not qualified according to the Protocol as amended by the Barts Health NHS Trust / Queen Mary, University of London and the Investigator, may be ineligible for analysis and thereby compromise the study.

Only when an emergency occurs that requires a departure from the Protocol for an individual will there be such a departure. The nature and reasons for the Protocol violation shall be recorded in the registry records.

The Investigator and designees will comply with all applicable national and local laws.

The programme will also be used to develop, assess and validate the PowerTrials™ management system for research (Appendices 10-13).

8.6.12 Summary Monitoring Plan

An observational study, or a study that does not test an intervention, is not a clinical trial and does not require a Data Safety Monitoring plan. However, a monitoring plan to comply with the requirements of the Sponsorship of the Barts BioResource will address issues of data accuracy and protocol compliance will be developed and agreed by all parties.

8.6.13 Audit and Inspection

Auditing: Definition "A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, Sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."

A study may be identified for audit by any method listed below:

- A project may be identified via the risk assessment process.
- An individual investigator or department may request an audit.

- A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.
- Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.
- Projects may be randomly selected for audit by an external organisation.

Internal audits will be conducted by a Sponsor's representative

8.6.14 Non-Compliance

***Definition**:* A noted systematic lack of both the CI and the study staff adhering to SOPs/protocol/ICH-GCP, which leads to prolonged collection of deviations, breaches or suspected fraud.

These non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The Sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which to be escalated. The Sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the JRMO will agree an appropriate action, including an on-site audit.

9.0 TRIAL COMMITTEES

Key groups have been established to make decisions on accessing registry data and monitor progress on the studies.

Key functions are listed below and reporting structures are displayed in appendix 9.

Barts BioResource: Steering Group

- Overarching BBR oversight
- Providing input to the development of the BBR, including strategy evaluation
- Providing advice on overall budget and resources
- Defining and helping to achieve BBR outcomes
- Identifying the priorities in the BBR
- Identifying potential risks and issues
- Monitoring risks; timelines and the quality of the BBR as it progresses
- Providing advice, guidance and (where appropriate) making decisions about changes to the BBR as it progresses
- Establishing and overseeing ad-hoc/ongoing project/programme functions to support the form and function of the BBR e.g. ICT management and development

Barts BioResource : Operational Group

- Management, delivery and oversight of day to day operational function of the BBR
- Adherence to GCP and related regulatory requirements
- Grant access to data and samples following peer review (with Material Transfer Agreements)
- Write amendments and reports
- Research nurse/ research assistant allocation
- Collection of metrics
- Communication to the researchers (internal/ external/ industry)
- Communication to Patient and Public Advisory Group
- Communication to the public/participants via www.bartsbioresource.org.uk and via Twitter (Twitter handle @BartsBioRes)
- Any other operational issues

Barts BioResource Peer Review Committee

- Review of Barts BioResource annual reports
- Review of Barts BioResource access applications, assurance that research proposals in keeping with patient consent provided and clinical sign off
- Authorship guidance (not prescriptive)
- Advice regarding feasibility of recruitment in clinical areas if or when conflict arises with other active research studies
- Approval of amendments prepared by Operational Group prior to submission to Barts R&D and ethics committee
- Patient and Public Advisory Group (PPAG) have access to access applications during and after Barts BioResource peer review and are invited to comment;
- Sponsor representatives (Barts Joint Research Management Office – JRMO) have access to access applications during and after Barts BioResource peer review to facilitate sponsor oversight;

Barts BioResource Biosample Management Group

- Tissue Bank and biosample SOP review and updating
- Scientific advice related to Barts BioResource, e.g. on scientific value of using depletable biosamples
- Sample quality assessment

Barts BioResource Data Management Group

- Data governance
- Data custodian
- Data management
- Pseudonymisation and data linkage
- Providing access to Barts BioResource once access granted by Peer Review Committee and Operational Group

Ethics Advisory Group

- Advises Barts BioResource Operational Group

- Advises Barts BioResource peer review committee
- Advises Barts BioResource data management group
- Input into amendments prior to sending to Barts BioResource peer review committee, REC and JRMO

Patient and Public Advisory Group (PPAG)

- Represent patient and public viewpoint
- Disseminate information to other relevant patient and public engagement groups
- Ability to comment on access applications during and after Barts BioResource Peer Review
- Representation on NIHR Barts Biomedical Research Centre Executive

Barts BRC Board

- Provides feedback on any aspect of the Barts BioResource science or operations

Barts BRC Executive

- Provides oversight to the Barts BioResource Operational Group
- Agrees Barts BioResource research priorities

10.0 PUBLICATION POLICY

Every publication originating from the Barts BioResource needs to acknowledge the BRC as follows:

Acknowledgement:

Acknowledgement phrases for BRC related publications

Either

This work forms part of the research areas contributing to the translational research portfolio of the Barts BRC which is supported and funded by the National Institute for Health Research.

Or

This work was directly funded by the National Institute for Health Research Barts BRC.

Authorship:

There are no rules for authorship. However, it is generally recommended the lead applicant to include colleagues from Barts Health NHS Trust and Barts and The London School of Medicine and Dentistry that have clinical (e.g. look after patients with a specific disease) or scientific expertise in the relevant publication topic.

Confidentiality:
Publications or disclosures of study results shall not include other, confidential information. If the proposed publication/disclosure risks the Barts Health NHS Trust's ability to patent any invention related to the study, the publication or disclosure will be modified or delayed, at the Barts Health NHS Trust's option, to allow the Barts Health NHS Trust to seek patent protection of the invention. If a written contract for the conduct of the study which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

10.1 OWNERSHIP

All data and records provided by the Barts Health NHS Trust or generated during the study (other than a subject's medical records) and all inventions discovered in the course of conducting the study are the property of the Barts Health NHS Trust. If a written contract for the conduct of the study, which includes ownership provisions inconsistent with this statement is executed, that contract's ownership provisions shall apply rather than this statement.

