NHS
Health Research Authority

STUDY PROTOCOL

Assessing the impact of using community-based heart testing to detect early signs of cardiovascular disease through a novel, quick, low-cost test which uses sophisticated AI-based analysis.

Cardisio - Detection of Heart disease in Primary Care/ Cardisio - PC

PREFACE

i. STUDY REFERENCE NUMBERS

IRAS Project ID:	330192
FUNDERS Number	SBRIH21P3013
PROTOCOL VERSION NUMBER:	Version 1.00 Revision ~~1~~3
ISRCTN registry ref:	ISRCTN13922377 ~~43809~~
DATE:	~~16h June~~ 10th August 2023
SPONSOR	Cardisio UK Limited

ii. SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the Study in compliance with the approved protocol and will adhere to the principles outlined in therein. I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the conduct of the study without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: **Date: 16/06/2023**

Name (please print): John Fitzpatrick

Position: Sponsor – Director Cardisio UK Ltd

Chief Investigator:

Date: 16/06/2023

Signature:

Name: (please print):

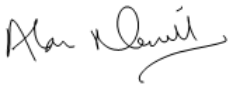
Dr Nisar H Shah

Position: Consultant Cardiologist

Statistician:

Date: 16/06/2023

Signature:



Name: Professor Alan Nevill

Position: Emeritus Professor University of Wolverhampton

iii. KEY STUDY CONTACTS

Chief Investigator	Dr Nisar H Shah MBBS; MRCPI; FCPS (Pak) Consultant Cardiologist Heart Failure, Syncope & Complex Devices Sandwell & West Birmingham NHS Trust Secretary: Sandra Payne; Tel: 0121 507 5048 (Ext 5048); Email: sandra.payne10@nhs.net
Study Co-ordinator	Gary J. Herbert, MSP, Prince-2 Heartscreen UK Ltd 45 Pall Mall, London SW1Y 5JG Tel: 0203 916 5133 Email: info@Heartscreen.co.uk
Sponsor	John Fitzpatrick Cardisio UK Ltd G1 2 Harris Close Frome, BA11 5JY (UK) info@cardis.io
Funder(s)	1. NHS Nottingham University Hospitals Hospital NHS Trust Trust Headquarters, City Hospital campus, Hucknall Road, Nottingham, Nottinghamshire, NG5 1PB 2. Cardisio UK Limited John Fitzpatrick G1 2 Harris Close, Frome, BA11 5JY, United Kingdom info@cardis.io 3. Cardisio GmbH Meik Baumeister, Klaus Tenderich The Squaire 12, 60549 Frankfurt am Main, Germany
Key Protocol Contributors	**1.** Protocol Compilation

	Caroline Schmidt-Lucke, MD, PhD Assistant Professor Charité Managing Partner, MEDIACC GmbH Medico-academic Consultings Sächsische Str. 70, 10707 Berlin Tel.: +49 30 521 044 80 Fax: +49 30 521 044 83 caroline.schmidt-lucke@mediacc.org www.mediacc.org 2. Chief Investigator oversight & protocol input Dr Nisar H Shah Kelly Hard 3. Cardisio Test oversight & protocol input John Fitzpatrick Gary Herbert
Committees	• STUDY STEERING COMMITTEE • STUDY MANAGEMENT GROUP • Public Patient Involvement and Engagement (PPIE) Advisory Board.

iv. TABLE OF CONTENTS

v. LIST OF ABBREVIATIONS

Definition of all specific, unusual or 'technical' terms related to the Study that have either been used in the Protocol documentation or in the references made to other Cardiovascular research.

(In alphabetical order for ease of reference) Revision Date: 2023 05 07

#	Abbreviation	Meaning
	5L3DVCG-AI	The Cardisio test – a 5-lead 3D-Vectorcardiography test using Artificial Intelligence to assess heart health risk
A	AE	Adverse Event
	AI	Artificial intelligence
	AR	Adverse Reaction
C	CA	Competent Authority
	CABG	Coronary artery bypass graft
	CARDISIO	The Cardisio Test - 5L3DVCG-AI
	CG	Control group
	CI	Chief Investigator
	CMG	Cardiogoniometry
	CRF	Case Report Form
	CRO	Contract Research Organisation
	CSG	Cardisiograph
	CVD	Cardiovascular disease
	CVRF	Cardiovascular Risk Factor
D	DHT	Digital Health Technology
	DMC	Data Monitoring Committee
	DoB	Date of Birth
	DR	Diagnostic result
E	EC	European Commission
	EHRA	European Heart Rhythm Association
	EMIS	Web Based system to store Medical records
	EU	European Union
	EUCTD	European Clinical Trials Directive
G	GCP	Good Clinical Practice
	GP	General Practitioner
	GP/PCN	General Practitioner/Primary Care Network
H	HADS	Hospital Anxiety and Depression Scale
I	IB	Investigator Brochure

	ICF	**Informed Consent Form**
	IG	**Intervention group**
	ISF	**Investigator Site File (This forms part of the TMF)**
	ISRCTN	**International Standard Randomised Controlled Trials Number**
M	**MA**	**Marketing Authorisation**
	MPS	**Myocardial SPECT**
N	**NHS R&D**	**National Health Service Research & Development**
	NYHA	**New York Heart Association**
P	**PCI**	**Percutaneous coronary intervention**
	PCN	**Primary Care Network**
	PI	**Principal Investigator**
	PIC	**Participant Identification Centre**
	PIS	**Participant Information Sheet**
Q	**QA**	**Quality Assurance**
	QC	**Quality Control**
	QP	**Qualified Person**
R	**REC**	**Research Ethics Committee**
	RAP	**Rapid Access test**
S	**SAE**	**Serious Adverse Event**
	SDV	**Source Data Verification**
	SMF	**Study Master File**
	SMG	**Study Management Group**
	SOP	**Standard Operating Procedure**
	SP	**Study Participant**
	SPECT	**Single-photon emission computed tomography**
	SSC	**Study Steering Committee**
	SSI	**Site Specific Information**
	STF	**Study Test File**
	SysTMOne	**Web Based system to store Medical records**

vi. LIST OF DEFINITIONS

Citizen:	Person at potential risk of CVD
Study Participant:	Person who meets the inclusion criteria to participate in the Study
Family history of CVD 1	Male next of kin were diagnosed with CVD before they were 55 Female next of kin were diagnosed with CVD before they were 65
Patient:	Person with a subsequent diagnosis made by the Secondary Care Team
PI, User or Administrator:	Person performing the Cardisio Test (5-lead 3D-Vectorcardiography with AI)
Cardisio Test	The Cardisio 4-minute heart screening test is approved for use in the UK and Europe. The test delivers the result three minutes later and is highly accurate. Using electrocardiograph (ECG) signals, the Cardisio CAD screening tool uses advanced computing techniques to create a 3D-image of the heart's electrical distribution. Artificial Intelligence-based analysis identifies differences in electrical patterns that are typical of the disease

vii. STUDY SUMMARY

Study Title	**Assessing the impact of using community-based heart testing to detect early signs of cardiovascular disease through a novel, quick, low-cost test which uses sophisticated AI-based analysis.**
Internal ref. no. (or short title)	**SBRIH21P2013**
Clinical Phase	**Post-market, non-invasive**
Study Design	**This is a multicentre, partly randomised controlled, non-invasive study, designed with a focus on the application of consistent methods and processes for recruitment and selection principles, test preparation as well as gaining consent and feedback. The study also has designed post-test processes and the role of the Secondary Care Team.**
Study Participants	**Participants at risk of cardiovascular diseases in the community, that meet the Study inclusion criteria (as detailed in the exclusion and inclusion methodology agreed by the Chief Investigator and Study team). The test can identify whether Study Participants have an additional risk of coronary artery disease, arrhythmias and structural heart defects that will help to inform the appropriate subsequent care pathway (secondary or primary).**
Planned Sample Size	**811 participants**
Treatment duration	**Not applicable. A Study Participant will follow the standard Secondary Care pathways if assessed with a CVD risk requiring attention or otherwise under the Primary Care pathway**
Follow up duration	**12 Months - based on current duration of standard Secondary Care pathways defined in the NHS.**
Planned Study Period	**9 months (Q2 2023 to Q4 2023 inclusive)**

viii. Objective and Outcomes of the Study

This study is designed to assess how a relatively simple CVD test procedure can be used in conjunction with existing NHS community-based CVD prevention strategies for earlier detection of CVD.

The proposed Cardisio test procedure is new to the UK market and uses sophisticated AI-based algorithms to detect the early signs of heart disease. The Cardisio Test is easy to train staff in its use, simple to conduct and produces results quickly and accurately.

The study objective is to show that the Cardisio Test can be easily integrated into an existing NHS care pathway (NHS Right Care CVD Prevention) in a variety of community & primary care settings.

The secondary outcome is to gain real world evidence of its performance as a tool to aid clinicians with the early detection of heart disease in community-based settings. Findings from this study will be incorporated into a proposed ICS-based national roll-out plan.

Study objectives and outcomes are detailed below.

Primary Objective	Primary Outcomes	Outcome measures
To assess how a relatively simple CVD test procedure can be used in conjunction with existing NHS community-based CVD prevention strategies for earlier detection of CVD.	1. Cardisio can be used in community settings without extensive training or specialist knowledge by the tester.	• Test results gathered. • Feedback from the test administrators and PI's. • Reported confidence of the secondary care team of the reliability of test collected.
	2. Secondary Care teams can review all the Cardisio Test results remotely in a single ICS-based portal.	• Secondary care team successfully access test results across the study participant group. • The number or percentage of correct predictions (true positives plus true negatives)
	3. The addition of Cardisio test / risk information results in fewer patient journeys to busy hospitals for tests. contributing to the NHS Net Carbon Zero targets	• Number of Patient Journeys • Comparison of referral after Cardisio test versus typical referral with current CVD Pathway V5. https://www.england.nhs.uk/rightcare/wp-content/uploads/sites/40/2018/02/cvd-pathway.pdf

	4. The Cardisio Test delivers a superior and richer test result when compared to a traditional 2D ECG. More data about disease conditions will improve the cardiologists ability to diagnose or clarify next steps.	• Feedback from CI and secondary team plus feedback from GP/PCN PI.
	5. To demonstrate that a revised care pathway could be considered by the NHS for future adoption, based on a "hub and spoke" central cardiology team reviewing test results and selecting patients for further diagnostic test procedures, a so-called "pull model". 6. Better availability of community testing should offer a better patient experience. 7. Through the use of Allied Healthcare Professionals to undertake routine testing, a reduction in GP appointments should be possible. 8. Secondary care teams will be able to triage and prioritise patients, making better use of scarce resources.	• Feedback from Participants Surveys. • Feedback from PIs in Pharmacy Setting and analysis of referrals made. • Feedback from CI and secondary care team.
Secondary Objectives	Secondary Outcomes	Outcome measures
To gain real world evidence of the Cardisio test performance as a tool to aid the early detection heart disease in community-based settings	**1.** Evidence of how the test environment is integrated into a Primary Care Setting.	• Ease with which the primary care administrators can undertake recruitment selection and testing of study participants as recorded in the "Participant Testing Log". • Test Environment Readiness assessment completed with ease.

	2. Feedback on the ease of training in person and online training materials.	• Feedback from PI's and test administrators gathered via survey and structured interviews.
	3. Feedback on the ease of test procedure and administration.	• Feedback from PI's and test administrators gathered via survey and structured interviews.
	4. Feedback on patient experience and preference for community-based testing	Feedback from Participants gathered via pre and post test surveys to assess: • How easy was it to understand the purpose of the study. • How easy it was to undertake the test. Using a scale of 1-5.
	5. The view of the secondary care (cardiology) team of the process and impact on the quality of their patient lists.	• Feedback from CI and team gathered via survey and structured interviews.

ix. Study Participant Selection Summary

Study Population	The Study Population is focused on an urban population with a demographic mix across ethnicities, socio-economic profiles. The Study Management team comprises primary and secondary care professionals, the study project team, the Cardisio team, and other specialists involved in various independent oversight roles including for the ESG aspects of the Study. This team is keen to understand how the early detection of CVD can also benefit those hard to reach patients, and those under-served communities, which has lead to health inequality. The Study location selected is the Sandwell and West Birmingham area, which offers an ideal population profile for the Study. Three different Primary Care Settings have been identified for inclusion as partners in the Study in addition to the Secondary Care Team at Sandwell & West Birmingham Hospitals NHS Trust. The Study Design has incorporated an agreed methodology for recruiting and selecting the Study Participants, and this allows for the differences in the Care Settings. The Study excludes persons who already present known CVD conditions, such as known CAD, previous myocardial infarction or typical angina, whether evidenced through their medical history or their medication profile. The Study also excludes: • those that are under 18 or over 75 years of age. • those that are pregnant And also where there is a Study conflict: • those that are participating in other studies • Or unable to provide consent due to offering poor compliance or have mental disorders, or are incapable of providing their consent to participate The full recruitment and selection methodology is outlined in this Protocol document.

Study Groups/Selection Group	All people in the Primary Care setting population that meet the inclusion criteria, and are not excluded by the factors detailed above, that are then selected for participation according to a randomised final selection or as walk-ins.
The Test	The Cardisio Test is a 5-lead 3D-Vectorcardiography with AI ("5L3DVCG-AI"), 5 Leads and a gateway device paired with the Cardisio Cloud, test analysis and reporting service.
Study Test Locations	GP practice, and pharmacies in 4 community locations in Sandwell and West Birmingham, United Kingdom **1.** Church Rd. Surgery, Aston – Single Location **2.** Dudley Integrated Health, NHS Trust – Various Locations as part of their community out-reach Pharmacy initiatives **3.** Shiraz Sons (Crest Pharmacies) 3a – Standalone Pharmacy locations - Faraday 3b – Co-located Pharmacy location (with GP surgery) - Ridgacre.
Study Timetable	Participant-related: - Pre-test ▸ Recruitment & Selection for inclusion in the Study - Test ▸ Administration of the Cardisio Test "5L3DVCG-AI" at time-point of initial presentation of the Study Participant - Post-test ▸ Report of results via correspondence from the Secondary Care team and further follow ups as necessary using the standard primary care pathway or secondary care pathway. Study-related: - Study Mobilisation & Start: Q1/Q2 2023 - Study Start: Q3 / 2023 - Preparation & Recruitment period: Q2/Q3 2023 - Secondary Care assessments: Q3 2023 - Post-Test Analysis & Reporting: Q4 2023 - Expected completion date: 11.12.2023

x. FUNDING AND SUPPORT IN KIND

Names and contact details of ALL organisations providing funding and/or support in kind for this trial.

FUNDER(S)	SUPPORT GIVEN (FINANCIAL AND NON FINANCIAL)
SBRI HealthCare Ltd 15 Church St, Twickenham TW1 3NL, UK	Non-Financial Support: Programme and Project management oversight
NHS Nottingham University Hospitals Hospital NHS Trust Trust Headquarters, City Hospital campus, Hucknall Road, Nottingham, Nottinghamshire, NG5 1PB, UK	Financial Support: Cardisio GmbH – awarded £342,484 – Assessing the impact of using community-based heart testing to detect early signs of Cardiovascular Disease through a novel, quick, low-cost screener which uses sophisticated AI-based analysis
Cardisio UK Limited John Fitzpatrick G1 2 Harris Close, Frome, BA11 5JY, UK	Financial & Non-Financial Support: Study Sponsorship and Governance
Cardisio GmbH Meik Baumeister, Klaus Tenderich The Squaire 12, 60549 Frankfurt am Main, Germany	Non-Financial: Study technical support and access to Cardisio servers to perform live participant testing.
Eastern AHSN Joanne Dempsey Ground Floor, Unit C, Magog Court, Shelford Bottom, Cambridge CB22 3AD	Non-Financial: Project Support, including Nice Metatool support

xi. ROLE OF STUDY SPONSOR AND FUNDER

The sponsor is Cardisio UK Limited who has entered into a contract with the funders, Nottingham University Hospitals Hospital NHS Trust, to undertake a study to assess the feasibility of implementing the Cardisio service into community and GP practice within the UK. The sponsors are the owners, manufactures and designers of the Test system being used and have overall responsibility for the design, conduct and completion of the Study project.

