Full study title: Characterising disease **M**echanisms in **P**atients with **C**oronary **M**icrovascular **D**isease (ChaMP-CMD)

Protocol Version number and Date	Version 6.0 and date 29.09.2022
IRAS Number	288132
REC Reference	20/LO/1294
ISRCTN number	ISRCTN94728379
Funding source	Medical Research Council

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Version number 6.0
Date 29.09.2022

2 Signature Page

The Chief Investigator and the R&D (sponsor office) have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP, the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005' 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

Professor Divaka Perera

29.09.22

Signature Date

Sponsor Representative

R&D to Add

GSTFT

Signature Date

This Protocol template is intended for use with UK sites only.

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3 List of Abbreviations and Definitions

ANOCA	Angina with unobstructed coronary arteries
CBF	Coronary blood flow
CCS	Canadian Cardiovascular Society
CFR	Coronary flow reserve
CMD	Coronary microvascular disease
CMR	Cardiac magnetic resonance
ETT	Exercise treadmill test
fCMD	Functional coronary microvascular disease
hMR	Hyperaemic microvascular resistance
LVEF	Left ventricular ejection fraction
METs	Metabolic equivalent
MPRI	Myocardial perfusion reserve index
NYHA	New York Heart Association
QOL	Quality of life
SAQ	Seattle Angina Questionnaire
sCMD	Structural coronary microvascular disease

4 Summary/Synopsis

Title	Characterising disease mechanisms in patients with coronary microvascular disease
Protocol Short Title/Acronym	Disease mechanisms in CMD
Protocol Version number and Date	Version 6.0 and date 29.09.2022
IRAS Number	288132
REC Reference	20/LO/1294
Study Duration	36 months
Sponsor name	King's College London and Guy's and St. Thomas' Hospital NHS Foundation Trust
Chief Investigator	Professor Divaka Perera
Funder	Medical Research Council
Medical condition or disease under investigation	Angina with non-obstructive coronary arteries
Study aim	To determine if invasive characterisation of patients with angina and non-obstructive coronary arteries (ANOCA) predicts response to anti-ischaemic therapy
Hypothesis I	Patients with ANOCA and coronary microvascular disease will have a greater improvement in their exercise capacity in response to anti-ischaemic therapy, compared to patients with ANOCA and normal microvascular function
Hypothesis II	Endotyping CMD will allow selection of more specific therapies than identifying CMD alone.
Number of Subjects/Patients	74 patients for hypothesis I 36 patients for hypothesis II
Study Type	Prospective single-centre phenotype-blinded randomised crossover study
Study duration	12 weeks
Anti-ischaemic therapy	4 weeks of amlodipine and 4 weeks of ranolazine (in a randomised order)

Main Inclusion Criteria	Inclusion criteria: i) Typical angina, ii) unobstructed coronary arteries (fractional flow reserve >0.80) and iii) normal left ventricular systolic function

5 Background and rationale for study

Stable exertional angina can be due to a flow limiting atheromatous plaque in the epicardial coronary arteries or due to dysfunction of the coronary microvasculature. Up to 50% of patients with angina have non-obstructive coronary arteries (ANOCA) [1], which comprises several distinct pathophysiological entities, such as coronary microvascular disease (CMD) and coronary artery spasm. CMD is diagnosed when there is an inadequate augmentation in coronary blood flow (CBF) in response to adenosine, and is referred to as an impaired coronary flow reserve (CFR); diagnostic threshold of 2.5 has the optimal sensitivity and specificity to detect a substrate for myocardial ischaemia and coronary perfusion inefficiency in response to exercise [2]. It has recently been demonstrated that CMD itself may be a heterogeneous condition comprising two distinct subtypes (functional and structural CMD) [3]. Functional CMD is characterised by an elevated resting baseline CBF, due to vasodilation at rest, leading to a suboptimal vasodilatory capacity in response to stress, despite normal microvascular resistance. By contrast, structural CMD is characterised by elevated microvascular resistance, which is the main determinant of diminished vasodilator capacity in response to stress. Both groups have attenuated flow reserve and a high prevalence of ischaemia. Impaired CFR predicts adverse cardiovascular outcomes [4] and patients with sCMD and fCMD both have similar rates of adverse outcomes [5]. Finally, stress perfusion cardiac magnetic resonance (CMR) imaging derived quantitative parameters, such as myocardial perfusion reserve index (MPRI), have been shown to predict invasively measured CFR [6]. However, it remains unknown whether impaired CFR and MPRI predict response to anti-ischaemic therapy in patients with ANOCA.