11.0 REFERENCES

[1] The Academy of Medical Sciences review, 'A new pathway for the regulation and governance of health research' January 2011.

[2] Principles for Best Practice in Clinical Audit (2002, NICE/CHI).

[3] NHS Connecting for Health Research Capability Programme. www.connectingforhealth.nhs.uk/systemsandservices/research

[4] UK Biobank: Protocol for a large-scale prospective epidemiological resource Protocol No: UKBB-PROT-09-06 (Main Phase) 21 March 2007

[5] Miller Sa, Dykes DD, Polesky HF. A simple salting method for extracting DNA from human nucleated cells. Nucleic Acids Res. 1988;16(3):1215

[6] Use of Electronic Informed Consent: Questions and Answers. Guidance for Institutional Review Boards, Investigators and Sponsors. US Department of Health and Human Services. December 2016

12.0 APPENDICES

Appendix 1: Safety Reporting in Non-CTIMP Research

Appendix 2: Governance Structure

Appendix 3: Sample Access Procedure

Appendix 4: PowerTrials™ Overview

Appendix 5: PowerTrials™ BHT Summary

Appendix14: PowerTrials™ BHT Default Security Matrix

Appendix 15: Registry Workflow

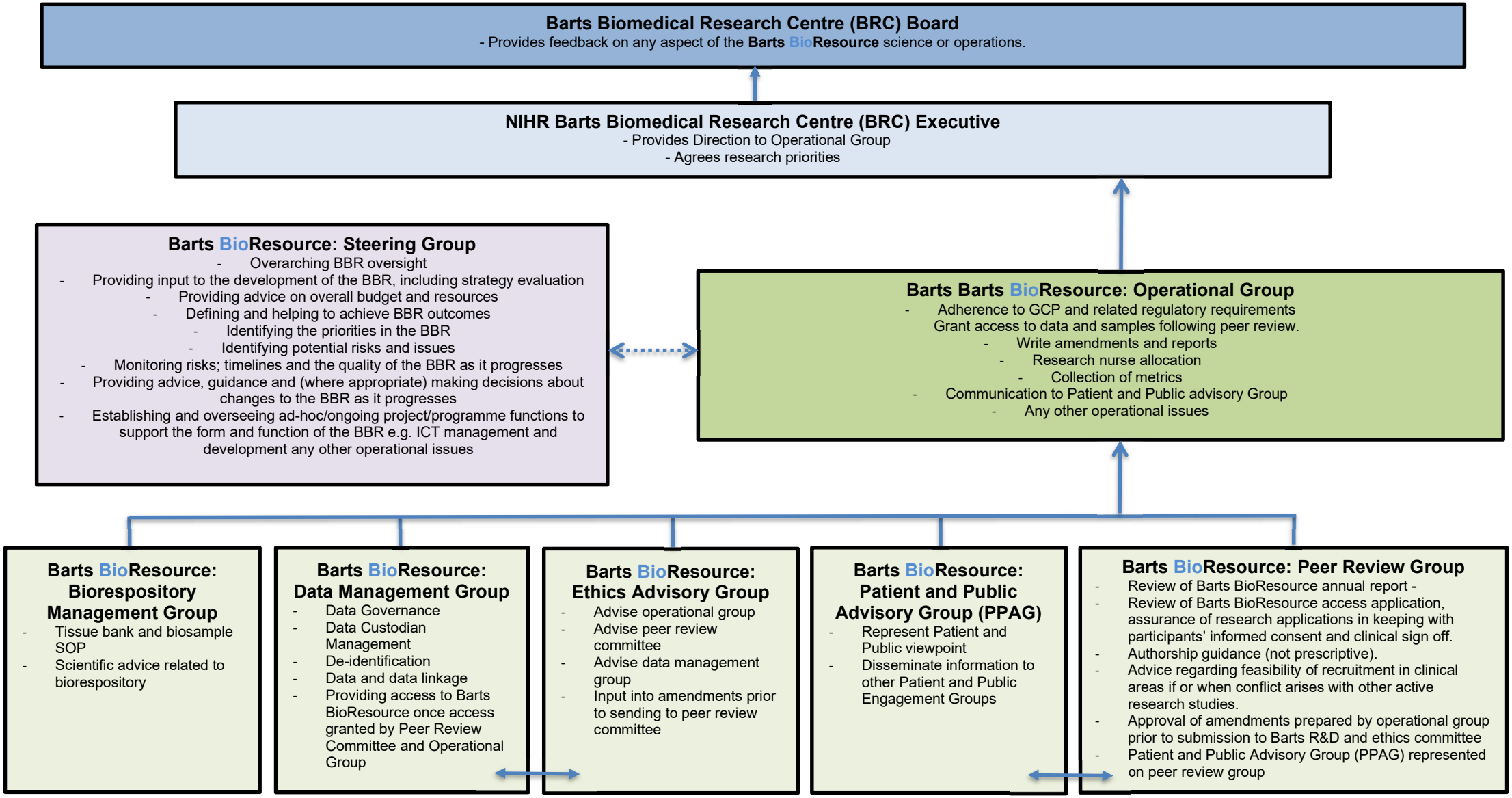
Appendix 16: Protocol Amendments

Appendix 1: Safety Reporting in Non-CTIMP Research

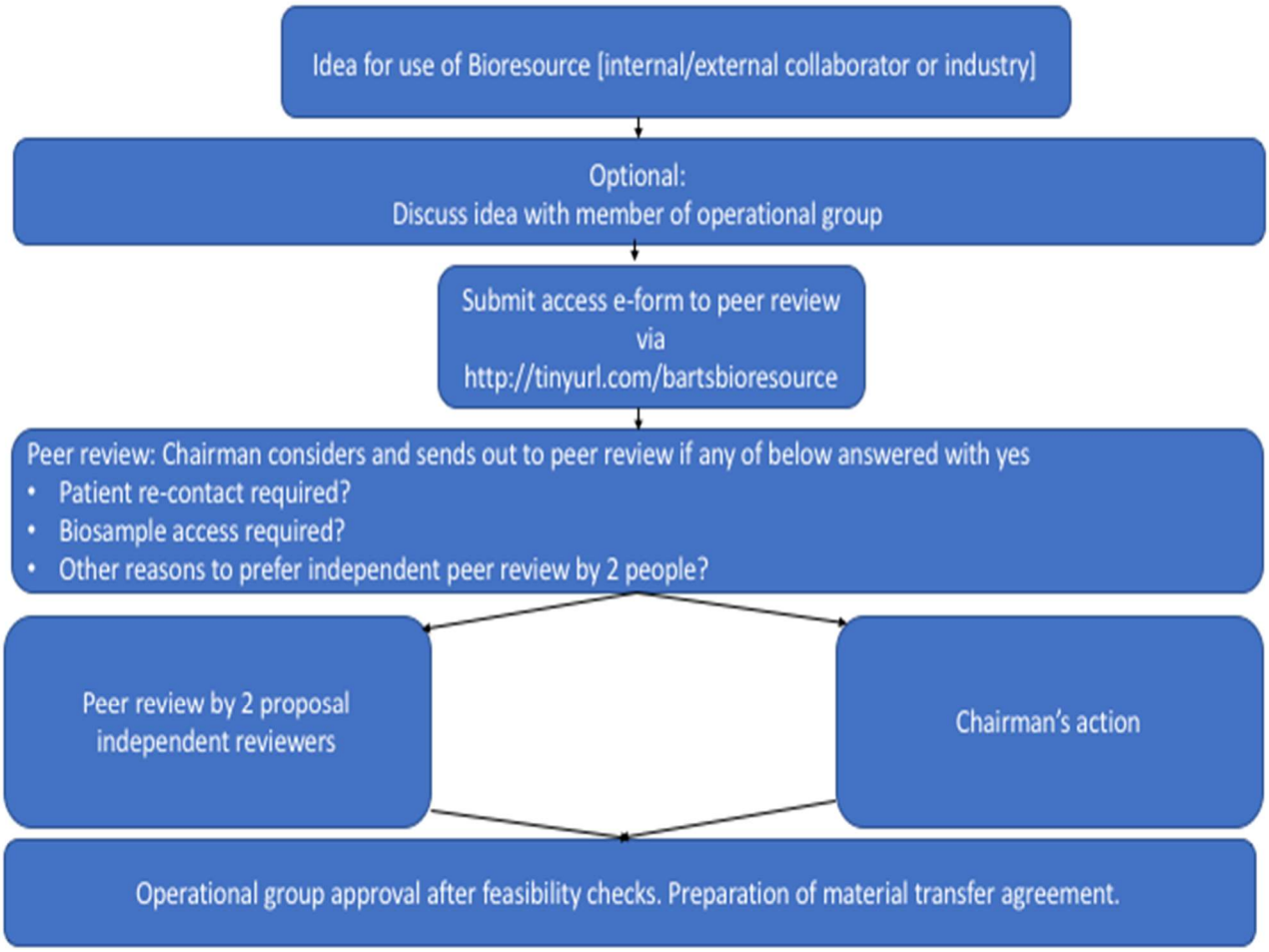
	Who	When	How	To Whom
SAE	Chief Investigator	Report to Sponsor within 24 hours of learning of the event Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the Sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the Sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:-	Main REC with a copy to be sent to the Sponsor

			Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	

Appendix 2: Governance Structure



Appendix 3: Barts BioResource Access Procedure



Appendix 4: PowerTrials™ Overview

LifeSciences

Supporting clinical trials

PowerTrials

Solution at a Glance

The *PowerTrials* facilitates clinical trials by integrating research processes into the workflow of clinicians and researchers who use Cerner's electronic health record.