The funder is Nottingham University Hospitals Hospital NHS Trust. They have provided the funding for the study via SBRI Healthcare Ltd, whose remit is to support and enable MedTech companies to engage and embed new technologies in the NHS to improve health and social care delivery through science and innovation.

xii. ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT

Role	Position and/or Organisation	Name
Chief Investigator	Consultant Cardiologist Sandwell and West Birmingham NHS Trust	Dr Nisar Shah
Study Advisor	Head of R&D Sandwell and West Birmingham NHS Trust	Kelly Hard
Project Manager / Study co-ordinator	Heart Screen Limited	Gary Herbert
Sponsor	Cardisio UK	John Fitzpatrick
Principal Investigator PCN	Church Road PCN	Dr. Sajjad Sarwar
Principal Investigator Community Health / Pharmacy	Dudley Integrated Health & Care Trust	Jaspal Johal
Principal Investigator Community Pharmacy (Commercial)	Shiraz & Sons Pharmacy	Junaid Duberia

xiii. PROTOCOL CONTRIBUTORS

Protocol Component	Name(s)
Study Design	Dr N. Shah (Cardiologist), Prof. C. Schmidt-Lucke (Cardiologist)
Writing of the Protocol	Prof. C. Schmidt-Lucke (Cardiologist)
Statistics	Alexander Passow (Statistician Sponsor), Professor Alan Nevill (Statistician)

xiv. KEY WORDS

Cardiovascular disease, Primary care, Diagnostic, Vectorcardiography, Community testing

xv. OVERVIEW OF THE STUDY PROGRAMME

STUDY STAGES	STAGE ACTIVITIES
[A] PREPARE	Focused on preparing the arrangements with participating parties and teams
[B] MOBILISE	Focused on mobilising the Study Group team including primary and secondary care teams, independent specialist support
[C] SETUP	Focused on setup of the study including formulating the Study Protocol, the development of the consistent methodologies to recruit and select study participants, provision of training for both primary and secondary care setting professionals, the arrangements for testing to be conducted, hardware and software provision, patient documentation, survey questionnaires, control documents
[D] TESTING	Focused on testing by the Primary Investigators from pre-testing which entails recruiting and selecting study participants consistently, testing which includes the rate of tests to be conducted, test shadowing, the interactions between primary and secondary care teams and subsequent case management. Post Testing activities including patient, PI and Secondary Care surveys.
[E] OUTCOME ANALYSIS	Focused on the analysis of post testing data at an a aggregate level by EHSN.
[F] POST STUDY	Focused on the development, finalisation of the Study reports
[G] STUDY CLOSE	Focused on closing out any final activities from the Study

1 BACKGROUND

Premature deaths caused by cardiovascular disease (CVD) is the single biggest area where the NHS might save lives over the next 10 years [4, 5], causing a quarter of all deaths in the UK. It is thus part of the NHS' Long Term Plan to improve early detection and rapid treatment of those with high risk of CVD. For this, pharmacists and nurses in primary care networks will be supported to broadly assess the population, identify those with a high-risk condition and refer them to secondary care. Likewise, It may be possible to use early preselection to triage patients more effectively to diagnostic imaging departments (CT angiography, etc) thus reducing over-referrals.

A non-invasive, easy-to-use 5-lead vectorcardiography (VCG, 3D-electrocardiography) test aimed at primary and community-based testing derived from 5 leads, including a dorsal electrode offers additional information with an ensemble of artificial neural networks (ANN) for detection of cardiac ischaemia and rhythm disturbance (e.g. atrial fibrillation) is deemed suitable for this. The test outcome is generated, and a complete report is available to the Test Administrator and to Secondary Care.

It is thus the primary aim of this study to determine the feasibility of implementing 5L3DVCG-AI into Primary Care for the early risk detection and management of CVD.

1.1 Addressing the challenge of Cardivascular Disease (CVD)

Cardiovascular diseases (CVDs) are the leading cause of death globally. An estimated 17.9 million people died from CVDs in 2019, representing 32% of all global deaths. Of these deaths, 85% were due to heart attack and stroke. Coronary Artery Disease (CAD), the largest type of Cardiovascular Disease (CVD), affects 110 million people globally and is the most common cause of death. In the U.K., 2.3 million men and women live with the condition, which causes 170 deaths every day, placing a huge burden on the NHS. People with CAD have a reduced flow of blood to their heart which eventually causes chest pain (angina) and, if it left untreated, can result in a heart attack. In 2019, CAD was the underlying cause of 9.6 million deaths among men and 8.9 million deaths among women, constituting about one third of all deaths worldwide. Thirty-three percent of them occurred between 30 and 70 years of age, according to Roth *et al.* [6]. These authors describe that, despite a 30-year decline in age-standardized CAD mortality rates globally, there has been an increase in mortality in many places since 2010 and little progress in reduction elsewhere, in the last 5 years, where the curves have flattened.

In a North American study to evaluate the causes of CAD mortality reduction, age ranges between 25 and 84 years were taken for a twenty years (1980-2000) analysis. This analysis showed that, for this reducing effect, very specific factors were used and not absolutely available in all places, such as: improvements in therapy with drugs of last generation at that time, preventive measures after myocardial infarction (MI) or post-infarction revascularization, treatments for the acute coronary syndrome (ACS), therapy for heart failure and revascularization intervention in cases of chronic angina. These variables were present in approximately half of the decrease in mortality due CAD, while the other half, of more universal application, were represented by strategies to change risk

factors (reduction of total cholesterol and systolic blood pressure, smoking prevention and encouragement of physical activity) [7].

However, other present and progressively prevalent risk factors act to still maintain the risk of severe coronary vascular damage and cardiovascular death at levels of concern, such as obesity and type 2 diabetes mellitus, which counteract the reductionist trends in CAD mortality [8].

There is a clear need to examine CVD further and to include CAD, as well as angina and stroke (CAD as myocardial infarction and its related sequelae), as in addition to the great challenge in the prevention and treatment of CAD, there are greater challenges when it comes to the early identification of this «silent disease». One of them is the need to improve practices and policies in the diagnosis of cardiovascular conditions, both at the primary care level and in complex health service centres, with greater sensitivity and specificity than current methods. The difference between early detection of CAD and its late diagnosis marks the variance in medium-and long-term prognosis. The World Health Organization (WHO) has pointed out that the key to reducing cardiovascular disease lies in the inclusion of a model for managing the care of CAD processes towards a more effective model, for patients to have access to appropriate technology, especially in relation to Primary Health Care [9].

1.2 The NHS perspective

The NHS perspective, too many people are still living with undetected, high-risk conditions such as high blood pressure, raised cholesterol, and atrial fibrillation (AF) compared to other countries. It is thus the aim to make progress on identification and diagnosis working towards people routinely knowing their 'ABC' (AF, Blood pressure and Cholesterol)[4]. It is the aim to identify, prevent or delay the progression of associated conditions or to promote active management of these people to reduce or mitigate individual modifiable risk factors to reduce their overall level of risk [2]. These patients should then receive annual review for 5 years to enable reduction of risk [2].

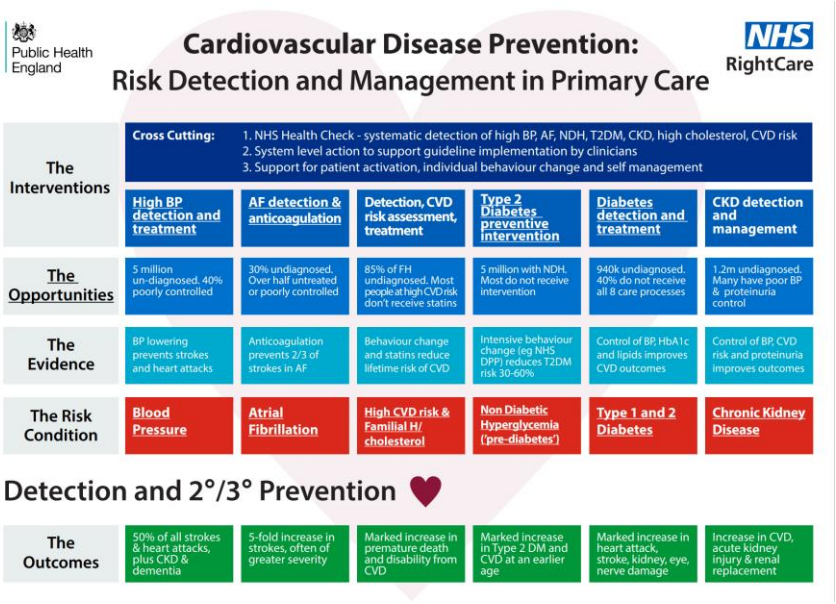
The basic diagnostic examination of cardiovascular disease (CVD) is performed in the medical consultation with the clinical history and examination, assisted by an electrocardiogram (ECG) at rest, classically 12 leads. In common practice, suspected cases of heart disease are referred to more complex confirmatory studies in some communities and are often laborious, time and resource consuming. One of the clinical examiner's biggest challenges is to ensure the presence or not of coronary artery disease (CAD), the use of additional screening tests can select appropriate individuals that needs further investigation.

Currently, CVD assessment in the UK is being undertaken using a range of solutions. Remote ECG interpretation consultancy services for cardiovascular disease is one such solution that entails the provision of expert analysis of ECGs to support clinical decision-making. The services can receive and interpret ECGs – along with other information – using telephone and digital methods. Proposed reporting times are – depending on organisation – between 2 hours up to 48 hours [10]. This is far from the standard in other countries where people at risk have got immediate access to diagnoses by ECG-interpretation.

Risk assessment using validated clinical risk scoring systems, like QRISK 2 and QRISK3 [11], Framingham [12], or ASSIGN [13], assess long-term cardiovascular risk by combining information from traditional risk factors and providing risk scores, therefore, that can be utilized to identify subgroups at risk [14].

In the UK, current National Institute for Health and Care Excellence (NICE) guidelines now recommend using QRISK3 (as opposed to the Framingham Risk Score) [11, 15]. A QRISK3 over 10 (10% risk of CVD event over the next ten years) indicates that primary prevention with lipid lowering therapy (such as statins) should be considered and will lead to include the patient in the so-called CVD-pathway [2].

Public Health England provides the following view of CVD prevention pathways for practitioners and the general public:



Source: CVD pathway v5 (england.nhs.uk)

The use of non-invasive diagnostics in coronary artery disease remains underdeveloped. To date, there is no simple and inexpensive method that can lead to a reliable diagnosis. Aside from costly and elaborate imaging techniques, exercise ECG, with its rather moderate sensitivity and specificity, is the main diagnostic method available [16]. This study aims to understand how to improve the health outcomes for many through the implementation of the innovative Cardisio Test into the primary care setting, and is planned to be undertaken for the West Midlands region, deemed to be the fifth highest in the UK according to premature heart and circulatory disease death rates (2028 to 2020) [5] in the UK.

2 RATIONALE

The 5L3DVCG-AI service is in routine daily use in Germany with over 270 private GPs and in 14 private testing centres (similar to Community Diagnostic Centres). It is also used in hospitals in Mauritius and a testing centre in the Dominican Republic.

There is significant focus on how to both support and utilise Primary Care Settings in the NHS and UK better. This Study aims to understand how implementation of the Cardisio test "5L3DVCG-AI" can be undertaken into Primary Care, and how the hand-off to the Secondary Care teams can be made more informed and effective.

The use of the Cardisio test narrows down the overall risk of CVD into three potential areas, which offers more accuracy for a Secondary Care professional than what is offered today.

This will enable the first level of care in England to make progress in early detection and thus enable effort for treatment of CVD to become more optimised [4]. It is recognised that subsequent studies will use the findings of this study to further improve the implementation in the wider Primary Care setting.

3 INTRODUCING THE CARDISIO TEST

The Cardisio Test, a 5-lead 3D-Vectorcardiography with AI-based calculation (5L3DVCG-AI) of 731 parameters, is presented as an alternative to meet the WHO goal of reducing Cardiovascular diseases, as it appropriates modern communications technologies by having a database with millions of values as a result of the processing of vectorcardiography data worldwide, with an algorithm that allows the risk estimation of the CAD in a precise way in Primary Care.

5L3DVCG-AI has been derived from the so-called Cardiogoniometry (CGM) [17], aligning two orthogonally opposite planes in the sense of Nebh's triangle and classical Vectorcardiography. The latter two enable the interpretation of orthogonal electric derivatives from only 3 linear projections, providing the spatiality of the cardiac electric field, connecting the vector loop of all instantaneous vectors, the envelope of the vector peaks in a projection plane, giving additional information to the 12-lead ECG. For ischaemia detection it focuses on spatial and temporal heterogeneity of cellular repolarization [18].

Deviations of vectors and angles were seen as sensitive indicators for changes in repolarization occurring, for instance, during coronary insufficiency [19, 20] and to diagnose CAD at rest [21, 22]. With a set of predefined parameters, CAD was diagnosed in 793 patients undergoing cardiac catheter (AUC in ROC-curve analysis 0.80, p<0.05) [23, 24]. In a prospective multicentre trial, CGM was shown to detect NSTE-ACS at first medical contact [25]. In a pilot study CGM compared favourably with the detection of ischaemia and/or structural myocardial lesions on perfusion cardiac magnetic resonance imaging with an accuracy of 83% (sensitivity 70% and 67%, respectively) [26, 27]. These results were confirmed in an independent study with CGM yielding a sensitivity of 84% and specificity of 81% (ECG sensitivity of 29% and specificity of 67%) compared with the coronary angiography [28]. Likewise, it has been used in detection or exclusion of graft vasculopathy in heart transplants with a sensitivity of 100% and specificity of 62.3%, positive predictive value 68.75%, negative predictive value 100%, negative likelihood ratio 0 and positive likelihood ratio 2.888 [29]. CGM detected cardiac ischaemia in patients with severe psoriasis [30]. Interestingly, the diagnostic accuracy of CGM was not improved by exercise in CAD [16].

Since angiographic evidence of CAD does not always correlate to physiologically significant disease, thus in single vessel CAD, CGM was performed at rest and during maximal adenosine-induced hyperaemia in 44 patients [31]. The diagnostic performance of CGM to detect physiologically significant stable CAD is poor at rest and during maximal hyperaemia to be used routinely in clinical practice.

The findings of the 10 studies published in 9 articles where CGM has been proposed as a new diagnostic tool for coronary artery disease were summarised in a meta-analysis [32]. Overall pooled sensitivity was 71.7% (69.1 to 74.1; Cochrane Q = 39.5; P < 0.00001; I^2 = 77.3%), and pooled specificity was 78.8% (76.3 to 81.1; Cochrane Q = 37.39; P < 0.00001; I^2 = 75.9%). Regarding Egger's regression test (P = 0.32), there was no published bias in the studies. It was concluded that CGM, as an easy-to-use and non-invasive modality, should be considered as a part of risk stratifying strategies for CAD in patients with suspected stable ischemic heart disease, especially in patients with contraindications for stress tests.

In cardiac resynchronisation therapy, CGM recorded in the XY plane can accurately detect differences between ventricular pacing sites and identify patients with have optimal response in CRT [33, 34].

3.1 Cardisio test and Cardiogoniometry (CGM)

3.1.1 Comparability to CGM[17]

The Cardisio Test (5L3DVCG-AI) from Cardisio UK Ltd. uses a technology very comparable to CGM:

- **It is based on vectorcardiography.**
- **It uses the same application scheme according to Sanz [17, 20] (5 leads and position of the electrodes)**
- **There is a similar transformation to the anatomical cardiac position.**
- **Calculation of the relevant "classical" VCG parameters is also undertaken.**
- **Focus on scatter QRS and T in spatial coordinate system is used.**
- **Display and evaluation of T amplitude in mV is made.**

The 5L3DVCG-AI consists of a modified vectocardiograph with a data transmission card, which connects to the supervised artificial intelligence algorithm with five vectocardioographic derivations. The data obtained is processed in the computing cloud under the algorithm and emits the results of the possible diagnosis of electrical disorders and/or structural injuries in a reasonably short time. With the use of 5L3DVCG-AI, the cardiac muscle excitation process can be described as a three-dimensional signal. The probable diagnosis can be received, first, by means of the specific calculation of physical parameters from the signs, and second, are analysed with a learning algorithm contained in a neural network. Interpretation of the results are immediately given in the health care providers' chosen language.