6 Study aim

To determine if invasive characterisation predicts response to anti-ischaemic therapy in patients with ANOCA.

7 Outcome measures

7.1. Primary outcome measure

Change in exercise time (in seconds) compared with baseline exercise time on a Full Bruce Protocol. An improvement in exercise duration is a meaningful outcome to patients and has been the gold standard endpoint for therapy trials in patients with stable angina.

A within-subject improvement in exercise time of 30 seconds on the Bruce protocol is taken as clinically relevant [7]. Our study is powered to identify an improvement in exercise time of 60 seconds or longer in response to anti-ischaemic therapy, which is in line with seminal anti-anginal therapies in patients with obstructive coronary artery disease.

Exercise test duration is a repeatable measurement. In a study of repeated exercise testing in older women the intra-class correlation coefficient of exercise duration was 0.88 [8].

7.2. Major secondary outcome measure

Change in Seattle Angina Questionnaire (SAQ) Summary Score compared with baseline.

7.3. Other secondary outcome measures

7.3.1. Exercise treadmill test:

- Change in Time (s) to 0.1mV ST-depression compared with baseline
- Change in rate pressure product at 0.1mV ST depression compared with baseline
- Change in Maximum ST-segment deviation (mV) compared with baseline
- Change in Metabolic equivalent (METs) compared with baseline

7.3.2. Seattle Angina Questionnaire

Change in SAQ Component scores (Angina Limitation, Angina Stability, Angina Frequency, Treatment Satisfaction and Quality of Life) compared with baseline

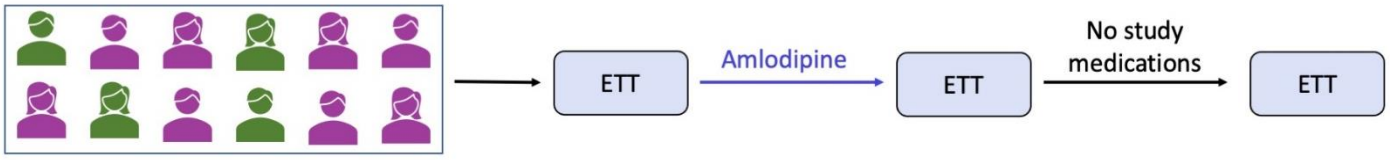
7.4. Exploratory outcome measures

- Change in delta (pre- and post- exercise) cardiac biomarkers compared with baseline
- Change in smartphone device derived stepcounts compared with baseline

8. Hypotheses and sample size calculations

8.1. Hypothesis I_A

Patients with ANOCA and coronary microvascular disease (CMD, defined by a CFR≤2.5) will have a greater improvement in their exercise capacity in response to Amlodipine, compared to patients with ANOCA and normal microvascular function (controls, defined by a CFR>2.5



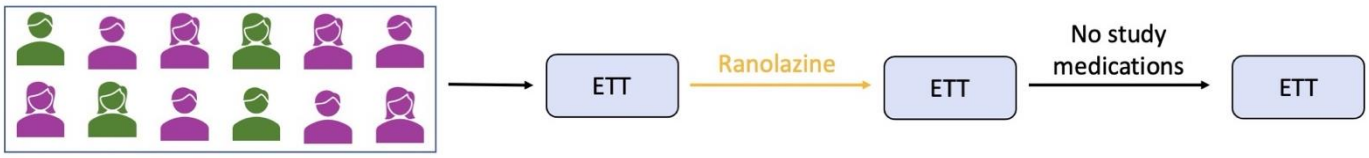
Control (no ischaemic substrate) Coronary microvascular disease (ischaemic substrate)

Assuming a 2:1 allocation ratio (as reported in the literature for patients with high pre-test probability of disease), 49 patients with CMD and 25 controls will provide 80% power (α=0.05) to detect a 60 second* difference in exercise time between the groups (standard deviation for change in exercise time is 85 seconds).

** The minimum clinically meaningful difference is considered 30 seconds.*

8.2. Hypothesis I_B

Patients with ANOCA and coronary microvascular disease (CMD, defined by a CFR≤2.5) will have a greater improvement in their exercise capacity in response to **Ranolazine**, compared to patients with ANOCA and normal microvascular function (controls, defined by a CFR>2.



