The Role of Biomarkers in Inherited Cardiac Conditions

STUDY PROTOCOL

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1. INTRODUCTION

1.1. Study Summary

Inherited cardiac conditions (ICC) comprise any hereditary condition, which may affect heart muscle, vasculature, or heart electrical conductive system. ICCs represent a major cause of heart disease in all age groups, and have significant implications for patients and their families.[1] Symptoms vary considerably, from no symptoms to sudden death. Our understanding of these conditions has increased over the past decade, however significant limitations remains in diagnosis and risk stratification of these patients and their families. [2,3]

The NIH has defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".[4]

This study aims to investigate the utility of biomarkers in a large cohort of patients with inherited cardiac conditions with the aim of improving diagnosis and risk stratification. Biomarkers will be related to the presence and severity of cardiovascular disease and other markers of cardiac disease.

As part of this study, all patients with or with suspected ICCs attending clinics in Manchester (University Hospital of South Manchester (UHSM) and Central Manchester University Hospitals (CMFT)) will be approached over a 5 year period. The expectation is to recruit 1000 patients. Patients will undergo their clinic appointments in the usual manner. As part of the study, clinical parameters collected as part of routine care (e.g. clinical history, imaging findings, blood test results, genetic information) will be assessed in relation to each other and in relation to patient outcome over subsequent 10 year follow-up. In addition, a peripheral blood sample of up to approximately 20mL will be taken and stored to allow measurement of blood biomarkers relating to the heart, including genetic analysis, which will be related to the clinical parameters and outcome.

1.2. Hypothesis

We hypothesise that biomarkers will provide important diagnostic and prognostic information in patients with inherited cardiac conditions.

2. BACKGROUND

Inherited cardiac conditions (ICC) comprise any hereditary condition, which may affect heart muscle, vasculature, or conductive system. More than 50 ICCs have now been recognised as our diagnostic capabilities improve. However, whilst our understanding of ICCs and their molecular basis has increased, diagnosis and management of these conditions remains challenging owing to their heterogeneity, both genetically and phenotypically. [1-3]

Sudden death may be the first presentation of ICC, and a new diagnosis has significant implications for patients and family members. Risk may be augmented by a multitude of clinical and genetic factors, which we do not fully understand. There is an urgent need for tools for clinicians to identify patients with ICCs, and identify those with ICCs at increased risk of adverse outcome. Biomarkers, including blood, imaging, genetic and clinical biomarkers may be help diagnosis patients with ICCs, improve prognostication/risk stratification and monitor treatment and disease progression

3. STUDY OBJECTIVES

To investigate the diagnostic and prognostic utility of biomarkers in a large cohort of patients with, or with suspected, ICCs.

4. STUDY DESIGN

4.1. Overview/Design Summary

This is an observational study of patients attending hospital clinics that specialise in the management of patients with ICCs.

4.2. Inclusion Criteria

Any adult patient attending a hospital clinic that specialises in the management of patients with ICCs at UHSM or CMFT.

4.3. Exclusion Criteria

Age < 16 years, imprisonment, inability to provide informed consent.

4.4. Recruitment

Patients due to attend hospital clinics that specialise in the management of patients with ICCs are sent appointment information regarding their clinic appointment as part of usual clinical practice. As part of the study, we will include the study Letter of Invitation and Participant Information Sheet with the information that is sent out and any questions patients have about the study will be answered during their clinic visit. When patients attend a member of the research team will ask them if they are willing to take part, discuss any aspects of the study that they wish and answer any questions. If they are willing to take part a member of the research team will ask them to sign the consent form.
Occasionally patients will attend clinic at short notice in which case the clinical information is not sent out in advance. Given the low risk nature of this study, and the large distances that patients can potentially travel to attend these clinics (tertiary service), in this situation a member of the research team will give patients the Letter of Invitation and Participant Information Sheet while they are in the waiting area. A member of the research team will discuss any aspects of the study that they wish and answer any questions. If they feel that they have had sufficient time to understand the study and what participation involves, and are willing to take part, a member of the research team will ask them to sign the consent form.

4.5. Consent

Patients are required to read the Patient Information Sheet. Fully informed written and verbal consent will be gained from patients before they elect to participate.

4.6. Details of Visits

There will be no visits in addition to standard clinical care.

4.6.1. Clinic Visit

Patients will attend clinic, and any additional clinically indicated hospital appointments, in the usual manner. A peripheral blood sample of up to approximately 20mL will be taken for blood markers of cardiac disease and genetic analysis. Clinical data, including that relating to any imaging, blood test or functional investigations, will be recorded.