3.1.2 Enhancements beyond CGM

However, several differences exist between the further developed 5L3DVCG-AI to CGM:

- **5L3DVCG-AI measures are "more sensitive", with 500 Hz, 24 bit resolution.**
- **Improved processing and annotation of the electrical signal.**
- **Development of own parameters like "energy density in QRS and T complex), super position etc.**
- **Incorporation of AI for pattern recognition of pathological signal structures of excitation propagation.**
- **Cloud-based (i.e., big data approach) processing to harness more computing power.**

In summary, the Cardisio test represents a further development of vector cardiography and of CGM, which has already been successfully applied in Primary and Secondary Care settings in different countries.

3.2 Safety and effectiveness of the Cardisio test and approach

The Cardisio Test "5L3DVCG-AI" is safe and effective tool for risk estimation of coronary artery disease and this has been shown in independent clinical studies.

In 595 unselected individuals (male: 355, female: 240, age 28 to 88 years) from 2 cardiac catheter units with clinical indication for catheterization 5L3DVCG-AI was performed prior to cardiac catheter and diagnoses for CAD (angiography, any relevant stenosis) and ischaemic patterns in 5L3DVCG-AI were independently assessed by 2 independent investigators [35]. After exclusion of individuals with less than 30 parsable heart beats in the measurements, data from 595 patients were analysed. In 369 patients (246/355 males, 123/240 female) CAD was present (angiography). The diagnostic accuracy in the study setting was evaluated by applying a five-fold cross validation. Each neural network of the five-fold cross-validation was trained with 192 female and 284 male patients and tested with 48 female and 71 male independent patients. 5L3DVCG-AI identified a CAD at rest with a sensitivity of 90 ± 4% for female and 97 ± 3% for male patients with a specificity of 74 ± 10% (female) and: 76 ± 9% male), and overall diagnostic accuracy of 82 ± 6% (female) and 91 ± 3% (male).

These results were confirmed in a prospective study in 209 consecutive patients with clinical indication for cardiac catheterisation in a single centre [36]. Patients with valvular heart disease, pacemaker or previous cardiac surgery were excluded. For final analysis in 106 patients (mean age 69.5±3.6, female 40.5%) relevant (>50% stenosis) was diagnosed by 5L3DVCG-AI in 82 of 86 patients (sensitivity of 95.3% and specificity of 90%).

In 62 consecutive patients with suspected and 26 with diagnosed CAD, 5L3DVCG-AI was validated against the planned perfusion scan (myocardial SPECT, MPS) in a single centre. Sensitivity of 5L3DVCG-AI for moderate to severe perfusion defects in myocardial SPECT was 86%, specificity was 57% and negative predictive value was 98%.[37]

In a consequent study, with 112 consecutive patients with the usual cardiovascular risk factor (CVRF) profile (m:w 61%:39%, aged 66 ±10 y), of these 76 with suspected (m:w 51%:49%, aged 64±9 y) and 36 patients with known CHD (m:w 81%:19%, aged 70±11 y), a strong trend towards accuracy of 5L3DVCG-AI related to pathological MPS was seen (Chi^2: 3.2, p=0.07) with sensitivity of 75% of 5L3DVCG-AI for a moderately or highly pathological MPS, specificity of 58% and a negative predictive value (NPV) of 97% [37] . In the subgroup of 76 patients with clinically suspected CHD, significant accuracy of 5L3DVCG-AI related to MPS was seen (Chi^2: 5.6, p<0.05) with sensitivity 83%, specificity 66%, and NPV 98%. Compared to pathological 5L3DVCG-AI , patients with normal 5L3DVCG-AI demonstrated significantly reduced (n=112, p<0.05) CHD diagnoses, as defined by MPS. Expectedly, ECG at rest was not able to differentiate between CAD requiring interventions or not. 62% were classified as low while 38% were classified as high risk for CVD by the P-Index. P-Index from 3D-VCG at rest differentiated between CAD and non-CAD (Chi2= 6.8, p<0.05) and between suspected CVD with or without consequent PCI or CABG (Chi2=4.02, p<0.05). In the subgroup of 76 patients with clinically suspected CVD, significant accuracy of 3D-VCG related to MPS was seen with sensitivity 83%, specificity 66%, and NPV 98%. Thus, in a preselected study group of patients with clinically suspected, or known CHD, 5L3DVCG-AI has the potential to identify those patients not requiring interventional procedures as detected by MPS, with a significant NPV of 96%.

In the most recent nationwide multicentre study (unpublished, under review for Congress of the European Cardiology Society 2023), data from 468 patients (m:w 61:39, age: 66 [40-87] years) number of CVRF was 3.6 [0 - 7], 16% had arrhythmias or conduction disturbances (AF, PM, BBB), 24% pts. had consecutive percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). 62% were classified as low while 38% were classified as high risk for CVD by the P-Index. Number of cardiovascular risk factors (modified PROCAM score) was significantly higher in the high-

risk CVD-group as defined by P-Index compared to low CVD-risk (4.0 [3.0 – 5.0] vs. 3.5 [2.0 – 4.0], p < 0.05). P-Index differentiated between suspected CVD with or without consequent PCI or CABG (Chi2 = 4.02, p<0.05) [38].

The Cardisio test is in routine daily use as a service in Germany with over 270 private GPs and in 14 private testing centres (like Community Diagnostic Centres). It is also used in hospitals in Mauritius and a testing centre in Primary Care in the Dominican Republic.

Currently, beyond business-as-usual usage, several different study trials are continuing to recruit participants in Germany, Brazil and the Dominican Republic to assist with the implementation of the Cardisio test into existing care pathways more effectively in these countries.

- **Study Registry number of the trial at IGESP Hospital Sao Paulo/Brazil: CAAE: 64738922.6.0000.5450**
- **Study Registry number of the trial in the Dominican Republic: 010/2023-P**
- **Study in Germany is awaiting registration.**

3.3 The SBRI Study and the Cardisio Test

The SBRI Study is being undertaken to understand how the Cardisio test can be introduced as an alternative to the 12-lead (2D) ECG, the NHS standard. The Study suggested in this protocol is the first to be run in the UK, and so the focus is on ascertaining how the care pathway can use this test in the Primary Care setting, and the hand-off to Secondary Care as appropriate.

The Study aims to demonstrate that the implementation of this new 5L3DVCG-AI technology is an accessible digital technology for the first level of care in the UK to make progress in early detection and thus enabling treatment of CVD in the primary sector [4].

As it is an easy-to-use procedure with immediate interpretation undertaken by a software service, it can help to perform non-invasive diagnosis of CVD, in particular of CAD, in a precise and sensitive manner, which should contribute to reducing the prevalence of deaths due to CAD.

3.4 The Cardisio Test - Specifications & Usage Method

3.4.1 Specifications – Accreditation and Certification

The Cardisio™ service is a Class I CE-marked medical device. The company is accredited to ISO 13485:2016 Quality Management System for medical devices, as part of the company's transition to MDR. Cardisio GmbH is the product manufacturer and is represented in the U.K. by its subsidiary, Cardisio UK Limited, which is in the process of transitioning the CE-mark to UKCA regulatory approval and has been initiated and is due to complete in 2024, and until that time, the Device conforms under UK regulation.

3.4.2 Cardisio Test Method

(A) **CONDUCTING A TEST**

The test requires a computer or laptop to access the Web service (Cardisio Cloud) via a Gateway device, which acts as the data collector using traditional EKG cables, as well as five disposable electrodes.

The recording technique requires the Gateway receiver to capture and transform analogue signals captured by the 5 electrodes into digital signals. The 5 electrode leads are essentially similar to the ECG leads used by standard ECG systems. The analogue to digital conversion is undertaken by the Gateway unit, which is the size of a paperback book.

Positioning of electrodes (Cartesian derivations).

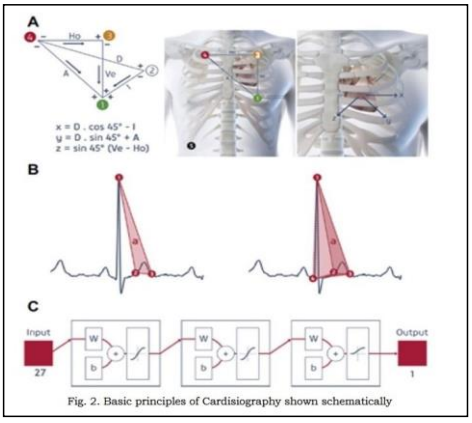


Fig. 2. Basic principles of Cardisiography shown schematically

The positioning of the electrodes allows the three-dimensional reading and spatial visualization of the cardiac electrical potentials during a period of 4 min. The measurable potentials, based on electrical cardiac impulses, are converted into digital values using bipolar cables. This bipolar derivation is transformed into an orthogonal derivation. The X and Y-axes represent the diagonal sagittal plane and the Z-axis is orthogonally aligned with the sagittal plane, with modifications according to Schuepbach *et al* [22].

(B) **ANALYSIS OF A TEST**

The captured measurements, now in the form of a digital model of the person's electrical heart activity offer the opportunity to be analysed to identify or define the heart health of the patient, and whether this state required action, interventional procedures or not.

The Cardisio cloud application program (5L3DVCG-AI) incorporates an AI that uses multiple algorithms and machine-learning methods to interpret the electrical vectors stored in the Patients digital model, in a similar way to the VCG, and a central cloud based server where the vector information becomes part of a statistical database to be analysed and stored anonymously. The 5L3DVCG-AI focuses on the spatial and temporal heterogeneity of cardiac excitation transmitted through electrical vectors resulting from the depolarization of myocardial cells. The five electrodes of the 5L3DVCG-AI correspond to those of the VCG: four are signal and the other is a grounding, placed in the thorax in two orthogonal planes. Each electrode provides a signal from which vectors are derived and with which potential differences are recorded (figure 2, modified from Braun *et al*) [35].

The 5L3DVCG-AI analyses the individual three-dimensional electrophysical profile of the heart and recognizes cardiac pathological patterns with the help of AI neural networks designed for this purpose.

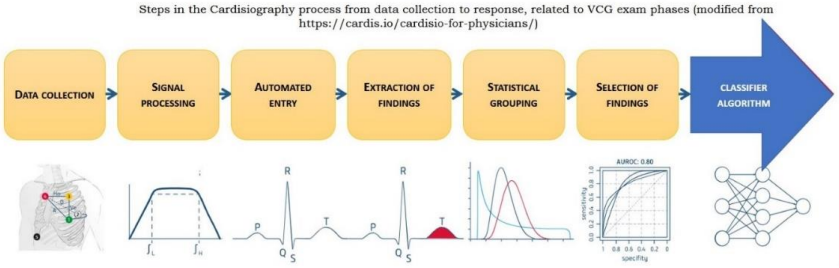
- ***Characteristic parameters of cardisiographic reading.***

  After four minutes of recording, the cardiography software automatically documents and analyses a set of 290 parameters including the start and end of the QRS complex. In addition, the R peak, the start and end of the T wave, T peak, as well as the area and overlap of the T wave and the QRS complex in the transverse plane of the vector loop [35].

- ***Operating system of the Cardisio AI***

  The operating network through which the data flows and the information received is stored to form a "memory" of increasing magnitude and mechanical learning, is represented by a set of five neural feedback networks. Each has incorporated a tissue of progression for learning. The "cells" of that tissue comprise 27 input neurons, two hidden layers of 22 and 20 neurons and one output neuron. Therefore, the algorithm itself is training the neural grid, configured for sensitivity and specificity with its own sensitivity, weighted in one and a half times.

Once the recorded information reaches the data centre, it is fed into the algorithmic flow of the AI. The 25 neural networks evaluate the 290 parameters for each heartbeat and then apply statistical analyses, also automated, to conclude significance and correlations, as shown in the diagram below.



(C) **TEST OUTPUTS**

The output of the Cardisio Test "5L3DVCG-AI" is given as three different factors (shown below). Each Factor is composed of the respective Index derived from the AI-Algorithm and/or relevant identified VCG-parameters. Based on the P-Index (result of the AI algorithm) the three factors are calculated and provided as output: P-, S- and A-Factors. The factors represent a compact interpretation of the analysis results of the "5L3DVCG-AI".

FACTORS	COMPONENTS	P-INDEX (AI)	VCG-PARAMETERS	ECG- & VCG-NORM DEVIATIONS	ECG-PARAMETERS
P-Factor					
The P-Factor indicates reduced perfusion (e.g. ischemia) of the heart at rest, caused, for example, by CAD or microvascular dysfunction.	Combination of trained P-Index (AI) and relevant VCG-parameters	●	●		
S-Factor					
The S-Factor indicates structural changes in the myocardium (which may also be caused by hypoxia), e.g. enlargement of the heart, thickening of the myocardium or vitia, as well as myo- and pericarditis.	Combination of trained P-Index (AI) and relevant ECG- and VCG-norm deviations, deviations NOT related to ischaemia	●		●	
A-Factor					
The A-Factor indicates the presence of arrhythmia and other abnormalities in the current waveform, such as extrasystoles, atrial fibrillation, atrial flutter, conduction disturbances (block images), tachycardia and/or bradycardia.	Combination of trained AI-based algorithm and relevant ECG-parameters				●

(D) **TEST RESULT PRESENTATION**

The combination of the different parameters will then result in three risk states the degree in which the Study Participants test results match the patterns of known disease pathologies as per the figures shown below.

P-Factor	
S-Factor	
A-Factor	

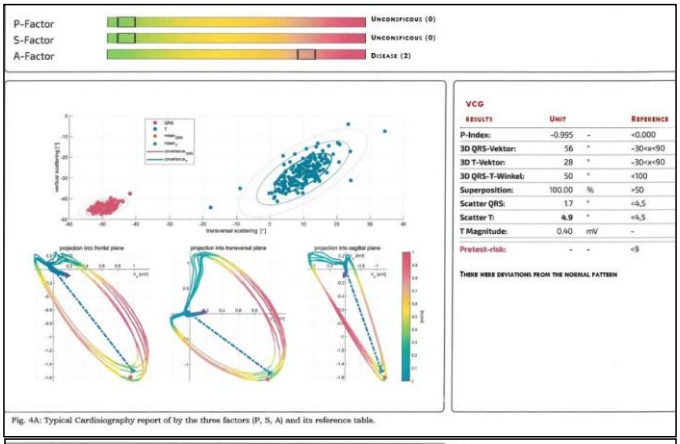


Fig. 4A: Typical Cardiisiography report of by the three factors (P, S, A) and its reference table.

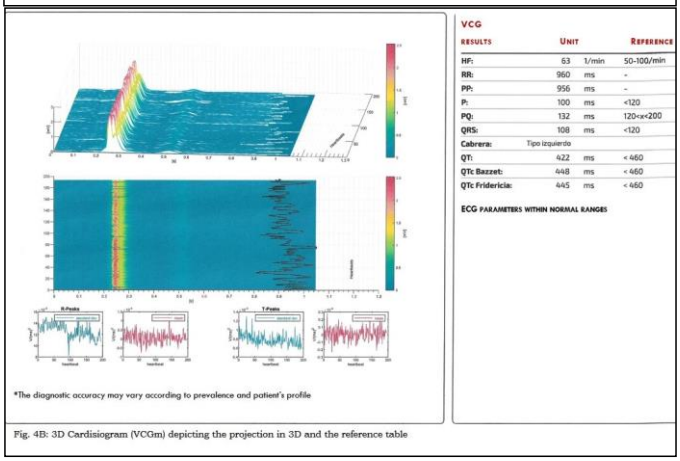


Fig. 4B: 3D Cardisiogram (VCGm) depicting the projection in 3D and the reference table

4 STUDY OUTCOMES

4.1 Outcomes Summary

This study is designed to assess how a relatively simple CVD test procedure can be used in conjunction with existing NHS community-based CVD prevention strategies for earlier detection of CVD.

The proposed test procedure is new to the UK market and uses sophisticated AI-based algorithms to detect the early signs of heart disease. The test is easy to train staff in its use, simple to conduct and produces results quickly and accurately.

The study outcome is to show that the Cardisio Test can be integrated into an existing NHS care pathway easily in a variety of community settings.

The secondary outcome is to gain real world evidence of its performance as a tool to aid the early detection heart disease in community-based settings. Findings from this study will be incorporated into an ICS-based national roll-out plan.