Control (no ischaemic substrate) Coronary microvascular disease (ischaemic substrate)

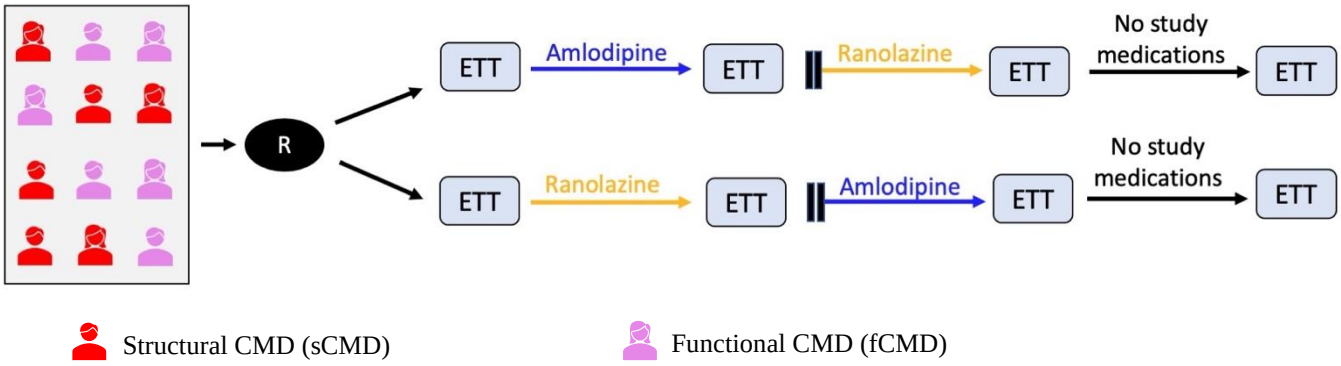
The power calculations for hypothesis I_A applies here.

8.3. Hypothesis II_A

Endotyping CMD will allow selection of more specific therapies than identifying CMD alone. We hypothesise that patients with *functional* coronary microvascular disease (fCMD, defined by a CFR≤2.5 and hMR<2.5mmHg/cm/s) will have a greater improvement in their exercise capacity in response to ranolazine compared to amlodipine.

8.4. Hypothesis II_B

Patients with *structural* coronary microvascular disease (sCMD, defined by a CFR≤2.5 and hMR≥2.5mmHg/cm/s) will have a greater improvement in their exercise capacity in response to amlodipine compared to ranolazine.



Assuming a 1:1 allocation ratio, 18 patients with functional CMD will provide 80% power (α=0.05) to detect a 60 second difference in exercise time in response to Ranolazine versus Amlodipine (hypothesis II_A) and 18 patients with structural CMD will provide 80% power (α=0.05) to detect a 60 second difference in exercise time in response to Amlodipine versus Ranolazine (hypothesis II_B) (standard deviation for change in exercise time is 85 seconds).

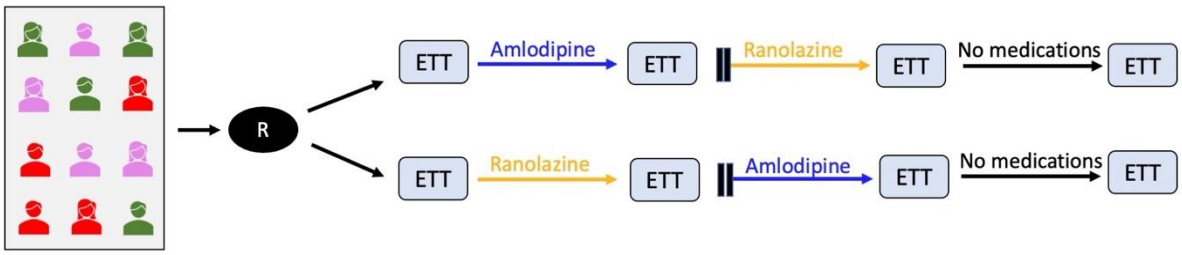
Additionally, the following sample sizes will be required to show the following treatment effects (80% power and (α=0.05):

Treatment effect (seconds)	Sample size
30	66 patients with fCMD and 66 patients with sCMD
45	30 patients with fCMD and 30 patients with sCMD

Carryover effects will be minimised by the inclusion of a 7-day washout period between the two anti-ischaemic therapies; however, we will carry out formal testing for carryover effects before assessing for treatment effects. The presence/absence of period (training) effects will be assessed by the change in exercise time at the 4th visit compared to the 1st visit.