4.6.2. Cardiovascular status

Follow-up information regarding cardiovascular disease status, demographics and concurrent medical conditions and treatments will be obtained over the 10 year period following the clinic visit using the following methods:

1. GP and hospital medical records.
2. Central UK bodies, registries, audits and databases (e.g. HSCIC, ONS, NICOR, MINAP) and local health bodies e.g. clinical commissioning groups.
3. Phone call to patients

None of these follow-up procedures will occur more than once yearly.

4.7. Associated Risks and Benefits

The study is associated with negligible risk. The blood sample will be taken peripherally by an experienced member of the research team. There is a rare potential risk associated with confidentiality of medical record information, however this risk will be minimised by running the study in accordance with the Trust guidelines on Confidentiality and Security and the NHS code of practice for confidential patient information.

The use of information collected for this research study may be of future benefit to patients with cardiovascular diseases.

5. STATISTICAL PLAN

5.1. Sample Size and Power Calculation

We will ask each adult patient scheduled to attend hospital clinics that specialise in the management of patients with ICCs at UHSM and CMFT to participate in this research study. The expectation is that over a 5 year period, approximately 200 participants per year may be enrolled in this study. Due to the diversity of the variables being collected, all patients who sign consent will provide meaningful information for this study.

5.2. Statistical Analysis

Multivariable regression modelling will be used to examine relationships between cardiac biomarkers and cardiovascular disease while adjusting for baseline differences of subjects. Chi square or Fisher exact tests will be used to compare categorical variables between patients with different marker levels. Independent samples t tests or Mann Whitney U tests will be used to compare continuous variables between patients with differing marker levels. Survival analysis will use logrank testing and Cox regression.

6. DATA HANDLING

6.1. Confidentiality and Security

Data collected during the study will be stored on a secure database on an NHS computer with restricted access and password entry. A unique identifier made up of numbers and letters will be allocated. All personal data collected during the study will be handled in accordance with the NHS code of practice for confidential patient information.

6.2. Training

It will be ensured that all members of the research team who handle the data are familiar with the policies governing the confidentiality and security of the data collected during the study and SOPs specific to the study will be adhered to. Training records for all members of the research team will be maintained.

6.3. Case Report Forms (CRF) and Source Documents

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, radiographic images and results, and correspondence. CRF entries will be considered source data in this study.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number, not by name. Data will be stored in a database on an NHS computer, with restricted access and password entry. Patients' NHS number and date of birth will be recorded in the database. Other identifiable information will be separated from the rest and stored with the associated study number on a separate computer under password protection in a locked office. This will be used for contacting patients and will not be kept with the study data. A back up copy will be made periodically and stored on a password-protected disk in a secure place.

6.4. Records Retention

Records will be retained in accordance with the UHSM SOP11: 'End of Study Document Storage'. The Principal Investigator (PI) or a nominated deputy will be responsible for all research related documents. Individuals responsible for data who leave the Trust must inform the Research and Development (R&D) Directorate of who will be acting as the custodian of that data.

After an end of study has been declared and acknowledged by the Ethics Committee and, where appropriate the MHRA, the following procedures will be adhered to:
Research documents less than 10 years old will be kept on-site by the PI to facilitate access for audit, information, etc. Where it is not possible to store the documents on-site the PI will arrange for off-site storage via the R&D Directorate. It will be ensured that the documents can be accessed, with short notice if required. A log will be kept by the PI of the documents stored, which will include the following information: box number (1 of 1 etc.), Trial ID, study name, PI, date of storage, date to be destroyed, emergency contact details, Sponsor and contact details.

Research documents over 10 but less than 20 years old will be stored off-site. A log will be kept by the PI of the documents stored.

Any research documents over 20 years old will be destroyed, but prior to destruction, a log will be made, and kept by the PI, of all the documents that are being destroyed. This log will include the following information: Trial ID, Study name, Patient ID, date of destruction, name and signature of authorised person.

7. STUDY ADMINISTRATION

7.1. Organisation and Participating Centres

This is a single-centre study. The study will be conducted at UHSM, which will act as sponsor.

7.2. Funding Source

The study is funded by an external grant from Singulex, who will provide the assays and analysis.

7.3. Study Timetable

Subject to obtaining a favourable opinion from the Research Ethics Committee, we aim to start the study from 1st January 2017.

8. PUBLICATION POLICY

Our expectation is that after data analysis, information from this study will be widely disseminated in the medical and scientific community. This will be achieved through a series of peer-reviewed publications and meeting abstracts at local, national and international events. Anonymised raw data will be shared with the scientific community.

9. REFERENCES

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