This requires the following study primary and secondary outcomes to be achieved:

4.2 Primary Outcomes

The Study will demonstrate that:

1. **Cardisio can be used in community settings without extensive training or specialist knowledge by the tester.**
2. **Secondary Care teams can review the Cardisio Test results remotely resulting in fewer patient journeys to busy hospitals for tests. This should also contribute to the NHS Net Carbon Zero targets.**
3. **The Cardisio Test delivers a superior and richer test result when compared to a traditional 2D ECG. More data about disease conditions will make the cardiologists ability to diagnose easier or clarify next steps.**
4. **To demonstrate that a revised care pathway could be considered by the NHS for future adoption, based on a central cardiology team reviewing test results and selecting patients for further diagnostic test procedures, a so-called "pull model".**
    a. **Better availability of community testing should offer a better patient experience.**
    b. **Through the use of Allied Healthcare Professionals to undertake routine testing, a reduction in GP appointments should be possible.**
    c. **Secondary care teams will be able to triage and prioritise patients, making better use of scarce resources.**

4.3 Secondary outcomes

Feedback and observations generated by all the study participants will provide a richer view on key metrics around user experience, from allied healthcare professionals, patients and cardiologist. For example:

1. **How the test environment is integrated into a Primary Care Setting.**
2. **Ease of training in person and online training materials.**
3. **Ease of test procedure and administration**
4. **Patient experience and preference for community-based testing**
5. **The view of the cardiology team in the process and impact on the quality of their patient lists.**

4.4 Primary Outcome Objectives and Measures

Primary Outcomes	Outcome measures
1. Cardisio can be used in community settings without extensive training or specialist knowledge by the tester.	• Test results gathered. • Feedback from the test administrators and PI's. • Reported confidence of the secondary care team of the reliability of test collected.
2. Secondary Care teams can review all the Cardisio Test results remotely in a single ICS-based portal.	• Secondary care team can successfully access test results across the study participant group. • The number or percentage of correct predictions (true positives plus true negatives)
3. The addition of Cardisio test / risk information results in fewer patient journeys to busy hospitals for tests. contributing to the NHS Net Carbon Zero targets.	• Number of Patient Journeys • Comparison of referral after Cardisio test versus typical referral with current CVD Pathway V5. https://www.england.nhs.uk/rightcare/wp-content/uploads/sites/40/2018/02/cvd-pathway.pdf
4. The Cardisio Test delivers a superior and richer test result when compared to a traditional 2D ECG. More data about disease conditions will improve the cardiologists ability to diagnose or clarify next steps.	• Feedback from CI and secondary team plus feedback from GP/PCN PI.
5. To demonstrate that a revised care pathway could be considered by the NHS for future adoption, based on a central cardiology team reviewing test results and selecting patients for further diagnostic test	

procedures, a so-called "pull model". **a)** Better availability of community testing should offer a better patient experience. **b)** Through the use of Allied Healthcare Professionals to undertake routine testing, a reduction in GP appointments should be possible. **c)** Secondary care teams will be able to triage and prioritise patients, making better use of scarce resources.	• Feedback from Participants Surveys. • Feedback from PIs in Pharmacy Setting and analysis of referrals made. • Feedback from CI and secondary care team.

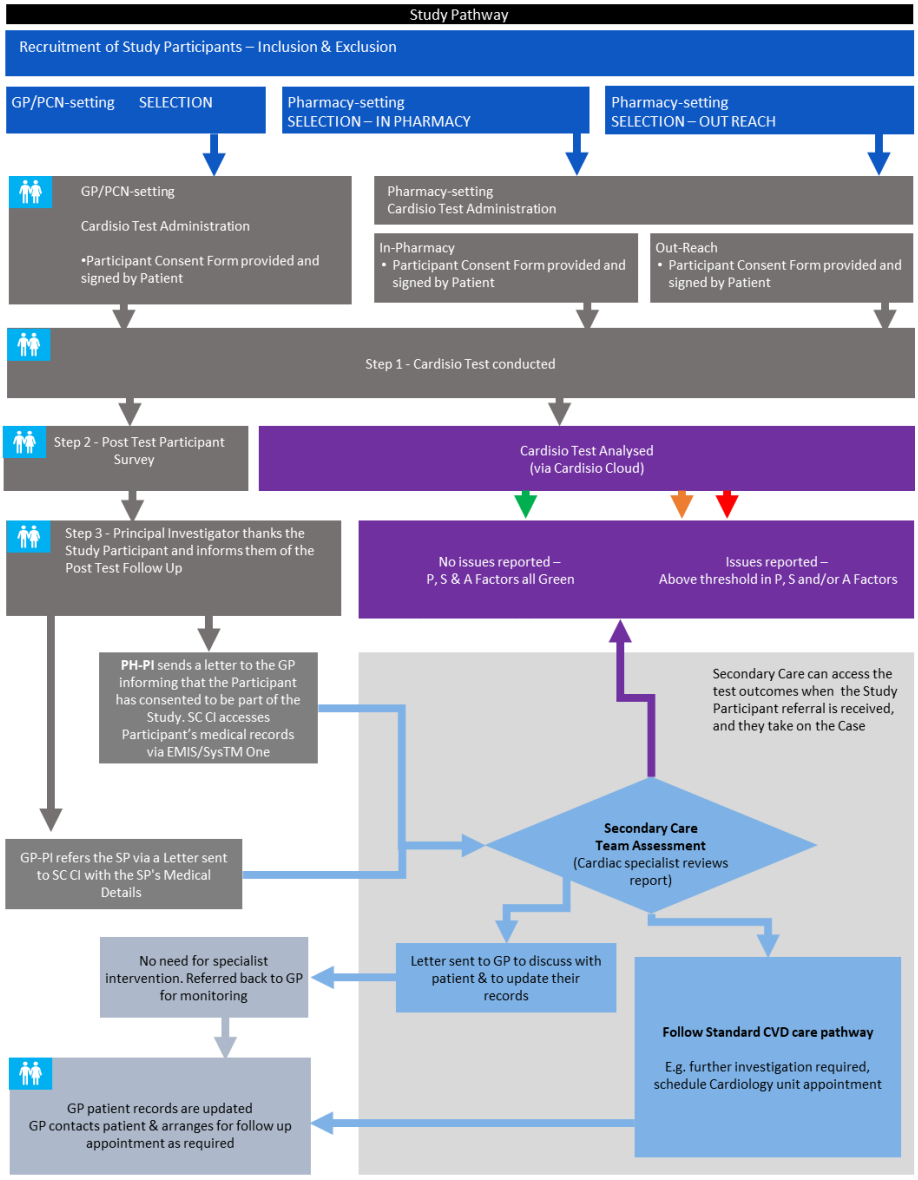
4.5 Secondary Outcome Objectives and Measures

Secondary Outcomes	Outcome measures
1. Evidence of how the test environment is integrated into a Primary Care Setting.	Ease with which the primary care administrators can undertake recruitment selection and testing of study participants as recorded in the "Participant Testing Log". Test Environment Readiness assessment completed with ease.
2. Feedback on the ease of training in person and online training materials.	Feedback from PI's and test administrators gathered via survey and structured interviews.
3. Feedback on the ease of test procedure and administration	Feedback from PI's and test administrators gathered via survey and structured interviews.
4. Feedback on patient experience and preference for community-based testing	Feedback from Participants gathered via pre and post-test surveys to assess: • How easy was it to understand the purpose of the study. • How easy it was to undertake the test. Using a scale of 1-5.
5. The view of the secondary care (cardiology) team in the process and impact on the quality of their patient lists.	Feedback from CI and team gathered via survey and structured interviews.

5 STUDY DESIGN

This is a multicentre, cross-sectional, partly randomised controlled, interventional, non-invasive study; with study design focused on three key aspects. The Study Pathway is defined in the following diagram which shows an overview of the process of recruitment and selection of Study Participants, in each Primary Care Setting, administration of the Cardisio test and the flow of communication and follow up action and by whom after the test results have been collected.

Cardisio – Use in Primary Care Settings



Note: Principle Investigator is the test administrator.

5.1 CONSISTENCY OF METHOD IN THE PRIMARY CARE SETTINGS

The Study requires a consistency of recruitment and selection across these settings, whilst taking into account that each setting has different levels and types of information on a patient to make their determination, and this is supported by a variety of tools and methods. The Recruitment step of study participants identifies the first study pool of those that meet the inclusion criteria for participation. The Selection step then enables the final selection of Study Participants.

5.1.1 Recruitment & Selection Principles

The Study Group have determined that to achieve the successful outcome of the Study, to understand how best to introduce the Cardisio Health Test in the Primary Care Settings and the wider NHS better, we require the following Recruitment & Selection principles to be applied across the settings:

1. **Apply the same inclusion and exclusion criteria.**

   These have been constructed based upon current NHS best practice and tools for assessing CVD risk, and to design a consistent method for use across the three Primary Care Settings that will provide a consistent profile of study participants.

2. **Ensure that gender and social diversity is considered.**

   This is critical factor given (a) the CVD risk that is under-served in women, and (b) the increasing concerns of health inequality that exists in the UK. Gender diversity is programmed into the Study at the Recruitment & Selection stage (refer to Stage D Procedures), the Social inclusion is programmed into the Study in the choice of Primary Care settings and the social demographic that they serve.

3. **Use the tools and methods available to each setting and avoid major changes for the Primacy Care Settings.**

   The Study team appreciate that there is a variance in the tools and methods available across the Primary Care Settings, and this variance has informed the Recruitment & Selection method by allowing the Primary Care teams to use what is best available to them and compensating for the lack of such tools in other settings, an example is the formulation of the comparative table (see section 8) which brings the medical profile and medication profiles together.

4. **Use QRISK2 / QRISK3 to aid risk assessment consistency.**

   QRISK 2 is already embedded into GP systems, and provides the ability to recruit potential Study Participants, this is not available for the Pharmacy Primacy Care Settings to undertake their identification of potential Study Participants. However, the Study Group view the opportunity for every Study Participant to obtain a QRISK score as a useful point of data for subsequent risk and care evaluation. Therefore, the Study will provide stand-

mounted Tablet PCs to allow for a QRisk 3 assessment for each Study Participant to complete on Test Day.

5. **Simulate the broad variance of Study Participants that would be expected normally.**

   The Study approaches any unintentional bias that may occur when selecting Study Participants by utilising a randomisation function within a spreadsheet listing each Study Participant that has been recruited into the study pool. This list then randomly selects the required number of Study Participants for the fixed settings, e.g., GP/PCN and In-Pharmacies. A certain number of Study Participants who meet the selection and inclusion criteria will be randomised either as Walk-ins in both fixed locations of GP/PCN and In-Pharmacy, whilst all the Pharmacy Out-reach Participants can be categorised as walk-ins given the nature of this service, and therefore is considered as suitably randomised at point of selection and inclusion.

The use of these principles has driven the Study's design and will enable the Study to build a baseline of information on each patient that aids analysis and control through the test process and engagement with the Secondary Care team.

5.1.2 Testing Preparation & Process

The Study Group have developed guides, in conjunction with these teams and the Cardisio test team, for each Primary Care Setting to follow a consistent test process as the facilities available in each setting vary. This has informed the provision of hardware and software needed to perform the tests.

5.2 CONSENT, COMPLIANCE & CAPTURING OF FEEDBACK

The Study Group is focused on making sure that each Study Participant has provided their consent to participate in the study and compliance to best practice for working with Study Participants is being observed:

1. **Clarity of Purpose for the Test, this is part of the recruitment and selection process, and requires each Primary Care Setting to provide a consistent explanation of the Study, the Test that will be performed, and how the outcome of the Test will be used and shared with the Participant and their GP. This entails the use of consistent Participant literature which has been approved for use by the PIs, CI, and Patient Participation groups.**

2. **Consent is sought verbally and in writing. The initial consent to participate is obtained differently in each Primary Care setting, in part due to the way in which the recruitment and selection takes place, and in part due to whether an existing and established relationship exists between the PI and the prospective Study Participant.**

   Written consent is obtained on Test Day as part of the Test process using the approved NHS consent template. This is required for completion prior to the Test process commencing.

It is recognised that a Study Participant may withdraw from the Study any time prior to Test Day, and even if they have previously given written consent. The PI guide outlines the steps if such a situation were to arise, initially with the PI to address any concerns that the Study Participant may have which may resolve their concern, leading up to allowing the Study Participant to withdraw. For the Study, in such cases, the Test participation would be re-offered to someone else who meets the inclusion criteria.

3. **Feedback will be sought from each Study Participant, even those that have chosen to withdraw. This allows for a broad sample of perspectives that can be used to adapt the Study and/or the Test process. The feedback has been standardised and is captured in paper forms that will be scanned manually for later consolidation and review.**

5.3 THE POST TEST PROCESS & THE ROLE OF THE SECONDARY CARE TEAM

The Study Group are focused on making sure that each Study Participant is either referred to the CI in secondary care via their GP, or the CI identifies Participants for further investigation when reviewing Participant Test results. Participant will not be excluded from the study if they are not registered with a GP. The fact that they have no GP will be noted and we will advise the participant to register with a GP as soon as possible.

Any participants identified as requiring further investigation will be invited to a study clinic arranged by the Secondary Care Team. Study Participants will not be given their test results on the day of testing but feedback will be provided either via their GP, or through the Secondary Care Team.

The aim of the Cardisio test is to provide more detailed input to the patient assessment than is currently provided by a referral of a patient to Secondary Care under the current Care Pathway. The Secondary Care team can therefore expect to receive the following information on each Study Participant, recorded in a Study Test File compiled at each test setting:

- **Basic details that identify them (Name, Date of Birth, NHS Number, Address, GP Details)**
- **The reasons for their inclusion in the Study, i.e. the risk factors identified.**
- **Details of their GP to help with any correspondence regarding their patient.**
- **The Test outcome itself as a standard Cardisio report that identifies the P, A, S result.**
- **In the case of Pharmacy tests, the possibility of a medication profile as well. This may or may not be included for GP/PCN tested Study Participants**

For this Study the role of the Secondary Care team is to:

A. **Assess the Test outcomes for every Study Participant that has an Amber or Red condition status on any one P, A, or S factor[1] that the test assesses.**

B. **Determine the next course of action for all Study Participants that have an Amber or Red condition status which may include, but is not limited to, arrangements for new medication therapy or further diagnostic testing, or both.**

[1] See section 3.4.2 (C)

C. **Assess the Test outcome of a sample of those Study Participants that show up with Green status on all of the three dimensions and compare this with the inclusion criteria that nominated the Study Participant for a test.**

D. **For all Study Participants that have Green status to communicate with their GP that they have been included in the Study as they met the inclusion criteria, they consented to participate, and if they have any medical issues, they are not CVD related at this time.**

6 USE OF QUESTIONNAIRES

There are two types of Questionnaires to be used in the Study, those that are focused on the Study Participant's feedback and those focused on the PI, PI Team and CI feedback. The Questionnaires are paper based forms, and as the Study Participant is associated with a Study ID, and once Tested, with a Test Number (that allows for the Study to pseudonymise the Study Participant whilst allowing NHS Care Teams to be able to identify them against Patient Records), the Questionnaires may be annotated with the Study ID for collation purposes.