Healthcare relies on controlled clinical trials to ensure the development of safe and effective pharmaceuticals, biologics and medical devices. But connecting clinicians and patients to clinical research is an ongoing challenge.

Recent surveys show that problems associated with the recruitment of trial participants delay approximately 75 percent of all clinical trials. At the same time, many physicians are reluctant to take on the burden of additional processes and documentation required by clinical trials.

Cerner developed the *PowerTrials*™ solution to provide clinicians and patients with increased opportunities to contribute to the development of new therapies. *PowerTrials* harnesses the unified *Cerner Millennium*® architecture to facilitate clinical trials.

The solution integrates research processes into the workflow of Cerner's electronic medical record so that clinical research and clinical care use the same system. This integrated approach enhances patient safety, increases efficiency and improves data quality.

PowerTrials facilitates the organization and flow of clinical trial data through the efficient identification of candidates, consistent management of study documentation and integrated data capture.

The solution has two components, *PowerTrials Screener*™ and *PowerTrials Manager*™.

Screening

PowerTrials Screener fuels clinical trial enrollment by unifying the patient care process with the identification of clinical research candidates. A screening engine in *Cerner Millennium* compares clinical trial inclusion and exclusion criteria to patient data within the system. Clinicians and researchers at the site then are alerted to patients who meet initial eligibility requirements.

Key Benefits

- Increased clinical trial participation by clinicians and patients
- Streamlined clinical trial screening, enrollment, documentation and data capture
- Rigorous site metrics for study feasibility, research prioritization and oversight

Researchers also use *PowerTrials Screener* to test study feasibility. Information gathered can guide protocol revisions and enable the discovery and prioritization of research opportunities.