Therefore, the sample size required to confirm/refute hypothesis I will provide adequate power for hypothesis II.

To maintain **phenotype blinding** throughout, both experiments will be carried out in parallel to each other as part of a master study design (study flow chart below).



8.5. Cardiac magnetic resonance (CMR) imaging substudy

A myocardial perfusion reserve index (MPRI) of <2.2 on quantitative stress perfusion CMR identifies patients with an impaired CFR with an excellent diagnostic accuracy. We wish to assess the utility of quantitative stress perfusion CMR in predicting response to anti-ischaemic therapy in patients with ANOCA. A cohort of patients who have undergone paired coronary physiology and quantitative stress perfusion CMR assessment will be included in this substudy.

8.5.1. Hypothesis III$_A$

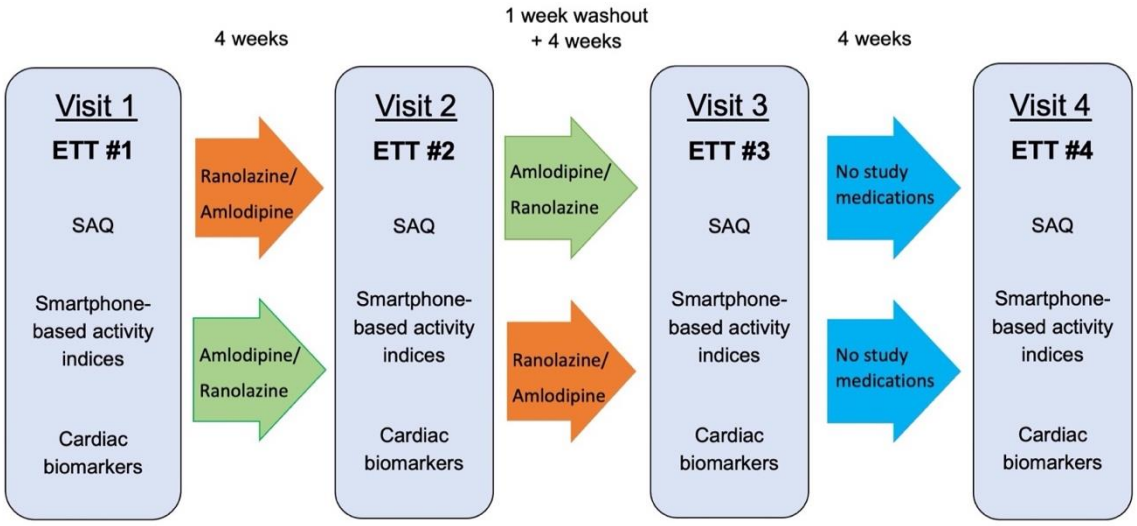
Patients with a *non-invasive diagnosis of CMD* (MPRI<2.2) will have greater improvement in their exercise capacity in response to amlodipine, than patients non-invasively classified as controls (MPRI≥2.2).

8.5.2. Hypothesis III$_B$

Patients with a *non-invasive diagnosis of CMD* (MPRI<2.2) will have greater improvement in their exercise capacity in response to ranolazine, than patients non-invasively classified as controls (MPRI≥2.2).

9 Study flow diagram

This is a randomised, phenotype-blinded, cross-over trial in patients with ANOCA.



Abbreviations: ETT: exercise treadmill test; SAQ: Seattle Angina Questionnaire

Trial activity	**Visit 0**	**Visit 1**	AML Or RNL	**Visit 2**	RNL Or AML	**Visit 3**	**Visit 4**
Coronary angiography with physiology assessment	√						
Written Informed Consent		√					
Vital signs		√		√		√	√
ECG, 12-lead		√		√		√	√
Blood test - lipid profile, HbA1c NTproBNP		√					
Exercise treadmill test		√		√		√	√
Seattle Angina Questionnaire		√		√		√	√
Delta (pre- and post- exercise) cardiac biomarkers		√		√		√	√
Smartphone-based activity indices		√		√		√	√
Randomisation		√					
Dispensing of study medicines		√		√			

10 Study eligibility criteria

10.1. Subject inclusion criteria

- Typical exertional angina (CCS≥2)
- Unobstructed coronary arteries (fractional flow reserve >0.80)
- Normal left ventricular systolic function (LVEF >50%)