The Questionnaires to be used in the Study are summarised in the table below:

Stage & Sub-Stage	Q #	Purpose	When?	Frequency?	Who? (Respondee)	How?
Stage D - Test Pre-Test	1	Pre-Test Questionnaire prior to administering a Cardisio Test	On Test Day	Every SP	SP input PI/PI-T administration	Paper Q
Post-Test	2	Capturing SP feedback on their Test experience	On Test Day	Every Test	SP input	Paper Q
Post-Test	3	Capturing PI feedback on their Test administration experience	Post Test Day	Every Week	PI input	Paper Q
Post-Test	4	Capture CI feedback on their Test administration experience	Post Test Day	Every Week	CI input	Paper Q

Abbreviations	
SP = Study Participant **PI = Principal Investigator** **PI-T = Principal Investigator's Team** **CI = Chief Investigator** **STF = Study Test File (list of all SPs collected the Primary Care Setting)**	

6.1 Study Participant Questionnaires

6.1.1 Participants Pre-Test Questionnaire

This questionnaire (Reference Q1) has been designed for the following purposes:

a. **To ensure the Participant is aware that they are participating in a study and are not anxious about the test.**
b. **Understand what test literature has been seen and understood by the Participant.**
c. **Confirm with the Participant their state of health, and fitness to undertake the test.**
d. **Document the Participants GP. This enables the NHS Care Teams to provide information of the test outcomes back to the GPs, especially important for the Pharmacy Setting tests. This will also highlight where a participant is not registered with a GP.**
e. **Confirm the Participant Consent to undertake the Test has been received.**
f. **Confirm the Participant Consent for their medical history to sent to the Secondary Care Team**
g. **Confirm the Participant Consent, if any health concerns are detected, the Participant might be requested to visit Sandwell Hospital for additional evaluation.**
h. **To identify the participant's socio-economic and ethnic background.**
i. **To understand the Participant's motivation to volunteer for the test.**
j. **To confirm the participant understands the right to withdraw from the study at any time.**

6.1.2 Participants Post-Test Questionnaire

This questionnaire (Reference Q2) has been designed for the following purposes:

a. **To understand how the Participant feels after the test itself to inform the design of the future test usage and administration both during the study and for wider adoption.**
b. **To understand the method and duration of travel to the Test Setting Location for the participant in order to assess the carbon miles expended to travel to and from the test.**
c. **to understand that the Study Participant is aware of the next steps that they could expect**

6.2 Study Investigator Questionnaires

6.2.1 Primary Care – Principal Investigator (PI) Questionnaire/Stuctured Interview

This questionnaire (Reference Q3) has been designed for the following purposes:

a. **To obtain feedback and perspectives from the PI about their participation in the study, specifically:**
    - **the process of setting up the study**

- **the administration of testing during the study**
- **the quality and effectiveness of literature and information provided regarding the study and the test itself**

b. To gain insight into the ease of use of the test in a primary care setting

c. The degree of confidence felt by the PI in administering the test

d. The degree of confidence of the PI in providing feedback and next steps to participants

e. The perceived benefits for participants in receiving the test in a Primary Care setting.

6.2.2 Secondary Care – Chief Investigator (CI) Questionnaire/Stuctured Interview

This questionnaire (Reference Q5) has been designed for the following purposes:

a. To obtain feedback and perspectives from the CI about their participation in the study, specifically regarding the administration of testing during the study

b. To gain insight into the usefulness of the test results gathered from primary care in helping to review Study Participant cases

c. The degree of confidence felt by the CI in the administration of the test and its use in assessing the risk factors relating to the cardiovascular health of the participants

d. The perceived benefits for Secondary Care receiving the test outcomes from the Primary Care setting.

6.3 Questionnaire collection

6.3.1 Anonymisation

Data collection at every stage of the questionnaire and feedback process has been reviewed to ensure that data collected is only that required to enable a full assessment of the outcomes of the study to be made. Study Participants are assigned a Study ID such that only their GP, pharmacist or those in Secondary Care required to review test results can identify a Participant.

This is achieved by equiping the PI a list of Study IDs to assign to Study Participants which also links to the Test Number assigned automatically by the Cardisio Test. No one outside of the Primary or Secondary Care teams has access to the information relating the Study ID to a particular test result of questionnaire response.

6.3.2 Questionnaire Administration

Paper copies of all questionnaires will be provided in each setting for completion with Participants. These paper questionnaires, also only identified by Participant Study ID will be loaded onto the Sharepoint system for later analysis by a member of the study team. Once loaded the paper copy will be securely stored for audit purposes.

The completed electronic records, identified by Participant Study ID will be stored in a secure Microsoft Sharepoint Environment, administered by the Research & Development team at Sandwell Hospital.

7 STUDY SETTING

7.1 The Primary Care Settings

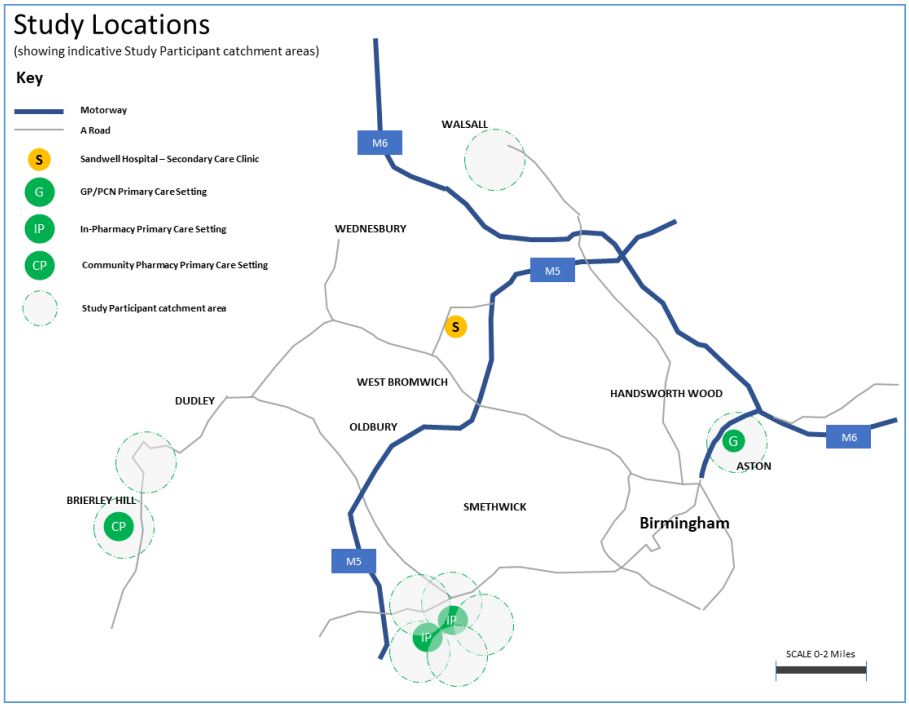
The Study aims to ensure a variety of locations and Primary Care Setting Types is used to present a representative view of the Test use in the Primary Care settings.

Thus, there are three testing Partners in the Study with 4 sites ranging from the GP/PCN setting, to the In-Pharmacy setting and the Pharmacy Out-Reach setting.

Primary Care Setting	Site Addresses
GP/PCN	Church Road Surgery, i3 Ladywood PCN, 28 Church Road, Aston, Birmingham B6 5UP
Pharmacy – Community Out-Reach	Dudley Health and Social Care Centre, Venture Way, Brierley Hill DY5 1RU
Pharmacy – In-Pharmacy	Ridgacre House Pharmacy, Ridgacre Medical Centre, B32 2JT
Pharmacy – In-Pharmacy	Crest Pharmacy - Faraday Crest Pharmacy – Faraday, 17 Faraday Ave, Quinton, Birmingham B32 1JP

These have been selected due to the diverse populations they serve and the variety of recruitment approaches needed to target high risk, hard to reach multi-ethnic populations.

This community-based testing capability ensures that health inequalities are reduced for underserved ethnic and socioeconomic groups, since the study participants are to be recruited and selected from all local communities to meet the health inequalities objectives of the NHS. In the UK people of South Asian and Black African or African Caribbean background have an increased risk of developing CVD [1].



7.2 The SECONDARY Care Settings

The Secondary Care Team will be based at the Sandwell Hospital (part of the Sandwell & West Birmingham Hospitals NHS Trust). Consulting areas already exist at the Hospital and these will be used to receive any Study Participants who have been tested in the Pharmacy settings, and by the GP/PCN PI in the GP/PCN Setting, and identified for further investigation.

8 STUDY PARTICIPANT ELIGIBILITY CRITERIA

The Study utilises an agreed set of eligibility criteria based on Exclusion and Inclusion Factors to provide the consistency needed in recruiting and selecting the study participants across the primary care settings. This is summarised in the table below:

EXCLUSION FACTORS	
Participant Medical Profile **Age, condition, indicative CVD risk**	**Participant Medication Profile** **Examples of typical medications indicating a medical risk or condition**
1. Already being treated for a CVD related condition or are symptomatic	**Combination of Anticoagulants, Blood Thinners, Antiplatelets, ACE Inhibitors, Angiotensin II Receptor Blockers, Beta Blockers, Calcium Channel Blockers, Diuretics, Vasodilators, Nitroglycerin and Statins**
2. Age is under 18 and over 75	
3. Pregnant	
4. Study conflict (participating in other studies) or unable to provide consent	
INCLUSION FACTORS	
Participant Medical Profile **Age, condition, indicative CVD risk**	**Participant Medication Profile** **Examples of typical medications indicating a medical risk or condition**
1. Type 1 or Type 2 diabetes and aged > 40 years	**Insulin, Metformin, Sulphonylureas, alpha-glucosidase inhibitors, prandial glucose regulators, thiazolidinediones or glitazones, GLP-1 analogues (incretin mimetics), DPP-4 and SGLT2 inhibitors, Statins**
2. Type 1 or Type 2 diabetes aged 18 – 39 years but who have been diagnosed with one or more of the following:	
2.1 Retinopathy	**Ranibizumab (Lucentis) and aflibercept (Eylea), steroid medications**
2.2 Nephropathy, including persistent microalbuminuria, persistent poor glycaemic control (HbA1c >9%)	**ACE inhibitors, dapagliflozin, statins, furosemide**
3. Elevated blood pressure requiring antihypertensive therapy	**ACE inhibitor or an angiotensin-2 receptor blocker (ARB), calcium channel blockers such as amlodipine, felodipine, nifedipine, diltiazem and verapamil. Diuretics such as indapamide and 48endroflumethiazide. Beta blockers such as atenolol and bisoprolol.**
4. Elevated single risk factor/s, e.g. total cholesterol >6.0mmol/l	**Statins**
5. Features of metabolic syndrome (central obesity and fasting triglycerides) >1.7mmol/l (non-fasting >2.0mmol/l)	**As per medication for blood pressure, blood sugar and cholesterol**
6. HDL cholesterol <1.0mmol/l in men or <1.2mmol/l in women	**Statins, and ezetimibe, fibrates, bile acid sequestrants and bempedoic acid. Also, injections – such as alirocumab, evolocumab and inclisiran**
7. Family history of premature CVD in a first degree relative	**Known medication profile of a close family member taking appropriate CVD medication.**
OR	
8. QRISK2 ≥ 10% or QRISK3 ≥ 10%	

9 STUDY PROCEDURES

The core Study procedures are in Study Stages C Setup, Stage D Testing, Stage E Outcome analysis.

9.1 STUDY STAGE C – SETUP

9.1.1 Locations

The Primary and Secondary Care locations have been identified, and in the Setup Stage these locations will be assessed for facility, amenity, size, accessibility, privacy and security. Once this has been completed there will be a confirmation that all selected locations are available to participate.

The Pharmacy Outreach (Community Setting) has the most variation given testing will be undertaken in community settings, such as temples, churches and gurudwaras, and the testing environment on each Test Day is likely to be setup many times. This will drive specific amendments to the Study's provision of equipment.

9.1.2 Training

Training of the Principal Investigators and their selected backups, and for the Chief Investigator and their selected backups is required. This training programme focuses on the administration of the Cardisio Test, the Testing Procedures, and for Secondary Care, the interpretation of the Test Outcomes.

Resources have been made available to support the training programme, with initial training already provided to the CI. It is planned to undertake the remainder of the training programme (and a refresher for the CI) prior to the commencement of the Testing Stage. To facilitate this each PI has been asked to nominate their teams with accompanying contact details.

9.1.3 Participant Literature

Study Participant-facing literature has been developed with support from the Patient & Public Involvement & Engagement Board (PPIE) and inputs from the PIs and their teams. It is recognised that the use of this literature will vary across the Primary Care Settings, for example the Study Overview document is unlikely to be used in the GP/PCN setting given that the GP/PCN CI (denoted as the GP-PI in the Study Procedures) is likely to have a direct relationship with a potential Study Participant and will verbally provide this overview.

9.1.4 Test Preparation and System Access

As part of the Test Phase preparation, each Primary Care Setting needs to be made ready with the provision of the appropriate Test materials and devices, and then system access to administer the Tests and access to the Cardisio Cloud to view the test outcomes needs to be arranged.

9.1.4.1 Site Preparation

A Test Setting Pack will be assembled that includes the PC technology, literature, consumables required for the Setting to undertake the required Tests. This includes:

- **Test Laptop with Power Supply Unit (if required)**
- **Colour printer and paper**
- **Cardisio Gateway Device with Power Supply Unit**
- **5 Lead ECG Pack**
- **Sensor (disposable) pads**
- **Tablet PC with Secure Stand (for Qrisk3 assessment on Test Day)**
- **WiFi dongle (for Community Outreach only)**
- **Amenity kits (disposable eg. Electric clippers, non-alcoholic wipes etc)**
- **Portable Screens (for Community Outreach only)**
- **Patient Literature**
- **Questionnaires**
- **Standard Letter to GP**
- **Cardisio Test Literature**

9.1.4.2 System Access

The Primary Care PIs will provide the names of their team to allow the provision of system access to the Cardisio Cloud to administer the Cardisio Test.

The Secondary Care CI will provide the names of their team to allow the provision of system access to the Cardisio Cloud to view the tests results.

9.1.5 Testing Site Readiness

Prior to the Testing phase commencing, each PI will submit a standard pre-prepared checklist to indicate their readiness for Testing to be undertaken, reviewed onsite by a member of the study team:

This checklist includes the following:

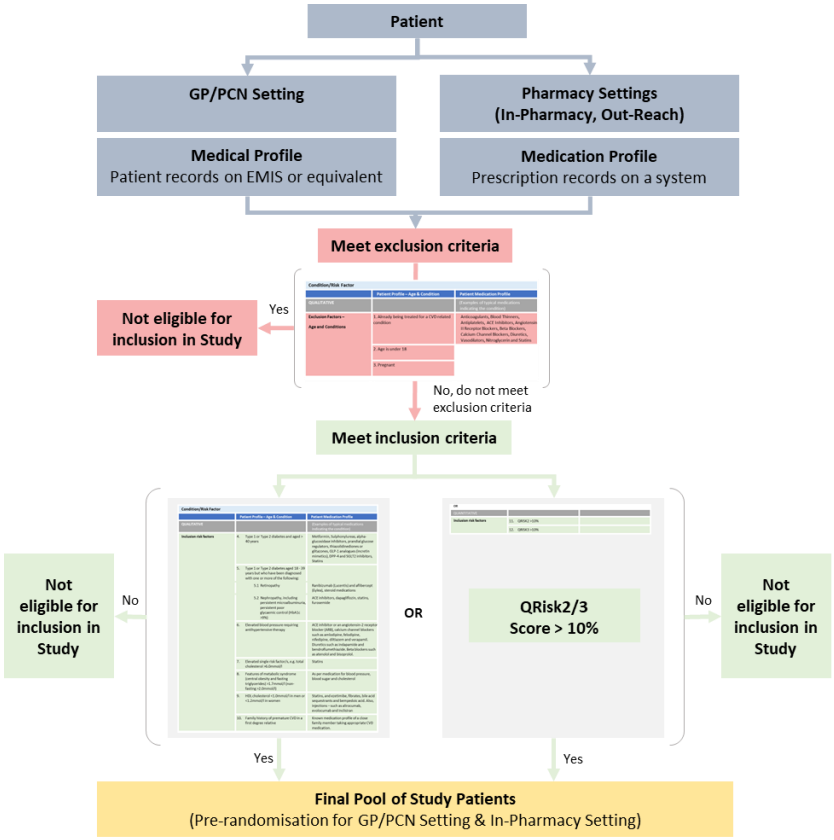
1. **Secure and private area is available for testing.**
2. **Chaperoning capability is available.**
3. **PI & Team are trained and ready to undertake tests.**
4. **A lockable cabinet is available to store participant documents securely overnight.**

5. **Secure storage is available for test equipment (Leads and sensor pads, Cardisio Device, Test Laptop and Printer, Tablet PC and secure stand, Wifi Dongle (for Community Outreach only), patient literature and PI/Test Administrator Manuals)**
6. **Has access to the Cardisio Cloud been tested.**

9.2 STUDY STAGE D - TESTING

9.2.1 Recruitment & Selection

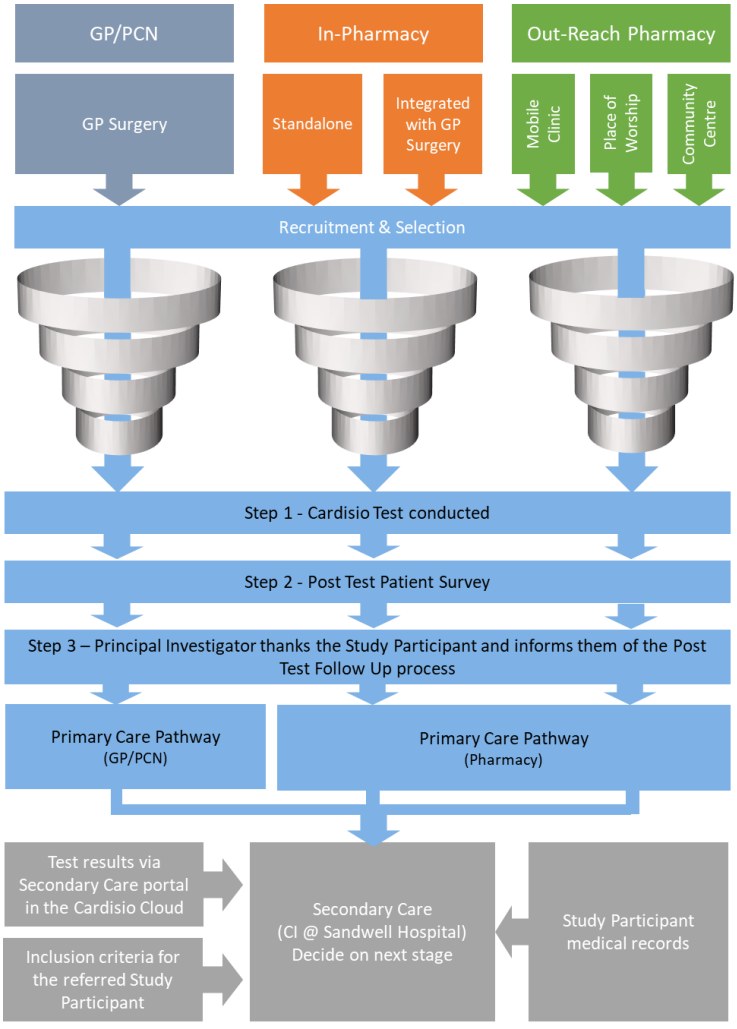
The Recruitment and Selection procedure aims to provide the consistent basis for each Primary Care setting to apply the eligibility criteria in a stepped process. This is outlined in the process shown below:



9.3 PROCEDURES AND PROCEDURE TABLES

9.3.1 Procedures

The study follows a consistent procedure across all three Primary Care Settings. Once the Participants for the Study have been Selected, there is a prescriptive handover to Secondary Care. The schematic below illustrates the flow for each of the Settings.