The protocol-specific screening modules created in *PowerTrials* support two distinct workflows for identification of potential research candidates:

- Screening of a specific protocol against a specified patient population (researcher workflow)
- Screening of a specific patient against available protocols (clinician workflow)

Cerner Corporation | 2800 Rockcreek Parkway, Kansas City, MO 64117 | 800.765.9072 | www.cerner.com/lifesciences

PowerTrials is the cornerstone of Cerner's suite of solutions that electronically facilitate clinical research activities:

- Protocol optimization (*Health Facts®*)
- Study feasibility (*Cerner Research Network*)
- Targeted genomic research capabilities (*Millennium Helix™*)
- Patient care (*PowerChart®*)
- Order sets and care plans (*PowerOrders®* and *PowerPlan™*)
- Decision support (*Discern Expert®*)
- Delineation of charges for clinical research studies (*Charge Services*)
- Integrated data capture for clinical trials (RFD functionality)
- Integrated data capture for registries and investigator-initiated studies (*Discovere™*)

Trial management

Researchers use *PowerTrials Manager* to organize and maintain protocol information and manage clinical trial initiation and enrollment activities. The management tools allow the orchestration of numerous trials diverse in size, complexity and sponsor-driven preferences. Additionally, these tools facilitate the tracking of accrual metrics across all protocols or at the protocol-patient level.

The solution also includes an enrollment indicator and clinical trials section in Cerner's electronic medical record. These features provide clinicians with information about a patient's current and previous trial enrollments, protocol information and study contact information.

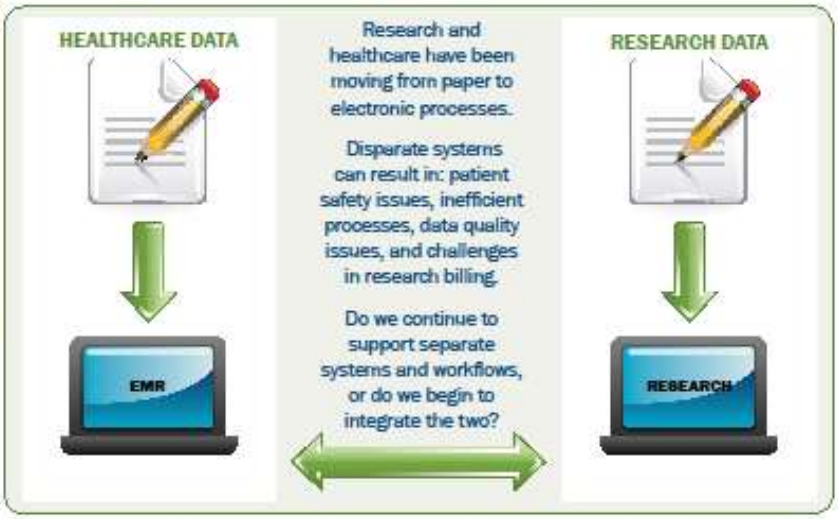
PowerTrials Manager facilitates trial oversight and administration activities, including:

- Determination of security rights and privileges for research personnel based on roles and defined per protocol
- Documentation of patient eligibility screening for each protocol
- Configuration of integrated data capture so research data can be pre-populated in case report forms and saved to a research-specific repository

A global healthcare leader

Cerner, a global leader in healthcare information technology (HIT), is the power behind *PowerTrials*. Working together with more than 6,000 clients worldwide, Cerner is solving healthcare's many challenges by connecting the right people with the right information at the right time. Building on more than a quarter century of experience, we are finding new and innovative ways to deliver value to our clients.

Let us put our expertise to work for your organization. For more information, please call 866.221.8877, or visit us at **www.cerner.com/ls.**



Cerner Corporation | 2800 Rockcreek Parkway, Kansas City, MO 64117 | 800.766.9072 | www.cerner.com/lifesciences

Appendix 5: PowerTrials™ BHT Summary

Cerner PowerTrials™ is a product designed for use as a management tool for Clinical Trials. Its strength is that it is fully integrated with the Millennium CRS currently in use at Barts Health NHS Trust. This allows a trial, once set up, approved and activated, to pre-screen for a potential trial cohort, according to a set of pre-defined criteria that ensure that only patients meeting trial requirements are displayed. This will aid patient recruitment and minimise the time taken to search for suitable subjects.

Patients can also be referred to a trial by trust Clinicians to relevant trials directly from PowerCharts™, where they are registered with a pending status awaiting confirmation of their eligibility and, where appropriate, enrolment by research staff.

The overarching security for PowerTrials™ is provided by the Millennium CRS and the Trust CRS Smartcards. Three central roles have been established:

- R&D Staff
- Researcher
- Auditor (MHRA or internal)

Access is controlled for each role by the use of existing defined B-Codes defined in the NHS Spine.

Further roles are defined in PowerTrials™ itself, by the R&D department, combinations of which are used to define the actions that a user can complete, including what data can be seen, accessed or edited by any Role:

- Principal Investigator (PI)
- Co-Investigator
- Research Coordinator/Associate
- Study Nurse
- Medical Student
- Chief Investigator
- Collaborator
- Internal Auditor/Monitor
- External Auditor
- CRA/Data Manager
- Creator
- Limited Creator
- R&D System Administrator
- R&D Information Officer

- Pharmacy

These rights for these roles can be further refined on a trial by trail basis by R&D. The PowerTrials™ system has been extensively tested to ensure that the required functionality is present, and that the system is configured as we require, and security has been a major part of this testing, ensuring that roles can only see the data that they require to complete their tasks. The detailed security matrix showing who can do what is attached the end of this document.

Eligibility checklists are designed following the protocol inclusion/exclusion criteria and are built into the system, and completion is logged together with confirmation of who completed the checklist with the patient.

