STUDY PROTOCOL

The Healthcare Evaluation of Absolute Risk Testing Study: A multi-centre, single arm, pragmatic study in primary care setting

The HEART Study
GEN2020-02

Version 2.0 06 December 2021

NCT05294419

[redacted]

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Previous Versions

Protocol Version 1.0, Date 24 July 2021

This protocol has regard for the HRA guidance and order of content.

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PROTOCOL 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 Declaration of Helsinki and the principles of Good Clinical Practice, the Sponsor's (and any other relevant) SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the study without the prior written consent of the Sponsor.

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Name: (please print): Prof [redacted]	
Position:	

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INVESTIGATOR STATEMENT

I have read the protocol, including all appendices and the Investigator Brochure, and I agree that it contains all necessary details to enable me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. Further, I agree to conduct this study in accordance with Good Clinical Practice and applicable regulatory requirements.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by Genomics plc. I will discuss this material with them to ensure that they are fully informed about the study.

Principal Investigator	
Signature:	Date: DD/MMM/YYYY
Name (please print):	

KEY STUDY CONTACTS

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TABLE OF CONTENTS

Table of Contents

TABLE OF FIGURES AND TABLES

LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
BAME	Black, Asian and Minority Ethnic
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CVD	Cardiovascular Disease
DNA	Deoxyribonucleic Acid
EMIS	EMIS Health (formerly Egton Medical Information Systems)
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practice
DMP	Data Management Plan
HCP	Healthcare Professional
IB	Investigator Brochure
IFU	Instructions For Use
ICF	Informed Consent Form
ID	Identifier
IRT	Integrated Risk Tool
ISF	Investigator Site File
ISO	International Organization for Standardization
IVD	In Vitro Diagnostic
LPLV	Last Participant Last Visit
MI	Myocardial Infarction
NECS	NHS North of England Commissioning Support
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research

PCC	Primary Care Commissioner
PI	Principal Investigator
PIC	Patient Identification Centre
PIS	Patient Information Sheet
PRS	Polygenic Risk Score
QALY	Quality-Adjusted Life Years
QC	Quality Control
QRISK	A clinical risk assessment tool for CVD used by GPs in the UK
REC	Research Ethics Committee
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SMF	Study Master File
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedure
TIA	Transient Ischaemic Attack
USADE	Unanticipated Serious Adverse Device Effect
YLL	Years of Life Lost

STUDY SUMMARY

Study Title	Healthcare Evaluation of Absolute Risk Testing: A multi-centre, single arm, pragmatic study in primary care setting
Short title	The HEART Study
Clinical Phase	Performance evaluation to assess clinical utility
In Vitro Device	Cardiovascular disease (CVD) Integrated Risk Tool (IRT) A risk assessment tool combining patient clinical and genetic information to provide a score of the risk of developing cardiovascular events (heart attack or stroke) within the next 10 years.
Study Design	Multi-centre, prospective, single arm, interventional, pragmatic study.
Study Participants	**Inclusion** Aged 45-64 years, either biological sex, any ancestry or background, eligible for National Health Service (NHS) Health Check using QRISK®2 assessment. **Exclusion** Those excluded from NHS Health Checks, Currently prescribed and taking HMG-CoA reductase inhibitors (lipid-lowering preventive treatments or statins) for any indication.
Planned Size of Sample (if applicable)	1000 participants will be recruited across 10-12 general practitioner (GP) practices in the North of England where they will provide blood samples and answer questionnaires. A subset of 100 participants will consent to and provide saliva samples. Additionally 20-30 participants who have answered the questionnaire will be invited to take part in an interview.
Duration for participants (if applicable)	Estimated 5-12 weeks per participant, with a questionnaire up to 2 weeks later. A subgroup of 20-30 participants will be invited for an interview within 2 months of the questionnaire.
Planned Study Period (Recruitment)	5-7 months