9.3.2 Study Procedure Tables

The table below gives a detailed stage by stage breakdown of the procedures each Setting will follow from Recruitment to Post-Test Secondary Care referral.

Study Stage: D Testing			
GP/PCN Primary Care Setting			
Study Sub-Stage	WHEN?	WHO? WHAT?	HOW?
		PI	Methods and Tools
Recruitment	Before Test Day	The PI (Primary Investigator) for the GP/PCN Primary Care setting will form their study pool of Participants from their registered patient population. A small number of walk-ins can also be recruited closer to Test Day based upon the GP-PI's assessment against the exclusion and inclusion criteria. At this stage a Study Participant is still a Candidate and not formally selected for inclusion in the Study.	The patient population will need to be filtered so those who cannot participate are excluded from the study. The GP-PI can then split their cohort by gender and then apply the inclusion criteria to arrive at their recruitment pool. They will use GP systems (EMIS or SysTMOne) which incorporate QRISK2 data. Participants selected must be close to an equal mix of genders; so, as testing progresses, if significant imbalances occur then the GP-PI can adjust their selection accordingly. The Recruitment Pool for the GP/PCN Primary Care Setting has been formed.
Selection	Before Test Day	GP-PI will form the Selection group from their study pool.	Each candidate Study Participant will be added to the Primary Care Setting's Study Test File. A randomisation function included in the Study Test File will be used on the Recruitment pool to choose participants to enter the Selection pool. They will not be assigned a Study Participant Number at this stage (which uniquely identifies the Study Participant without revealing their name and personal details). The Selected Participants Pool for the GP/PCN Primary Care Setting has been formed.
Post-Selection	Before Test Day	GP-PI will send a letter to the Study participant to tell them that they have been selected.	A letter will be sent by the GP-PI to the potential participant informing them that they would like their Participation in the Study.
	Before Test Day	The GP-PI will explain why they have been invited to have the test.	A Participant pamphlet will be sent with the letter above explaining that they have been invited, why they were recommended and what the Study entails, and what the next steps are.

Pre-Test	On Test Day	The Study Participant will be given information by the GP-PI on what the test involves and will provide the GP-PI with other additional information. Step 1 that they agree to participate in the Study and give their informed consent to have the test administered and for the follow up. Step 2 to do the test itself and complete the Study Participant Questionnaire and then, Step 3 Post Test Follow Up: a letter or clinic appointment for some.	A Participant pamphlet will be given to the Study Participant provides information for what the test involves, and other additional information will be captured in the Study Test File. The written consent form will be given to the Study Participant to sign before the test procedure can be undertaken. Three copies of the Consent Form will be signed, one will be retained for the Study Participant, one for the GP-PI and the third for the Study Group administrator. The Study Test File can now be amended to allocate a Study Participant Number for the Study Participant.
	On Test Day	The Study Participant will be asked to undertake a QRISK3 assessment which will be recorded in their Study Entry.	For the GP/PCN setting, we would also encourage a Study Participant, where possible, to undertake the QRISK3 assessment and for the results to be recorded. A stand-mounted Tablet PC will be connected to the Internet to provide access to the QRISK3 assessment. The results of the QRISK 3 assessment will be entered into the Study Test File.
	On Test Day	The Study Participant will take a short pre-test questionnaire to capture any broad socio-economic information which aims to help address health in-equality.	A pre-test questionnaire (Questionnaire #1) will be given to the study participant to fill out before the test is performed.
	On Test Day	Study Participant prepares for the Test to be undertaken including any request for a chaperone. The Test will be conducted in a secure and private area in the GP/PCN setting.	Female Study Participants may request a Chaperone to accompany them and/or a female GP-PI during the test. Both genders are required to present their Chest for preparation and attachment of the 5 Lead ECG, a procedure like the use of a 12 lead ECG. However, the Cardisio test requires a precise placement of the 5 leads, which will be explained and practised during the Training given.
Test	On Test Day	The Test is performed by the trained GP-PI. This is referred to as Step 1 in the Participant Pamphlets.	The GP-PI will help the Study Participant to prepare for the Test in the secure and private area. This requires the placement and secure attachment of the 5 leads and sensor pads connected to the Cardisio Test Gateway device connected to a Laptop PC.

			If the 5 Leads have been correctly applied then the test cycle can take 4 minutes, though it can be slightly longer. The Cardisio App, installed on the Study Laptop PC, will inform the GP-PI that the test has been successfully completed. Please note: In exceptional circumstances the Leads may have to be re-applied and the test repeated.
	On Test Day	The Test is concluded.	After the test is concluded the GP-PI can remove the leads and sensor pads. Study Participant can get dressed.
Post-Test Primary Care	On Test Day	The GP-PI will ask the Study Participant to fill-out a post-test questionnaire which asks about their test experience and to provide any other feedback.	A short questionnaire (Questionnaire #2) will be given to the Study participant to fill-out.
	On Test Day	The GP-PI will inform the Study Participant that Step 2 has been completed, and that Step 3 Post Test Follow Up will happen in due course.	The Cardisio Test results are not shared with the Study Participant, they will leave the Testing area with only their copy of the signed Consent Form and the Participant Pamphlets provided.
Post Test – Primary Care	After Test Day	GP-PI determines care pathway for the Study Participant	GP-PI reviews the Cardisio Heart Test results. If all Cardisio test Indicators are green then the GP-PI sends a Green letter to the Study Participant informing them that no further action is required ~~generates a standard letter to refer the Study Participant to Secondary Care if they choose to do so, otherwise they can~~. If the test results are Red or Amber, GP-PI will make a telephone call to the Study Participant, informing them that a Cardiologist at the hospital will be reviewing the results and will make direct contact ~~update records for the Study Participant (as they are already their patient)~~. The GP-PI follows this up with a Red letter, confirming the details of the phone call.~~-~~
Post Test – Secondary Care	After Test Day	~~General~~ Weekly review and analysis of the Cardisio Heart T~~t~~ests conducted ~~that day~~since the last weekly review.	The Secondary Care team can access the Secondary Care Portal in the Cardisio Cloud to ~~understand the rate~~ review and analyse ~~and results from the Day's testing.~~the tests performed during the previous week. All ~~t~~Test results are accessible (in real time) by the Secondary Care team, via the Secondary Care (ICS-based) Portal in the Cardisio cloud.
Post Test – Secondary Care	After Test Day	Secondary Care ~~receive a GP-PI referral~~ review Red and Amber test results and	Secondary Care have three sets of information pertaining to the Study Participant: **(1)** Cardisio Test Result, accessible via the Secondary Care Portal

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		accesses~~with~~ the Study Participant's medical history.	~~(1)~~(2) The Study Test File record for the Study Participant is available via the ~~NHS Sharepoint Form~~Microsoft Teams Environment, hosted by the NHS (which includes Study Participant details as well as the basis for the inclusion). ~~(2)~~(3) Study Participant's medical history via the EMIS or SysTMOne, (Authorisation given via the Consent Form - C) ~~(3) Cardisio Test Result, accessible via the Secondary Care Portal~~ ~~The lead cardiologist will analyse the results of the test and determine next steps, which could be a combination of, but is not limited to, the following: medication therapy, in person clinic appointment, further diagnostic imaging is required etc.~~
		Review of Non-Green Cardisio Heart Tests	The Chief Investigator / Lead Cardiologist will review and analyse the red and amber test results in conjunction with the Participants medical history. A determination of next steps is then made in line with current secondary care procedures and guidelines.
		Secondary Care / Study Participant communication.	The secondary care team are responsible for all communication to Study Participants that have a red or amber test result. Secondary Care Standard letters have been provided as follows: • No Action required. A letter informing the participant that their test results have been reviewed and no action is proposed. • Appointment Letter A letter inviting the Participant to a virtual or face to face appointment.

Study Stage: D Testing			
Pharmacy Setting (In-Pharmacy)			
Study Sub-Stage	WHEN	WHAT	HOW
		PI	Methods and Tools
Recruitment	Before Test Day	The PH-PI (Pharmacy Primary Investigator) will form their Recruitment pool of study candidates from their known patient population based on their medication profile. A small number of walk-ins will also be recruited based both on the medication requested and a QRISK3 assessment. At this stage a Study Participant is still a Candidate and not formally selected for inclusion in the Study.	The PH-PI will form their recruitment pool by assessing their known customer population based on their medication profile. The customer population will need to be filtered so those who cannot participate are excluded from the study. The standard set of exclusion and inclusion criteria has indicative medication for each outlined in the Recruitment & Selection Schema, and this can be used by the PH-PI. They can also split their cohort by gender and then apply the criteria to arrive at their recruitment pool. Participants selected must be close to an equal mix of genders; so as, testing progresses, if significant imbalances occur then the Pharmacist can adjust their selection accordingly. The Recruitment Pool for the In-Pharmacy Primary Care Setting has been formed.
Selection	Before Test Day	PH-PI will form the Selection group from their study pool.	The Pharmacy Primary Care Settings can use the Participant pamphlet to help a potential Participant decide to join the Study. Each candidate Study Participant will be added to the Primary Care Setting's Study Test File. A randomisation function included in the Study Test File will be used on the Recruitment pool to choose participants to enter the Selection pool. They will not be assigned a Study Participant Number at this stage (which uniquely identifies the Study Participant without revealing their name and personal details). The Selected Participants Pool for the Pharmacy Primary Care Setting has been formed.

Post-Selection	Before Test Day	PH-PI will send a letter to the Study participant to tell them that they have been selected.	A letter will be sent by the PH-PI to the potential participant informing them that they have been selected for the Study.
	On Test Day	The PH-PI will explain why they have been invited to have the test.	Participant pamphlet will be sent with the letter above explaining that they have been invited, why they were recommended and what the Study entails, and what the next steps are.
Pre-Test	On Test Day	The Study Participant will be given information by the PH-PI on what the test involves and will provide the PH-PI with other additional information. Step 1 that they agree to participate in the Study and give their informed consent to have the test administered and for the follow up. Step 2 to do the test itself and complete the Study Participant Questionnaire and then, Step 3 Post Test Follow Up: a letter or clinic appointment for some.	A participant pamphlet will be given to the Study Participant provides information for what the test involves, and other additional information will be captured in the Study Test File. The written consent form (Form #2) will be given to the Study Participant to sign before the test procedure can be undertaken. Three copies of the Consent Form will be signed, one will be retained for the Study Participant, one for the PH-PI and the third for the Study Group administrator. The Study Test File can now be amended to allocate a Study Participant Number for the Study Participant.
	On Test Day	The Study Participant will be asked to undertake a QRISK3 assessment which will be recorded in their Study Entry.	For the In-Pharmacy setting, we would also encourage a Study Participant, where possible, to undertake the QRISK3 assessment and for the results to be recorded. A stand-mounted Tablet PC will be connected to the Internet to provide access to the QRISK3 assessment. The results of the QRISK 3 assessment will be entered into the Study Test File.
	On Test Day	The Study Participant will take a short pre-test questionnaire to capture any broad socio-economic information which aims to help address health in-equality.	A pre-test questionnaire (Questionnaire #1) will be given to the study participant to fill out before the test is performed.
	On Test Day	Study Participant prepares for the Test to be undertaken including any request for a chaperone. The Test will be conducted in a secure and private area in the In-Pharmacy setting.	Female Study Participants may request a Chaperone to accompany them and/or a female GP-PI during the test. Both genders are required to present their Chest for preparation and attachment of the 5 Lead ECG, a procedure like the use of a 12 lead ECG. Generally a bra is okay to wear during the test, unless it interferes with the placement of sensors. Underwire bras may affect the signals.

			However, the Cardisio test requires a precise placement of the 5 leads, which will be explained and practised during the Training given.
Test	On Test Day	The Test is performed by the trained PH-PI. This is referred to as Step 1 in the Participant Pamphlets.	The PH-PI will help the Study Participant to prepare for the Test in the secure and private area. This requires the placement and secure attachment of the 5 leads and sensor pads connected to the Cardisio Test Gateway device connected to a Laptop PC. If the 5 Leads have been correctly applied then the test cycle can take 4 minutes, though it can be slightly longer. The Cardisio App, installed on the Study Laptop PC, will inform the PH-PI that the test has been successfully completed. Please note: In exceptional circumstances the Leads may have to be re-applied and the test repeated.
	On Test Day	The Test is concluded.	After the test is concluded the PH-PI can remove the leads and sensor pads. Study Participant can get dressed.
Post-Test Primary Care	On Test Day	The PH-PI will ask the Study Participant to fill-out a post-test questionnaire which asks about their test experience and to provide any other feedback.	A short questionnaire (Questionnaire #2) will be given to the Study participant to fill-out.
	On Test Day	The PH-PI will inform the Study Participant that Step 2 has been completed, and that Step 3 Post Test Follow Up will happen in due course.	The Cardisio Test results are not shared with the Study Participant, they will leave the Testing area with only their copy of the signed Consent Form and the Participant Pamphlets provided.
Post Test – Primary Care	After Test Day	The PH-PI provides a standard letter to the Study Participant and the GP of the Study Participant	**The** PH-PI generates a standard letter to inform the study participant's GP that they have consented to be part of the study and have also consented to share their GP Medical and Medicine history with the Secondary Care team. If all Cardisio test Indicators are Green then the ~~GP~~ Study Participant will be informed, **using the PH-PI Green Letter,** that there is no further action required. The GP (where known) will be copied on any communication with the study participant. If any of the Cardisio test indicators are Red or Amber, then the GP (where known) will be informed that the secondary care team will be

			assessing the results and will inform the GP of next step. From this point the secondary care team will be responsible for all communication with the study participant and the study participant's GP (where known).
Post Test – Secondary Care	After Test Day	Weekly review and analysis of the Cardisio Heart Tests conducted ~~since the last weekly review~~.~~General analysis of the tests conducted that day~~	The Secondary Care team can access the Secondary Care Portal in the Cardisio Cloud to review and analyse the tests performed during the previous week. All test results are accessible (in real time) by the Secondary Care team, via the Secondary Care (ICS-based) Portal in the Cardisio cloud. ~~Secondary Care team can access the Secondary Care Portal in the Cardisio Cloud to understand the rate and results from the Day's testing.~~ ~~**All Test results are accessible (in real time) by the Secondary Care team, via the Secondary Care (ICS-based) Portal in the Cardisio cloud.**~~
Post Test – Secondary Care	After Test Day	~~Secondary Care receive a GP referral with the Study Participant's medical history~~Secondary Care review red and Amber test results and accesses the Study Participant's medical history.	Secondary Care have three sets of information pertaining to the Study Participant: **(1)** Cardisio Test Result, accessible via the Secondary Care Portal **(2)** The Study Test File record for the Study Participant is available via the Microsoft Teams Environment, hosted by the NHS (which includes Study Participant details as well as the basis for the inclusion). ~~(1)~~(3) Study Participant's medical history via the EMIS or SysTMOne, (Authorisation given via the Consent Form - C) ~~Secondary Care have three sets of information pertaining to the Study Participant:~~ ~~**(1)** The Study Test File record for the Study Participant is available via the NHS SharePoint Form (which includes Study Participant details as well as the basis for the inclusion).~~ ~~**(2)** Study Participant's medical history (Consent provided via the Participant consent form)~~ ~~**(3)** Cardisio Test Result, accessible via the Secondary Care Portal~~ ~~The lead cardiologist will analyse the results of the test and determine next steps, which could be a combination of, but is not limited to, the following: medication therapy, in person clinic appointment, further diagnostic imaging is required etc.~~

Post Test – Secondary Care	After Test Day	Review of Non-Green Cardisio Heart Tests	The Chief Investigator / Lead Cardiologist will review and analyse the red and amber test results in conjunction with the Participants medical history. A determination of next steps is then made in line with current secondary care procedures and guidelines.
Post Test – Secondary Care	After Test Day	Secondary Care / Study Participant communication.	The secondary care team are responsible for all communication to Study Participants that have a red or amber test result. Secondary Care Standard letters have been provided as follows: • No Action Required Letter A letter informing the participant that their test results have been reviewed and no action is proposed. • Appointment Letter A letter inviting the Participant to a virtual or face to face appointment.