The consent workflow manages the consent process, and logs the patient consent, and who obtained the signed consent.

Documents such as the consent form can be uploaded to the system and stored in designated folders. The system provides version control, and an auditable log showing who uploaded the document, accessed or edited any document stored.

Appendix 6: PowerTrials™ BHT Default Security Matrix

Default Security Rights			Roles																
Functionality Name	Function	Access Rights	Principal Investigator (PI)	Co-investigator	Research Coordinator/Associate	Study Nurse	Medical Student	Chief Investigator	Collaborator	Internal Auditor/Monitor	External Auditor	CRA/Data Manager	Creator	Limited Creator	R&D System Administrator	R&D Information Officer	Pharmacy
Administrative changes	Edit the On Study, Off Study, and Off Treatment Dates in PPM	Execute	X	X	X	X	X										
Administrative changes	Edit the protocol mnemonic in POM	Modify											X	X	X	X	
Amendment Development	Creating new amendments	Write											X	X	X	X	
Amendment Development	Editing amendments	Modify											X	X	X	X	
Amendment Development*	Access custom fields in POM	Execute											X	X	X	X	
Assign Roles and Access User Rigl	Adding roles	Write											X	X	X		
Assign Roles and Access User Rigl	Modify roles	Modify											X	X	X		
Assign Roles and Access User Rigl	Delete roles	Delete											X	X	X		
Assign Roles and Access User Rigl	Access Role Assignment Tool	Execute											X	X	X		
Assign Roles and Access User Rigl	If the Protocol View Security preference is on, this determines it	Read	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Associate Questionnaires with Cons	Associating checklists with documents	Read	X	X	X	X	X						X	X	X	X	
Batch enrollment*	Allows batch enrollment	Execute															
Data Capture*	Allows data capture and turns on the data	Execute	X	X	X	X	X						X	X	X	X	
Delete Enrolment Information	Delete Enrollment or Consent Pending Information□	Execute	X	X	X	X	X										
Document Manager	Viewing Documents in Document view	Read	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Document Manager	Uploading documents/modifying	Modify			X	X	X						X	X	X	X	
Document Manager	Accessing Document Manager	Execute	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Document Manager	Deleting documents	Delete			X	X	X						X	X	X	X	
Eligibility Checking	Accessing Eligibility Checklist Launcher to create new checklis	Execute															
Eligibility Checklist Development	Viewing Checklists in Elig Checklist View	Read	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Eligibility Checklist Development	Accessing Eligibility Checklist Builder	Execute	X	X				X					X	X	X	X	
Eligibility Checklist Development	Adding a new eligibility checklist	Write	X	X													
Eligibility Checklist Development	Modifying an existing eligibility checklist	Modify	X	X													
Eligibility Status Over-ride	Overriding eligibility for enrollment	Execute															
Eligibility Verification	Verifying an Eligibility Checklist	Execute	X	X													
Library Question Development	Viewing Library Questions for an eligibility checklist	Read	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Library Question Development	Adding Library Questions for an eligibility checklist	Execute	X	X	X	X	X						X	X	X	X	
Milestones	Viewing milestones in milestone view	Read	X	X	X	X	X		X	X	X	X	X	X	X	X	
Milestones	Accessing Milestone Manager	Execute											X	X	X	X	
Milestones	Adding a new milestone	Write											X	X	X	X	
Milestones	Modifying an existing milestone	Modify											X	X	X	X	
Milestones	Deleting an existing milestone	Delete											X	X	X	X	
Patient Consenting	Viewing existing consent information	Read	X	X	X	X	X										
Patient Consenting	Adding Consents	Execute	X	X	X	X	X										
Patient Consenting	Modify consent information	Modify	X	X	X	X	X										
Patient Enrollment	Allows users to modify patient's accession number	Modify	X	X	X	X	X										
Patient Enrollment	If the Patient List Security preference is on (set to 1), it will allo	Read	X	X	X	X	X			X	X	X					
Patient Enrollment	Enrolling Patients and Editing the Enrollment of Patients	Execute															
Patient Transfer	Transfer patients to other amd/rev	Execute	X	X	X	X	X										
Pre-screening capabilities	Run Pre-screening for Protocol	Execute	X	X	X	X	X										
Pre-screening capabilities	Run Prescreening for Protocol	Read	X	X	X	X	X										
Pre-screening capabilities	Run Prescreening for Protocol	Write	X	X	X	X	X										
Pre-screening capabilities	Run Prescreening for Protocol	Modify	X	X	X	X	X										
Pre-screening capabilities	Run Prescreening for Protocol	Delete	X	X	X	X	X										
Protocol Configuration	Access Protocol Configuration within POM	Execute											X	X	X	X	
Protocol Development	Editing protocol information	Modify											X	X	X	X	X
Protocol Development	If the Protocol View Security preference is on, this determines it	Read	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Revision Development	Adding and editing new revisions	Write											X	X	X	X	
Revision Development	Viewing revision information in Revision View	Read	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Appendix 7: Protocol Amendments

PROTOCOL NO.: Barts Cardiovascular Registry

Number of Protocol amendments issued:

[X] 1 - 23rd May 2014

1. Substantial Amendment to Protocol
Amendment the protocol on page 23 to include the potential of up to 5 minutes extra scanning time to a CMR acquisition or echocardiogram. I have attached a version of the protocol with track changes so you are able to see the amendments in addition to the final version.

2. Substantial Amendments to the Registry Patient Information Sheet (PIS)
The Registry patient information sheet has also been updated to inform the patient of the potential increase in scan time. (Information for patients for the Barts Cardiovascular Registry – Appendix 3 Protocol (modified in this document).