Study Aim	The aim of this study is to describe the operational acceptability and impact of predictive genetic testing for CVD risk within a primary health care setting.
Primary Objective	To demonstrate that an IRT (combining genetic and non-genetic risk factors) for CVD can be incorporated into routine primary care.
Secondary Objectives	1. To explore and assess the impact of the CVD IRT on clinical decision-making. 2. To assess the magnitude of the change in risk score between QRISK®2 and CVD IRT. 3. To explore and assess to what extent healthcare providers (HCPs) and primary care commissioners (PCCs) perceive the CVD IRT as operationally efficient and enhancing the service that they provide. 4. To explore and assess to what extent HCPs and PCCs perceive the CVD IRT as clinically relevant. 5. To explore and assess to what extent participants perceive the information received through the CVD IRT as informative for health and wellness. 6. To explore and assess the impact of the CVD IRT on patient engagement. 7. To identify and explore effective ways to communicate risk and genetics information about CVD IRT to patients, HCP and PCCs. 8. To evaluate the performance of saliva as compared to blood for use in the CVD IRT. 9. To monitor the study for any potential safety concerns.

ROLE OF STUDY SPONSOR AND FUNDER

There are two parties involved in the conduct of this study: Genomics plc and NHS North of England Commissioning Support (NECS).

The Sponsor, Genomics plc, is assuming overall responsibility for the conduct and management of the study. The sponsor is also part funder of the study.

NECS is part funder of the study, as well as providing a qualitative research service to collate and analyse questionnaires, interviews and focus group data.

The study is to be adopted as a NIHR CRN portfolio study.

ROLES AND RESPONSIBILITIES

A Study Management Group will include study management, statistical input, and subject matter experts, including qualitative research expertise provided by NECS.

The Study Management Group will meet regularly and as required from study set-up to close-down and archive, to manage the study and review progress, quality, and safety.

No further study committees will be established for monitoring this study.

PROTOCOL CONTRIBUTORS

The following parties have contributed to the development of this protocol:

Party	Contribution role	Responsibilities
Genomics plc	Accountable & responsible	Owner of and development of the protocol
NECS	Contributing	Contributing to the qualitative research aspect of the protocol
Study CI	Contributing	Contributing to the development of the protocol

Table 1: Summary of protocol contributors.

1. BACKGROUND

Every individual has a unique set of genes (or genome), and variation in the genome can affect an individual's risk of developing disease. Sometimes, diseases are caused by rare changes (mutations) in one particular part of the genome. For example, 55%–72% of women who inherit a harmful BRCA1 variant and 45%–69% of women who inherit a harmful BRCA2 variant will develop breast cancer by 70–80 years of age[1].

More frequently, common diseases such as cardiovascular disease (CVD) do not stem from rare high-risk variants, but rather are known to be influenced by many tiny changes, called single nucleotide polymorphisms (SNPs), across many different parts of the genome[2]. These variations (often hundreds of thousands or more) have small effects individually, but together, these variants can be powerful in understanding and measuring the genetic risk of developing certain diseases. Summing these effects together results in a Polygenic Risk Score (PRS), a single numerical score which provides a summary of an individual's propensity to develop that disease based on their genetics[3].

This PRS can be combined with clinical risk factors to create an Integrated Risk Tool (IRT), which can give a more accurate picture of an individual's overall risk of developing a health condition in the future[4,5].

Importantly, genetic risk factors do not change over time, and so can be measured much earlier (before any symptoms of a disease develops) in a person's lifetime. This means that genetic risk factors are potentially very powerful tools for preventative healthcare. Preventing disease is a fundamental challenge for public health. Not only do we need to know how to treat, but also who and when to treat. Timing matters, as interventions often need to be initiated early. Improved prevention lies at the heart of the NHS 10-year plan[6].

Identifying rare mutations such as the BRCA1 and 2 variants usually requires reading entire blocks of the genome (an expensive process known as sequencing); however, the many common variants which affect risk of common diseases can be measured with genotyping chips, which measure a predetermined set of about 1 million of the 3 billion positions in the human genome[7]. This technology opens the prospect of offering cost-effective genetic analysis in primary care.

1.1. Cardiovascular Disease

In addition to being a burden to affected individuals, CVD events are a major operational and financial burden for the NHS. Research by Danese et al[8] estimates that myocardial infarction (MI) has an initial mean cost for the NHS per patient of £4,275 and thereafter a yearly cost of £922. The costs of managing co- or multi-morbid patients with CVD is higher due to the increased complexity of care.