Study Stage: D Testing			
Pharmacy Setting (Community Outreach-Pharmacy) PHC			
Study Sub-Stage	WHEN	WHAT	HOW
		PI	Methods and Tools
Recruitment	Before Test Day	The PHC-PI (Pharmacy Primary Investigator) will form their Recruitment pool of study candidates from the likely walk-in patient population based on their medication profile. At this stage a Study Participant is still a Candidate and not formally selected for inclusion in the Study.	The PHC-PI will develop their participant pool through the following activities: • advertise via social media and through posters placed in the community settings to invite visitors to Participate • Setting us a sign up desk when they visit different settings Inclusion and exclusion criteria will be reviewed with candidates before being invited to join the Participant pool. The standard set of exclusion and inclusion criteria has indicative medication for each outlined in the Recruitment & Selection Schema, and this can be used by the PHC-PI. They can also split their cohort by gender and then apply the criteria to arrive at their recruitment pool. Participants selected must be close to an equal mix of genders; so as, testing progresses, if significant imbalances occur then the Pharmacist can adjust their selection accordingly. The Recruitment Pool for the Pharmacy Outreach Primary Care Setting has been formed.
Selection	Before Test Day	PHC-PI will form the Selection group from their study pool.	The Pharmacy Outreach Primary Care Settings can use the Participant pamphlet to help a potential Participant decide to join the Study. The nature of the Community Pharmacy means that candidates who come forward to join the study are unknown to, and not selected by the PHC-PI and so are deemed a randomised sample. Each candidate Study Participant will be added to the Primary Care Setting's Study Test File. They will not be assigned a Study Participant Number at this stage (which uniquely identifies the Study Participant without revealing their name and personal details).

			The Selected Participants Pool for the Pharmacy Outreach Primary Care Setting has been formed.
Post-Selection	Before Test Day	PHC-PI will send a letter to the Study participant to tell them that they have been selected.	A letter will be sent by the PHC-PI to the potential participant informing them that they have been selected for the Study.
	Before Test Day	The PHC-PI will explain why they have been invited to have the test.	Participant pamphlet will be sent with the letter above explaining that they have been invited, why they were recommended and what the Study entails, and what the next steps are.
Pre-Test	On Test Day	The Study Participant will be given information by the PHC-PI on what the test involves and will provide the PHC-PI with other additional information. Step 1 that they agree to participate in the Study and give their informed consent to have the test administered and for the follow up. Step 2 to do the test itself and complete the Study Participant Questionnaire and then, Step 3 Post Test Follow Up; a letter or clinic appointment for some.	A participant pamphlet will be given to the Study Participant provides information for what the test involves, and other additional information will be captured in the Study Test File. The written consent form will be given to the Study Participant to sign before the test procedure can be undertaken. Three copies of the Consent Form will be signed, one will be retained for the Study Participant, one for the PHC-PI and the third for the Study Group administrator. The Study Test File Form can now be amended to allocate a Study Participant Number for the Study Participant, as consent has been given.
	On Test Day	The Study Participant will be asked to undertake a QRISK3 assessment which will be recorded in their Study Entry.	For the Pharmacy Outreach setting, we would also encourage a Study Participant, where possible, to undertake the QRISK3 assessment and for the results to be recorded. A stand-mounted Tablet PC will be connected to the Internet to provide access to the QRISK3 assessment. The results of the QRISK 3 assessment will be entered into Study Test File.
	On Test Day	The Study Participant will take a short pre-test questionnaire to capture any broad socio-economic information which aims to help address health in-equality.	A pre-test questionnaire (Questionnaire #1) will be given to the study participant to fill out before the test is performed.
	On Test Day	Study Participant prepares for the Test to be undertaken including any request for a chaperone. The Test will be conducted in a secure and private area in the Pharmacy Outreach setting.	Female Study Participants may request a Chaperone to accompany them and/or a female PHC-PI during the test. Both genders are required to present their Chest for preparation and attachment of the 5 Lead ECG, a procedure like the use of a 12 lead ECG.

			However, the Cardisio test requires a precise placement of the 5 leads, which will be explained and practised during the Training given.
Test	On Test Day "	The Test is performed by the trained PHC-PI. This is referred to as Step 1 in the Participant Pamphlets.	The PHC-PI will help the Study Participant to prepare for the Test in the secure and private area. This requires the placement and secure attachment of the 5 leads and sensor pads connected to the Cardisio Test Gateway device connected to a Laptop PC. If the 5 Leads have been correctly applied then the test cycle can take 4 minutes, though it can be slightly longer. The Cardisio App, installed on the Study Laptop PC, will inform the PHC-PI that the test has been successfully completed. Please note: In exceptional circumstances the Leads may have to be re-applied and the test repeated.
	On Test Day	The Test is concluded.	After the test is concluded the PHC-PI can remove the leads and sensor pads. Study Participant can get dressed.
Post-Test Primary Care	On Test Day	The PHC-PI will ask the Study Participant to fill-out a post-test questionnaire which asks about their test experience and to provide any other feedback.	A short questionnaire (Questionnaire #2) will be given to the Study participant to fill-out.
	On Test Day	The PHC-PI will inform the Study Participant that Step 2 has been completed, and that Step 3 Post Test Follow Up will happen in due course.	The Cardisio Test results are not shared with the Study Participant, they will leave the Testing area with only their copy of the signed Consent Form and the Participant Pamphlets provided.
Post Test – Primary Care	After Test Day	PH-PI provides a standard letter to the Study Participant and the GP of the Study Participant**, where known.**	PH-PI generates a standard letter to inform the study participant's GP **(where known)** that they have consented to be part of the study and have also consented to share their GP Medical and Medicine history with the Secondary Care team. If all Cardisio test Indicators are Green then the Study Participant will be informed that there is no further action required. The GP (where known) will be copied on any communication with the study participant. If any of the Cardisio test indicators are Red or Amber, then the GP (where known) will be informed that the secondary care team will be

			assessing the results and will inform the GP of next step. From this point the secondary care team will be responsible for all communication with the study participant and the study participant's GP (where known).
Post Test – Secondary Care	After Test Day	Weekly review and analysis of the Cardisio Heart Tests conducted.	The Secondary Care team can access the Secondary Care Portal in the Cardisio Cloud to review and analyse the tests performed during the previous week. All test results are accessible (in real time) by the Secondary Care team, via the Secondary Care (ICS-based) Portal in the Cardisio cloud.
Post Test – Secondary Care	After Test Day	Secondary Care review red and Amber test results and accesses the Study Participant's medical history.	Secondary Care have three sets of information pertaining to the Study Participant: **(1)** Cardisio Test Result, accessible via the Secondary Care Portal **(2)** The Study Test File record for the Study Participant is available via the Microsoft Teams Environment, hosted by the NHS (which includes Study Participant details as well as the basis for the inclusion). (3) Study Participant's medical history via EMIS or SysTMOne, (Authorisation given via the Consent Form - C)
Post Test – Secondary Care	After Test Day	Review of Non-Green Cardisio Heart Tests	The Chief Investigator / Lead Cardiologist will review and analyse the red and amber test results in conjunction with the Participants medical history. A determination of next steps is then made in line with current secondary care procedures and guidelines.
Post Test – Secondary Care	After Test Day	Secondary Care / Study Participant communication.	The secondary care team are responsible for all communication to Study Participants that have a red or amber test result. Secondary Care Standard letters have been provided as follows: • No Action Required Letter A letter informing the participant that their test results have been reviewed and no action is proposed. • Appointment Letter A letter inviting the Participant to a virtual or face to face appointment.

9.4 STUDY PARTICIPANT - CONSENT & RIGHT OF WITHDRAWAL

The Study recognises the requirement to obtain the Study Participant's Consent to participate in the study and the right of withdrawal of the Study Participant at any point during the Study Test process up to an including any in person assessment by the Secondary Care Team.

9.4.1 Study Participant Consent

It will be the responsibility of the Primary Investigator (PI), who will undertake the Test process to obtain the Study Participant's written informed consent on the Study Participant's Test Day. A key aspect of this is to inform the Study Participant that their data will be pseudonymised before analysis and may be anonymously published, and of the data privacy statement of the Study.

The PI will obtain a written, informed consent form that will be signed and personally dated by the Study Participant and then counter-signed by the PI. The signature confirms that the consent is based on understood information. The PI will retain the original written informed consent document, a copy will be given to the Study Participant. Informed consent requires the PI to have explained the Test process, test objectives, expected benefits and any potential risks of the study to the study participant.

Study information document containing a written summary of all relevant information will be given to the study participant before written, informed consent is obtained. The study information document will make it clear that access to the participant's medical records by the Secondary Care team may be required based on the outcome of the Test.

Study Participants will be advised that their Study documents may be accessed by the Secondary Care Team and their GP to the extent permitted by applicable laws and/or regulations without breaching their confidentiality. By signing the informed consent form, the Study participant authorises such access.

9.4.2 Study Participant's Right of Withdrawal

Before informed consent can be obtained, the PI will give the Study Participant sufficient time and opportunity to inquire about details of the study and to decide whether he/she wishes to participate in the study (ref. §5.8.2 (f) DIN EN ISO14155:2020).

The PI will explain to the Study Participant that he/she is free to refuse to participate in the study or, if he/she decides to participate, to withdraw from the Study at any time.

If a Study Participant chooses to withdraw from the Study prior to their Test being administered, then another Study Participant will be invited to participate from the recruited and then selected study pool using the randomisation spreadsheet.

If a Study Participant chooses to withdraw from the Study after their Test has been completed but prior to their assessment by the Secondary Care team, then their data set will not be used in the Study beyond that point. The statistical analysis may still be valid for the Study, however, the Study Group, comprising the Study Project Manager and PIs from all three settings and a representative of the CI, may choose to select an alternative Study Participant as a replacement.

If a Study Participant chooses to withdraw from the Study after they have been assessed, then this will not affect their opportunities for future medical care or treatment.

9.5 STUDY STAGE E OUTCOME ANALYSIS

9.5.1 Data collection

The data collected during the following stages will be collated and analysed after the final Participant is tested:

a. Study Stage C - Testing site readiness
b. Study Stage D - PI Training
c. Study Stage D - Recruitment and selection
d. Study Stage D - 811 Participants tested
e. Study Stage D - Secondary Care referral

The following Table shows at what stage, which data is collected, for what purpose, from whom and recorded on which Form (F#), or in which Questionnaire (Q#).

Stage & Sub-Stage	Q #	F #	Purpose	When?	Frequency?	Who? (Respondee)	How?
Stage D - Test **Pre-Test**		**F1**	Capture SP details as part of Recruitment & Selection. [Name, Address, GP, NHS #, DoB, Contact Number, Inclusion Criteria)	After SP is selected (and before a unique Study Participant ID is allocated)	Whenever a SP is selected to Participate	PI/PI-T	Study Test File
Pre-Test		**F1+**	On-Boarding SP to administer a Cardisio Test Complete & Validate SP details prior to Test	On Test Day Prior to Test	Every SP	SP with PI/PI-T	Study Test File
Pre-Test		**F2**	QRisk3 assessment	On Test Day	Every Test	SP	QRisk3 website
Pre-Test		**F1++**	Adding QRisk 3 result to SP's Record in the STF	On Test Day	Every Test	PI/PI-T	STF
Pre-Test		**F3**	Obtaining an informed Consent Form	Prior to Test	Every SP	PI, PI-T, SP countersigned	Paper F
Pre-Test	**-**	**F1+++**	The unique Study Participant ID is allocated	Post Test	Every Test	PI/PI-T	STF
Pre-Test	**1**		Pre-Test Questionnaire prior to administering a Cardisio Test	On Test Day	Every SP	SP input PI/PI-T administration	Paper Q
Test	**-**	**F1++++**	Adding the Cardisio Unique Test Number to SP Record in the STF	On Test Day Prior to Test	Every Test	PI/PI-T	STF
Post-Test	**2**		Capturing SP feedback on their Test experience	On Test Day	Every Test	SP input	Paper Q
Post-Test	**3**		Capturing PI feedback on their Test administration experience	Post Test Day	Every Week	PI input	Paper Q
Post-Test	**4**		Capture PI-T feedback on their Test administration experience	Post Test Day	Every Week	PI's Team input	Paper Q
Post-Test	**5**		Capture CI feedback on their Test administration experience	Post Test Day	Every Week	CI input	Paper Q
Pre-Test, Test, Post-Test		**F4**	Right of Withdrawal	At any point during the "On the day Test"	n/a	SP	Standard Form

Abbreviations	
SP = Study Participant PI = Principal Investigator PI-T = Principal Investigator's Team CI = Chief Investigator STF = Study Test File (a long list of all SPs at a Primary Care Setting)	

9.5.2 Outcome Analysis

Primary Outcomes	Outcome measures	Analysis
1. Cardisio can be used in community settings without extensive training or specialist knowledge by the tester.	• Test results gathered. • Feedback from the test administrators and PI's. • Reported confidence of the secondary care team of the reliability of test collected.	• Correlate the number of tests administered with feedback from the PI team on the testing process in terms of effectiveness and throughput.
2. Secondary Care teams can review all the Cardisio Test results remotely in a single ICS-based portal.	• Secondary care team successfully access test results across the study participant group. • The number or percentage of correct predictions (true positives plus true negatives)	• Analyse how Secondary Care can access test results based on the feedback provided • Patients (811) will be assessed/diagnosed as to whether they have CVD (yes=1 vs no=0). This will be the binary outcome variable. • Step 1 will use standard CVD Prevention Pathway to predict the presence or absence of CVD using binary logistic regression. This will result in the number or percentage of correct predictions (true positives plus true negatives). Step 2 will assess, to what extent the information obtained from the Cardisio Heart Test in addition to the CVD Prevention Pathway, will improve this prediction of patients diagnosed with CVD.
3. The addition of Cardisio test / risk information results in fewer patient journeys to busy hospitals for tests. contributing to the NHS Net Carbon Zero targets	• Number of Patient Journeys • Comparison of referral after Cardisio test versus typical referral with current CVD Pathway V5. https://www.england.nhs.uk/rightcare/wp-content/uploads/sites/40/2018/02/cvd-pathway.pdf	• Calculate reduction in patient journeys. • Carbon reduction using postcode information

4. The Cardisio Test delivers a superior and richer test result when compared to a traditional 2D ECG. More data about disease conditions will improve the cardiologists ability to diagnose or clarify next steps.	• Feedback from CI and secondary team plus feedback from GP/PCN PI.	• Analyse the feedback and report
5. To demonstrate that a revised care pathway could be considered by the NHS for future adoption, based on a "hub and spoke" central cardiology team reviewing test results and selecting patients for further diagnostic test procedures, a so-called "pull model". 6. Better availability of community testing should offer a better patient experience. 7. Through the use of Allied Healthcare Professionals to undertake routine testing, a reduction in GP appointments should be possible. 8. Secondary care teams will be able to triage and prioritise patients, making better use of scarce resources.	• Feedback from Participants Surveys. • Feedback from PIs in Pharmacy Setting and analysis of referrals made. • Feedback from CI and secondary care team.	• Analysis on the test process and how it was undertaken in the Primary Care setting from recruitment and selection through to testing.