3. Substantial Amendment
Posters to be used to inform patients of the Barts Cardiovascular Registry.

Minor Amendments
4. All the consent forms have been amended to add a box in the corner where a sticker will be placed with the patients hospital record number (MRN) and where available NHS number.

5. The phone number in the Patient information sheets will be amended to reflect the contact details of the Lead Research Nurse who will be taking phone calls from the patients.

[X] 2 – 1st January 2015

1. Substantial Amendments
a) Based on feedback from patients that the form was too long and a review of other similar registry studies we have simplified the consent forms. We have been careful to ensure that all the information is included and that it is clear what the consent is for, but have reduced the amount of times a patient needs to initial the form.

b) The consent forms have been amended so that patients only need to sign one consent form to sign up for each arm of the study rather than multiple forms. There are 3 consent forms:

i) Consent Registry (data);

ii) Consent Registry and biological samples;

iii) Consent Registry and biological samples including tissue.

c) The consent form for collection of blood/saliva has been updated to ask patients to provide urine in addition to blood and saliva. In addition, the consent form has been updated to ask for permission to take multiple blood, saliva and urine samples under the same consent. The consent for blood, urine and saliva is now known as consent for biological samples.

2. Substantial Amendment to Patient information sheet for collection of biological samples

b) The patient information sheets have been amended so that patients only need to read one patient information form rather than a separate form for each arm of the study. There are 3 patient information forms

i) Patient Information Sheet Registry (data);

ii) Patient Information Sheet Registry and biological samples;

iii) Patient information sheet Registry and biological samples including tissue

c) The Patient Information Sheet for collection of blood/saliva has been updated to ask patients to consent to provide urine in addition to blood and saliva. In addition, the Patient Information Sheet has been updated to ask for permission to take multiple blood, saliva and urine samples under the same consent. The Patient Information Sheet for blood, urine and saliva is now known as the Patient Information Sheet Registry and biological samples.

Minor Amendments
3. The list of appendices in the Protocol has been updated in Section 12 of the protocol. (Track changes used to highlight changes).

[X] 3 – 26th October 2015

Substantial Amendments

a) Change to PIS and consent forms: Driven by feedback from surgical colleagues involved in tissue collection, we have clarified sections relating to tissue sampling. We also aim to enable collection of other cardiovascular tissue, such as vascular plaque, cardiac biopsies. We specifically ask permission to acquire biopsy samples for research purposes where there is a minimal additional risk and a defined and documented request has been made to the patient. We have also included information related to email information security as advised by Barts Health Information Governance team if participants choose to be contacted by email from the Barts Cardiovascular Registry Team. We have increased the blood sample volume to up to maximum of 50mls from 29 ml. This will not increase the risk to participants. The blood sample collection now allows for specific groups of patients and research questions to take an extra 20 mls of blood. The details of how this blood will be processed, store and analysed will be available in the project's specific access application, which will be reviewed and approved according to our existing access procedures.

b) Change to research protocol: the above changes to the PIS and consent forms have also been incorporated in our revised research protocol. As we have moved from the London Chest Hospital to the new Barts Heart Centre, St Bartholomew's Hospital, the revised governance structure in the research protocol (appendix 9) reflects the new working structures and tidied up some loose ends.

Minor Amendments

Some minor changes to language/ grammar/typos in the research protocol.

[X] 4 – 26th March 2017

1. Substantial Amendments to Protocol

Patients eligible for entry to the Bioresource will be directed to the use of Electronic platforms either on site or at home using an on line computer based Patient Information/Consent system.

On site, the Bioresource staff will approach the participant's using an electronic device for the consenting process. The device may be used for adults irrespective of the details of their individual clinical pathway and every patient will be given ample time to consider giving their consent for the study. Web links to the online pathway will be supplied with routine clinical correspondence.

Should the patient prefer then an individual information sharing and paper based consenting process will be followed.

Any patient, irrespective of 'traditional' paper-based or eConsenting will be provided with a clear pathway to seek personal one-to-one support, guidance and opportunities to ask questions to facilitate and conform the Informed Consenting Process.

Patients can "sign" their consents by typing their name utilising the "wet signature" feature. The Research Nurse/ Assistant will then generate a Bioresource number. Good Clinical Practice (GCP) will be followed and patients will be provided with a signed copy of their consent form. This will be converted to a PDF and printed in the clinic or the patient's address can be collected and a signed copy of the form may be mailed to the participant.

Extensions to the study will be carefully planned and will only take place if appropriate resources have been identified to consent consecutive patients. If participants consent and at a later stage wishes to opt out, they will still be given an opportunity to do so at any point after consenting. e-Consent also has the potential to standardise the informed consent process and make it more accessible to a wider range participants in terms of education, culture and language.

Upon completion of the pilot assessment of e-Consenting; the Bioresource Operations team will direct an audit of the user interface, data integrity, and Public & Patient experience dimensions. If the system is demonstrated to be legally, ethically and technically 'fit for purpose' then a stage implementation plan will be executed across the Bioresource.

Key elements of the evaluation of the quality control and assurance of the eConsenting platform will be an ongoing evaluation of the core Informed Consenting Process; such as is the patient competent to consent? did they read and understand the information provided? did they make a fully informed decision to consent? did they opportunity to seek additional support and information? and do they understand their right to withdrawal consent at any time and that this will not affect the standard or type of treatment they will receive from the hospital or doctors, now or in the future?

Further, the proposed e-Consenting platform will enable the delivery a range of assessments relating to Patient Reported Outcome Measures (PROMS) and Patient Reported Experience Measures (PREMS). The former are standard healthcare activities, such as Sort Form-36

Health Survey (SF-36), General Health Questionnaire (GHQ) and Depression Patient Health Questionnaire (PHQ-9). These documents are in common usage. The later form the basis of universal healthcare audit within the NHS.