10.2. Subject exclusion criteria

- Patients who are unable or unwilling to consent
- Contraindications to adenosine
- Contraindications to Amlodipine and/or Ranolazine

- Patients who are already taking the study medications for clinical reasons and are unable to stop them
- Presence of more than moderate valve disease
- Previous percutaneous coronary intervention or bypass surgery
- Known structural heart disease (e.g. cardiomyopathy or congenital heart disease)
- Pregnant or breastfeeding females
- Patients who are unable to exercise on a treadmill or those who can exercise for >540seconds in the absence of any revealed cardiac symptoms on baseline exercise test

11 Study procedures

11.1.Clinical evaluation and documentation following consent

The following information will be gathered after written informed consent has been obtained. This information will be reviewed at subsequent visits to inform the current medical status at each visit.

Demographics: Age, sex, ethnic group
Medical History: LVEF (%) from cardiac imaging, Hypertension, Diabetes, Hyperlipidaemia, Smoking history
Concomitant Medications
Clinical Assessment: Body mass index, NYHA, CCS, angina typicality score

11.2.Schedule of assessments for each visit

There will be four visits as part of the exercise protocol (see study flow chart above). Patients will undergo an exercise treadmill test, fill out an angina-specific quality of life questionnaire (Seattle Angina Questionnaire; SAQ), undergo pre- and post- exercise blood tests (post-exercise blood test will be taken 2 hours after exercise) and their smartphone-based step counts will be recorded. Patients will be randomised to either Ranolazine or Amlodipine using a 1:1 randomisation model during visit 1. Patients will return after four weeks for their visit 2 and undergo the same measurements as above. Patients will then observe a one-week washout period, following which they will cross over to the other anti-ischaemic agent. Patients will

return after four weeks of taking the second anti-ischaemic agent for their visit 3 and undergo the same measurements as above. Patients will then be requested to stop the study medications and return for visit 4 after 4 weeks, where they will have the measurements as above. This will mark the end of the protocol.

11.3.Randomisation

Randomisation will occur during Visit 1 after the baseline assessments. Eligible and consenting patients will be randomised with equal probability to the two groups reflecting the sequential order of Amlodipine or Ranolazine (Amlodipine-Ranolazine and Ranolazine-Amlodipine). The crossover nature of the trial means that each patient serves as their own control and, therefore, a more complex means of randomisation (such as block or stratified randomisation) is not necessary.

11.4.Blinding

The study is phenotype-blinded, i.e the trial participants and researchers will be blinded to patients' coronary physiology and cardiac MRI data as soon as the data is acquired. Outcome assessment (end point adjudication) will be undertaken in a blinded fashion.

11.5.Trial medication

Adherence with trial medication will be assessed at Visits 2 and 3 by a tablet count and participant-reported adherence with therapy. If participants have less than 80% adherence to a medication then they will not be included in the analysis pertaining to that medication [9]. Ranolazine will be started at 375mg twice a day regimen, with a view to uptitrate in 1-2 weeks after a repeat ECG (to ensure there hasn't been QTc prolongation). If dose uptitration is not possible then the reason for this will be documented. Amlodipine will be started at 5-10mg and then uptitrated to the maximal tolerated dose within 1-2 weeks of commencing the drug.

12. Treatment Interruptions and Withdrawal criteria

12.1. Withdrawal from Study Drug

Participants may be withdrawn from receiving study treatment based on their own preference or based on the clinical judgement of their physician. Participants experiencing symptoms potentially attributable as severe side-effects from study treatment should have the trial medication withheld.

If a patient withdraws from one drug but is able to complete four weeks of the other drug, then they will be included in the analysis of the completed drug.

12.2. Withdrawal from the study

Participants have the right to withdraw from the study at any point as stated within the patient information sheet. If a patient completes four weeks of one drug but withdraws during the second drug phase then the response to the first drug will be included in the analysis. Patients who have a >1 week delay in attending their exercise treadmill test (during visits 2-4) will be excluded from analysis and the reasons for the delay documented.

13. Role of study sponsor and funder

King's College London and Guy's and St. Thomas' NHS Foundation Trust (sponsor)

The lead sponsor, King's College London, will take primary responsibility for ensuring that the design of the study meets appropriate standards and arrangements are in place to ensure appropriate conduct and reporting. King's College London also provides cover under its No Fault Compensation Insurance, which provides for payment of damages or compensation in respect of any claim made by a research subject for bodily injury arising out of participation in a clinical trial or healthy volunteer study (with certain restrictions).