Secondary Outcomes	Outcome measures	Analysis
1. Evidence of how the test environment is integrated into a Primary Care Setting.	• Ease with which the primary care administrators can undertake recruitment selection and testing of study participants as recorded in the "Participant Testing Log". • Test Environment Readiness assessment completed with ease.	• Analysis of how the test environment was setup to enable testing, and how Study Participant recruitment and selection took place, specifically on the performance of the exclusion and inclusion criteria.
2. Feedback on the ease of training in person and online training materials.	• Feedback from PI's and test administrators gathered via survey and structured interviews.	• Analysis of how the test training was provided and how it can be improved.
3. Feedback on the ease of test procedure and administration.	• Feedback from PI's and test administrators gathered via survey and structured interviews.	• Analysis of how the test process was completed and how it can be improved.
4. Feedback on patient experience and preference for community-based testing	Feedback from Participants gathered via pre and post-test surveys to assess: **A.** How easy was it to understand the purpose of the study. **B.** How easy it was to undertake the test. Using a scale of 1-5.	• Analysis of how the Patient Journey was and how it can be improved.
5. The view of the secondary care (cardiology) team of the process and impact on the quality of their patient lists.	Feedback from CI and team gathered via survey and structured interviews.	• Analysis of how Secondary Care engaged in the Test Process and how this can be improved.

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9.6 End of Study Defininition

The End of Study is defined as the point when:

1. All testing is complete in the primary care settings (811 Participants tested)
2. All questionnaires have been completed.
3. All Red and Amber Cardisio Test Results assessed by the Chief Investigator
4. All results have been checked in the Study Test file**.**

9.7 Blinding

There is no requirement for blinding of the test results in this study.

See section 9.4.1 for details of anonymisation and pseudonymisation of Participant personal data**.**

10 DATA & DATA MANAGEMENT OVERVIEW

The Primary Investigator (PI) and their Team members within the Primary Care setting will use the data they have access to in relation to their patients whether this is their medical or medication profile as appropriate to develop their study pool of Participants. This is outlined in Section 9.2 Study Stage D – Testing. Up to this point all data relating to participants will have been stored only using the existing Primary Care or NHS information systems.

Study Data can be grouped into three categories and will be focused and limited to the need to link a test result to a participant to enable the outcome measures required for the study.

1. Study Participant Data – Core and Study Specific, which is Forms related data.
2. Study Primary & Secondary Care Teams, which is spreadsheet and Test system related data.
3. Study Data and Test Outcome Data, which is questionnaires and Test system related data.

The Table in Section 9.5.1 shows at what stage, which data is collected, for what purpose, from whom and recorded on which Form (F#), or in which Questionnaire (Q#).

In the following sections the data collected is listed.

10.1 Study Participant Data

10.1.1 Study Participant Core Data

Data Item	Mandatory / Optional
• Family Name, First Name	Mandatory
• Date of Birth	Mandatory
• Gender	Mandatory
• Ethnicity	Mandatory
• Weight, height	Mandatory
• NHS number	Mandatory
• Home Address	Mandatory
• Home Post Code	Mandatory
• Registered with GP (Y/N)	Mandatory
• GP surgery details (Name of GP, Address)	Mandatory (if they have a GP)
• Primary Care Setting Location	Mandatory
• Socio-economic status (highest educational qualification, yearly income / household, number of people in household)	Optional

Point of Capture, Usage, Access & Storage Statement

The data above is captured in primary care, once a Study Participant has been selected to participate in the Study and will be recorded as a line entry into the Study Test File. It will be validated and completed prior to the Test being administered with the Study Participant. It will be used for statistical analysis for ESG assessment, test outcome analysis, and for any follow ups by a GP and/or the Secondary Care team. This data is captured on a Form stored in the NHS environment, and only accessible in its complete form by NHS staff. ESG assessment is reliant on Post Codes, Locations, and any socio-economic data where captured. Storage and destruction post-study will follow ~~existing NHS IS guidelines~~ protocol in section 10.4.

10.1.2 Study Participant - Study Specific Data

Data Item	Mandatory / Optional
• Inclusion Criteria	Mandatory
• Study Participant Number	Mandatory
• QRisk3 Assessment Score	Mandatory
• Primary Care Setting Location	Mandatory
• Date of Test	Mandatory
• Time of Test	Mandatory
• PI / Test Administrator	Mandatory
• Informed Consent Received	Mandatory
• Pre-Test Questionnaire Completed	Mandatory
• Unique Cardisio Test Number	Mandatory
• Cardisio Test Outcome – P	Mandatory
• Cardisio Test Outcome – A	Mandatory
• Cardisio Test Outcome – S	Mandatory
• Post-Test Feedback Questionnaire Completed	Mandatory
• Right of Withdrawal exercised & Reason	Optional

Point of Capture, Usage, Access & Storage Statement

The data above is captured as part of the Test administration and will be recorded as additions to the SP's line entry in the Study Test File. It will be used for statistical analysis for ESG assessment, test outcome analysis, and for any follow ups by a GP and/or the Secondary Care team. This data is captured on a Form stored in the NHS environment, and only accessible in its complete form by NHS staff. ESG assessment is reliant on forecasting possible travel that maybe required post-test. Storage and destruction post-study will follow ~~existing NHS IS guidelines~~protocol in section 10.4.

10.2 Study Primary & Secondary Care Teams

Data Item	Mandatory / Optional
• Name	Mandatory
• Title/Role	Mandatory
• Date of Birth	Mandatory
• Educational Level	Optional
• Setting Location	Mandatory
• Date of Test Administration Training	Mandatory
• E-mail Contact	Mandatory
• CI/PI/ Test Administrator Number	Allocated (and joined with E-mail)

Point of Capture, Usage, Access & Storage Statement

The data above is captured as part of the Test Setup and Training in Study Stage C – Setup. It allows the Study to provide access to the Cardisio Cloud – based Test Portal. It will be used for statistical analysis on test administration performance. This data is captured on a Form stored in the Cardisio environment, and only accessible in its complete form by Study Management. Storage and destruction post-study will follow existing Cardisio Data Privacy guidelines.

10.3 Study Data and Test Outcome Data

Study Data

This includes the data captured in the Questionnaires which is used to capture the qualitative feedback useful in informing the Study Objectives and outcomes. The data is used in an anonymised format for analysis purposes, for example, to understand how test administration can be improved, ease of participating etc. It is also an input into the ESG assessment to understand the use of the test in the Primary Care setting, specifically to understand the Study Participant's perspective of having done a primary care-based test.

This data is paper-based and transcribed into spreadsheets as anonymised data entries. These spreadsheets will be stored in a SharePoint environment.

Test Outcome Data

Each Test administered generates a Unique Test ID which acts as the unique reference link back to a Study Participant. The Cardisio Cloud portal does not hold any of the Study Participants data except for Age, Gender, Height and Weight.

10.4 Archiving – Post Study

10.4.1 Introduction

i. The documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced are defined as essential documents according to Guideline for good clinical practice E6(R2)
ii. These documents service to demonstrate the compliance of the investigator, sponsor and monitor the standards of GCP and with applicable regulatory requirements. They will be filed in an organised way that will facilitate management of the study, audit and inspection (Study Master File).
iii. Essential documents will be retained (archived) to allow for audit and inspection by regulatory authorities and will be readily available upon request.
iv. The Study Master File will be maintained throughout the study. Archiving will apply to both the investigator sites and the central study coordinating office.

10.4.2 Storage

i. Essential records will be maintained in a legible condition. Prompt retrieval will be possible. Plans for archiving study documents were made in the design phase of a study. Secure storage of all essential records has been planned for at study completion.
ii. Access to archives will be restricted to authorised personnel. Any change in the ownership and location of the documentation will be documented in order to allow tracking of the stored records.
iii. An archive index/log will be maintained to record all essential documents that have been entered into the archive,
iv. Storage of personal data is subject to applicable elements of EU Directive 95/46/EC and the Data Protection Act 1998.
v. Archiving will be authorised by the Sponsor following submission of the end of study report.

10.4.3 Duration of archiving

As the study is not going to be used in regulatory submissions, documents will be retained for at least five years after completion of the study.

10.4.4 Destruction of essential documents

i. The documents in sections **10.4.5** will be deleted after 5 years. This will be authorised by the Study Sponsor.
ii. The Study Test File will be anonymised by Sandwell Hospital and passed to the Study Sponsor to enable the Study reports to be created. The Sponsor may retain these anonymised records indefinitely.
iii. The Secondary Care Patient notes will be retained as per the hospital's standard procedures.
iv. All other essential study paper documents and electronic documents will be deleted as they contain personal data.
i. The Study Sponsor will notify investigators in writing when their study records can be destroyed.

10.4.5 Documents to be Archived.

Document Name	Site variant	Where Stored During Study	Where Stored After Study	Destruction Instructions	Planned Destruction Date	Who is Responsibility During Study	Who is Responsibility After Study
Consent Form	Ridgacre	Paper - Ridgacre PDF Version - NHS MS/Teams	Paper - Ridgacre PDF Version - NHS MS/Teams	After 5 years Paper to be shredded Electronic Versions to be deleted	01/01/2029	Junaid Duberia	Junaid Duberia - Paper Sandwell Hospital - MS Teams
Consent Form	Church Road	Paper - Church Road PDF Version - NHS MS/Teams	Paper - Church Road PDF Version - NHS MS/Teams	After 5 years Paper to be shredded Electronic Versions to be deleted	01/01/2029	Dr Sajjid Sawar	Dr Sajjid Sawar - Paper Sandwell Hospital - MS Teams
Consent Form	Dudley Integrated Health	Paper - Dudley Integrated Health PDF Version - NHS MS/Teams	Paper - Dudley Integrated Health PDF Version - NHS MS/Teams	After 5 years Paper to be shredded Electronic Versions to be deleted	01/01/2029	Jaspal Johal	Jaspal Johal - Paper Sandwell Hospital - MS Teams
Questionnaire Q1	Ridgacre	Paper - Ridgacre PDF Version - NHS MS/Teams	Paper - Ridgacre PDF Version - NHS MS/Teams	After 5 years Paper to be shredded Electronic Versions to be deleted	01/01/2029	Junaid Duberia	Junaid Duberia - Paper Sandwell Hospital - MS Teams
Questionnaire Q1	Church Road	Paper - Church Road PDF Version - NHS MS/Teams	Paper - Church Road PDF Version - NHS MS/Teams	After 5 years Paper to be shredded Electronic Versions to be deleted	01/01/2029	Dr Sajjid Sawar	Dr Sajjid Sawar - Paper Sandwell Hospital - MS Teams
Questionnaire Q1	Dudley Integrated Health	Paper - Dudley Integrated Health PDF Version - NHS MS/Teams	Paper - Dudley Integrated Health PDF Version - NHS MS/Teams	After 5 years Paper to be shredded Electronic Versions to be deleted	01/01/2029	Jaspal Johal	Jaspal Johal - Paper Sandwell Hospital - MS Teams
Questionnaire Q2	Ridgacre	Paper - Ridgacre PDF Version - NHS MS/Teams	Paper - Ridgacre PDF Version - NHS MS/Teams	After 5 years Paper to be shredded Electronic Versions to be deleted	01/01/2029	Junaid Duberia	Junaid Duberia - Paper Sandwell Hospital - MS Teams
Questionnaire Q2	Church Road	Paper - Church Road PDF Version - NHS MS/Teams	Paper - Church Road PDF Version - NHS MS/Teams	After 5 years Paper to be shredded Electronic Versions to be deleted	01/01/2029	Dr Sajjid Sawar	Dr Sajjid Sawar - Paper Sandwell Hospital - MS Teams
Questionnaire Q2	Dudley Integrated Health	Paper - Dudley Integrated Health PDF Version - NHS MS/Teams	Paper - Dudley Integrated Health PDF Version - NHS MS/Teams	After 5 years Paper to be shredded Electronic Versions to be deleted	01/01/2029	Jaspal Johal	Jaspal Johal - Paper Sandwell Hospital - MS Teams
Site Spedific Study Test File	Ridgacre	NHS MS/Teams	NHS MS/Teams	After 5 years Electronic Versions to be deleted	01/01/2029	Sandwell Hospital	Sandwell Hospital
Site Spedific Study Test File	Church Road	NHS MS/Teams	NHS MS/Teams	After 5 years Electronic Versions to be deleted	01/01/2029	Sandwell Hospital	Sandwell Hospital
Site Spedific Study Test File	Dudley Integrated Health	NHS MS/Teams	NHS MS/Teams	After 5 years Electronic Versions to be deleted	01/01/2029	Sandwell Hospital	Sandwell Hospital
Anonymised Study Test File	Study Sponsor	N/A	Study Sponsor MS/Teams	N/A	N/A	Sandwell Hospital	Study Sponsor
Secondary Care Patient Notes	Sandwell Hospital	Sandwell Hospital	Sandwell Hospital	To be retained as per Secondary Care standard procedures	As per Hospital procedures	Sandwell Hospital	Sandwell Hospital

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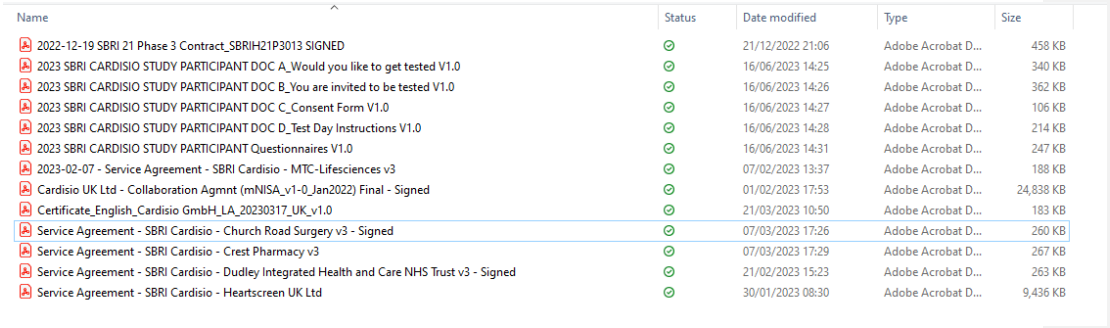
Appendix

12 APPENDICIES

In order to keep the size of this document reasonably small we have attached the appendices separately.



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2023 SBRI CARDISIO STUDY PARTICIPANT DOC A_Would you like to get tested V1.0	✓	16/06/2023 14:25	Adobe Acrobat D...	340 KB
2023 SBRI CARDISIO STUDY PARTICIPANT DOC B_You are invited to be tested V1.0	✓	16/06/2023 14:26	Adobe Acrobat D...	362 KB
2023 SBRI CARDISIO STUDY PARTICIPANT DOC C_Consent Form V1.0	✓	16/06/2023 14:27	Adobe Acrobat D...	106 KB
2023 SBRI CARDISIO STUDY PARTICIPANT DOC D_Test Day Instructions V1.0	✓	16/06/2023 14:28	Adobe Acrobat D...	214 KB
2023 SBRI CARDISIO STUDY PARTICIPANT Questionnaires V1.0	✓	16/06/2023 14:31	Adobe Acrobat D...	247 KB
2023-02-07 - Service Agreement - SBRI Cardisio - MTC-Lifesciences v3	✓	07/02/2023 13:37	Adobe Acrobat D...	188 KB
Cardisio UK Ltd - Collaboration Agmnt (mNISA_v1-0_Jan2022) Final - Signed	✓	01/02/2023 17:53	Adobe Acrobat D...	24,838 KB
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