The Bioresource Ethics and Operational Groups will review, manage and approve all information released on the e-Consenting Platform via Standard Operating Procedures. Specific review and approval will be gained from the linked Public and Patient Advisory Group.

The development and application of the Electronic Consenting and Information system will reflect the guidance document of the Office for Human Research Protection, US. Department of Health 2016; which is currently the leading resource.

2. Substantial Amendments to Protocol
We may add a maximum of ~~5~~ 10 minutes at the end of clinical assessments such as clinical CMR acquisition, ultrasound or echocardiogram, but not to investigations using radiation (e.g. cardiac CT). The main purpose is to test and/or develop new imaging techniques and sequences that may improve our clinical service in the future. The additional scanning is not associated with radiation and will not cause harm to participants.

3. Substantial Amendments to Protocol
The application of Technology Evaluation activities which will be restricted to **non-invasive** cardiovascular monitoring systems.

As such these systems will not be utilised to diagnose or alter patient care.

Appropriate governance structures are in place to approve and monitor study procedures ((see Appendix 11). Examples of devices include activity monitors such as Fitbit®, heart rate monitors, novel and evolving systems for recording circulatory dynamics. Where required, full regulatory approvals will be ensured, such as Medicines and Healthcare products Regulatory Agency (MHRA) letters of “Non-Objection”. All relevant internal Barts Health Policies will be followed such as electrical safety and devices management.

The aim of such activities is to provide the necessary scientific confirmations and data with which to prepare full stand-alone research programmes, where appropriate.

4. Substantial Amendments to the Registry name to Barts Bioresource
The Barts Bioresource Operational Group have reflected and enquired into the effects “The Barts Cardiovascular Registry“ name had on the complexity of the work undertaken within the project. Therein a change to Bioresource has been proposed.

5. Substantial Amendments to reflect that Barts has a National Institute for Health Research (NIHR) Barts Biomedical Research Centre (BRC) which supersedes the NIHR Cardiovascular Biomedical Research Unit (CVBRU) at Barts.
Appropriate changes to the naming of what is now the Barts BRC.

6. Substantial Amendments to the Barts Bioresource

The protocol has been updated to inform access to the use of the Barts Bioresource database, and biorepository.

7. Minor Amendments to the protocol

A range of non-substantive administrative changes have been included to correct and clarify the protocol.

[X] 5 – 8th April 2020

1. Substantial Amendments to Protocol

SCOPE OF RESEARCH – The amendment will expand the remit of the Barts BioResource (BBR) from Cardiovascular patients and research to cover all patients/specialties and more encompassing health and healthcare related research delivered by Barts Health NHS Trust.

Rationale: To date the current BBR has recruited >23,400 cardiovascular patients at a primary recruitment rate in excess of 80% approval. Approximately 50 patients have withdrawn their consent. Further, approximately 2,500 patients have been re-consented illustrating an ongoing commitment to inform at retain patient participation (this is recorded as 100% wishing to re-affirm their informed consent). Finally, during this time we have encountered 5 complaints, each of which was resolved transparently and with patient engagement.

Risk Analysis: There is no expectation that cardiovascular patients have a different expectation of a major teaching hospital and largest NHS Trust in the United Kingdom. Further, the metrics achieved to date by the BBR clearly illustrate the infrastructure, experience and capability of the BBR team, Standard Operating Procedures, and governance.

The expanded scope of research will enable a much broader application of the patient information and donated tissues in areas where the clinical question is not purely cardiovascular but overlaps with other specialisations.

2. Substantial Amendments to Protocol

CONSENT relating to existing BBR patients

We propose to re-consent existing Barts BioResource patients via email / post / or at their next scheduled visit to the hospital with a revised Patient Information Sheet (PIS) and Informed Consent forms to inform them of the extension of the scope of research. This approach is compliant with section 4.1 of the approved protocols.

During the COVID-19 restriction of travel, a consent form may be sent electronically to participants who have expressed interest in volunteering to the Barts BioResource.

Each existing BBR patient has indicated their preferred method of contact at the time of consent. Their options will be presented as

[a] Continue to participate but restricting their data and tissues to cardiovascular research,

[b] Continue to participate with no restriction to the use of their data and tissues to approved research via the expanded access approval system,

[c] Withdrawal of consent and destruction of any remaining tissue samples and removal of data access permissions.

Until each consented BBR patient confirms their Informed choices, their last Informed Consent endures and option [a] will be respected.

For the avoidance of doubt, data and tissue samples will not be provided for non-cardiovascular sub-projects until the patients consent to the revised Patient Information sheets.

Risk Analysis: Minimal risk, our experience of both recruitment and retention clearly demonstrates the comprehension and cooperation of the patient population. An approximation of drop-out rate may be illustrated by the ~11,000 participants of the NHSBT BioResource (07/Q0104/14) who were written to/emailed and invited to join the NIHR BioResource (17/EE/025); participants were asked to withdraw if they did not want to continue. The withdrawal rate was approximately 4%, however the cohort dated back over 15yrs.

3. Substantial Amendments to Protocol

CONSENT to incapacitated patients

Generally, and with reference to the COVID19 pandemic, Barts Health NHS Trust have a number of patients who are intubated on ventilators or for other clinical management, and therein lack capacity.

This is specifically relevant to all patients in the NHS Nightingale hospital and in the Barts Health NHS Trust Intensive Care Units. It is in the National Interest, and also potentially in the interest of the patient's welfare, that their clinical information and biological samples are collected and made available to research teams.

This section of the protocol seeks to recruit patients lacking capacity (such as those on ventilators, severe trauma, cardiogenic shock and similar) to the BBR programme. The following are the required considerations to achieve this in an ethical and legal framework:

Some patients may have an Advanced Directive in place, if this is established in a timely manner then we will conduct their care and potential BBR participation in accordance with their wishes.