The co-sponsor, Guy's and St Thomas' NHS Foundation Trust, take ultimate responsibility for ensuring that appropriate standards and conduct are adhered to regarding its facilities and staff involved with the project. They will ensure that facilities and permissions are correct, and access to patients is allowed.

Medical Research Council (MRC) (funder)

The study has been funded by a clinical research training fellowship (CRTF) grant from the Medical Research Council. The Medical Research Council does not have a designated role or responsibility in trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. Reports in relation to progress of the trial will be submitted to the MRC. Support from the MRC will be acknowledged in any publications related to the study.

14. Roles and responsibilities of the Trial Steering committee (TSC)

The role of the TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The TSC will:

- Agree the trial protocol and substantial protocol amendments
- Agree the statistical analysis plan
- Advise on the results dissemination strategy

Decisions about continuation or termination of the trial or substantial amendments to the protocol will be the responsibility of the TSC who will advise the co-sponsors. The TSC will meet at the start of the study, and annually thereafter.

15. Ethics

15.1.Ethics reporting

The study will be conducted in compliance with the principles of the Declaration of Helsinki (2013) and the principles of GCP and in accordance with all applicable regulatory guidance, including but not limited to the UK Policy Framework for Health and Social Care 2017.

This protocol and related documents (and any subsequent amendments) will be submitted for review to the relevant parties (HRA and REC). Annual progress reports and a final report at the conclusion of the study will be submitted to the REC within the timelines defined.

The CI shall submit once a year throughout the study or on request, a progress report to the REC and sponsor. In addition, an end of study notification and final report will be submitted to the same parties.

Reports of related and unexpected adverse events will be submitted to the Main REC within 15 days of the chief investigator becoming aware of the event, using the NRES template. A copy of the adverse event notification and acknowledgement receipt will be sent to the R&D Directorate.

15.2.Ethics and Regulatory Approvals

- Before the start of the study, approval will be sought from HRA and REC for the protocol, informed consent forms and other relevant documents.
- Amendments that require review by HRA and REC will not be implemented until approval is granted.
- The chief investigator also needs to notify the R&D offices and local research teams about the amendment(s).
- All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.
- A progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the Chief Investigator's responsibility to produce the annual reports as required.
- The Chief Investigator will notify the REC of the end of the study.
- If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.
- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

16. Data handling and record keeping

16.1.Managing, storing and curating data.

Study numbers will be generated for each participant at the time of recruitment. A recruitment log, linking each participant's details to their study number will be kept in hard copy locked in the research office in the hospital and an electronic backup held on the hospital trust network. No patient identifiable information will be transferred from the NHS trust to the university. Demographic data will be collected in an anonymised fashion from the patient's clinical notes. Data will be stored on King's College London University computers with centralised storage and automated back-up, along with a working set on an encrypted removal drive, and on our own group's internal server. Data will be subject to encrypted regular back-up to King's College London secure server using King's College London Encryption Policy: http://www.kcl.ac.uk/governancezone/InformationPolicies/Encryption-Policy.aspx. In addition, we maintain a full audit trail of all data. Data will be kept stored on University computers for up to 5 years.

16.2.Access to Data

Direct access will be granted to authorised representatives from the sponsor and host institution for monitoring and/or audit of the study to ensure compliance with the relevant data protection legislation. Only members of the Research Team will have access to data.

16.3.Participant Confidentiality and Data Protection

All investigators and study site staff must comply with the requirements of the General Data Protection Regulation (GDPR) and Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

17. Reporting and dissemination

We aim to communicate the results of our work to a wide audience. The work will be published on the department's website on the King's College London server, as well as my own personal page on the King's College London server. In addition, it is intended that the findings will be presented as abstracts at key public meetings including the British Cardiovascular Society, European Society of Cardiology, American Heart Association and American College of Cardiology, where others will have the chance to obtain insight into our work. They will also be submitted for publication in the leading peer-review journals in the field of Cardiology.

We will make available the raw data within supplementary appendices of published articles or directly to interested third parties. This will permit other groups to test and validate our results and inform further research they may wish to undertake.

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9. Essential Medicines and Health Products Information Portal - A World Health Organization resourcehttp://apps.who.int/medicinedocs/en/d/Js4883e/