We acknowledge the HRA guidance on research without consent, that it can be justified if the gravity of the rights infringement is minor and outweighed by the expected social value of the research and obtaining consent is impractical. We propose that this test is clearly met with reference to:

http://www.hra-decisiontools.org.uk/consent/principles-ALC-EnglandandWales.html

We further note and refer to the Medical Research Council's guidance of the **Key principles when considering the participation of adults who lack capacity in research**

• The interests of the individual must always outweigh those of science and society.

• The research must relate to a condition or impairment that affects the individual or the treatment of this condition.

• It must not be possible to conduct equally effective research with adults who have the capacity to consent.

• The potential benefits of the project should outweigh the risks: the level of acceptable risk depends partly on the possible benefit to the individual.

• Views of those close to the participant should always be sought, unless this is not possible due to particular circumstances.

• A participant who lacks capacity should only be included in a study when there are no indications that he or she objects to this.

Wherever possible, Next-of-Kin will be consulted as "Consultee" in relation to their understanding of the wishes and intentions of the patient, this will be supplemented with the opinion of the nominated clinician (Nominated Consultee) not involved in any Barts BioResource research present or in future on the data/samples.

As Next-of-Kin [NOK] will generally not be physically present during the current pandemic, the pathway will be by a nominated clinician (Nominated Consultee), not involved in any Barts BioResource research present or in future on the data/samples; followed by informing the NOK (their wishes to be observed) as soon as is reasonably practicable and appropriate, and finally informed written consent with the patient should they hopefully recover.

Should participants regain capacity we will involve them in the on-going consent process at the earliest appropriate opportunity. In most cases it is appropriate to ask them to give their own consent when and if they are able. Both the Consultees and the Nominated Consultees will be informed of this intention at the outset. We have prepared an appropriate Participant Information Sheet and consent form for the participants themselves that explains what has happened so far, and what you are seeking their consent for.

The Consultees are not asked to give consent on behalf of the adult, but rather to provide an opinion on the views and feelings of the potential participant. Further, the consultee will be

[a] Told that they are being asked to advise on the views and feelings they believe the adult would have towards participation in the BBR study.

[b] Told that they are free to decide whether they wish to provide this advice or not and

[c] Given sufficient information, in an understandable form, about the BBR study to ensure that they provide you with informed advice.

To this end, we are working directly with the Safeguarding Leads at each individual hospital site to ensure compliance and transparency of the BBR activities and clearly document such activities.

During the COVID-19 restriction of travel, a consent form may be sent electronically to participants who have expressed interest in volunteering to the Barts BioResource.

The participant would, if possible print, sign and then scan and return the completed consent form electronically, keeping the original, or they could sign the consent form electronically and return it electronically.

Telephone/electronic means support by Barts BioResource staff would be available to ensure any queries are answered and the participant provides informed consent. An offer to record the conversation could be made if the volunteer wishes and is feasible (and securely stored until full consent is received), but no recording will be done without asking the volunteer first and the volunteer explicitly consenting to recording the conversation.

For Incapacitated hospitalised patients, where necessary verbal consent from a Consultee will be sought in the first instance via telephone/ electronic means conversation. This verbal consent will be documented (or recorded, with the Consultee's explicit consent to record the conversation) and sent electronically to the Consultee, alongside the full consent form for signature and return to the study team.

The same approach will be applied to the Next of Kin as soon as is reasonably practicable and appropriate.

The BBR will develop a robust, transparent and auditable withdrawal system prior to recruitment of these patients and will regularly review such.

Further, we note the principles, provisions and requirements of the Mental Capacity Act 2005 and our teams are experienced in this area.

Risk Analysis: The participation of any patient in the BBR does not convey any significant risk of physical or mental harm. The BBR seeks to collect clinical data and biological materials such as blood, , saliva, throat, buccal or nasopharyngeal swabs, urine, faeces, soft/hard tissue and residual samples from clinically relevant procedures.

The application of this amendment will be continuously reviewed by BHT governance systems.

4. Minor Amendments to the protocol

A range of non-substantive administrative changes have been included to correct and clarify the protocol.

5. Clarifications

SCOPE OF VENUES – The existing REC approval applies to all Barts Health NHS Trust sites – we hereby confirm that the newly formed Nightingale Hospital is part of the Barts Health NHS Trust, and therein is covered by the existing BHT Indemnity and current REC permissions for the BBR.

6. Clarifications

Residual tissue from routine clinical activities – The existing REC approval permits the retention of residual biological tissues and samples that remain after all clinical requirements are completed and the samples related by the relevant Pathology lead(s).

7. Clarifications

Participation in ongoing clinical research studies does not preclude participation in the BBR as it would have no increased risk to the patient or scientific validity of either project, unless said studies specifically preclude entry into observational studies such as the BBR.
Participation in the BBR programme would not preclude participation in additional clinical research studies as it would have no increased risk to the patient or scientific validity of either project.

8. Clarifications

CONTROL GROUP – Existing ~23,400 BBR patients could be considered pre-COVID19 cohort. Currently possible only if the primary question is cardiovascular; however, secondary questions may have broader context. This will remain until these patients have approved the revised BBR scope and have completed a new informed consent form.

[X] 6 – 1st January 2022

1. Non-Substantial Amendments to Protocol

Study Protocol now updated to reflect and further clarify that the Initial Pilot Studies have now finished and their audit findings implemented into the Extended Study.

Further, corrections and clarifications have been added to reflect evolving guidance relating to the UK Dta Protection Act, GDPR and the Barts BioResource compliance strategies such as our Data Security & Protection Kit.

Also, Minor formatting, spelling changes.

None of the changes are regarded as Substantive or in anyway change the nature of the Barts BioResource nor affect the participants.