- CVD is a leading cause of morbidity, mortality, and expenditure. It accounts for a quarter of all deaths in the UK (170,000 deaths a year), and £9 billion in healthcare cost[9].
- Each percentage of reduction in cardiovascular events in England and Wales would result in 3,500 fewer deaths, 98,000 more Quality-Adjusted Life Years (QALY), and gains of £265M over 10 years[10].
- The Global Burden of Disease Study identified ischaemic heart disease as the leading cause of Years of Life Lost (YLLs) in the UK in 2016 for both sexes[11].

Given this burden, the NHS Long Term Plan[6] has identified CVD prevention as a national clinical priority, with an ambition to prevent 150,000 heart attacks and strokes over the next 10 years by

improving the detection and management of high blood pressure, high cholesterol, and atrial fibrillation. The Long Term Plan also commits to the commissioning of a new national CVD prevention audit for primary care. The audit is aimed at improving the earlier identification of patients with CVD.

HMG-CoA reductase inhibitors (lipid-lowering preventive treatments or statins) and other low cost management strategies (including support for lifestyle changes) are already well established strategies for the reduction of CVD incidence[12]. Improving the identification of individuals at increased risk is a key opportunity for the targeted delivery of these low-cost and accepted preventive interventions within the NHS.

The current widely used risk calculation tool used by healthcare practitioners is QRISK®, a calculator which combines a range of non-genetic risk factors, to measure ten-year CVD risk in patients[13]. The latest version of QRISK® is QRISK®3; however, QRISK®2[14] is still widespread due to the embedding of the calculator in primary care patient administration systems such as EMIS and SystmOne. QRISK®2 remains the version officially recommended by National Institute for Health and Care Excellence (NICE) guidelines[12]. Under current NICE guidelines, patients identified by QRISK®2 of having a ten-year risk greater than 10% are at-risk and considered for intervention by GPs.

1.2. The Integrated Risk Tool for Cardiovascular Disease (CVD IRT)

The CVD IRT is a system-supported algorithm that combines an individual's PRS with their QRISK®2 score to calculate the integrated risk of developing CVD over the next 10 years, including events such as angina, myocardial infarction (MI), stroke, or transient ischaemic attack (TIA). Research performed by Genomics plc has demonstrated that IRTs combining disease-specific PRSs with existing clinical CVD risk assessment tools can significantly improve risk prediction[4,5], and that when it comes to the risk of developing heart disease, genetics are as important to measure as factors such as blood pressure.

Using UK Biobank data, of younger middle-aged individuals that are currently invisible to the system under QRISK®2, 6.4% would be flagged at high risk (≥10%) by the use of the CVD IRT of developing CVD within the next ten years. Extrapolated to the UK population, this represents 27,250 patients presenting as CVD cases within a ten-year period[4].

This CVD IRT has been validated for use in 45-64 year old individuals of all biological sexes of any ancestry, who do not have pre-existing cardiovascular disease and do not currently take statins[5].

1.3. Management of QRISK®2 and CVD IRT report for participant discussion

Although the CVD IRT makes use of sophisticated techniques including genetic analysis and the application of complex algorithms, the system is simple for the HCP and patient to use and understand. The CVD IRT requires the patient to provide a blood sample that is sent for genetic analysis and the HCP to complete a QRISK®2 assessment for the patient.

When the PRS is combined with the QRISK®2 score to generate the IRT score, the GP will receive a report to share with the patient and to inform treatment options as per NICE guidelines. Current NICE guidance recommends intervention if the ten-year risk of CVD is greater than 10%. Both QRISK®2 and CVD IRT produce estimates of 10-year CVD risk, therefore, where the QRISK®2 and / or the CVD IRT score exceeds 10%, NICE guidance is recommended to be followed.

The CVD IRT report will be available up to 12 weeks after the sample is taken. If QRISK®2 indicates intervention is needed within this timeframe, the physician's discretion should be used.

2. RATIONALE

The aim of this study is to demonstrate the integration and use of CVD IRT in an environment as close to real-world as possible.

This study will recruit participants of both biological sexes and any ancestry or background who require and are eligible for a CVD risk assessment[15] as part of the NHS Health Check. Those aged 45-64 years are most likely to benefit from CVD IRT and will be included in the study, as they are more likely to be asymptomatic but also derive most benefit from preventative measures.

The study will be conducted in GP surgeries as the CVD IRT will have its greatest impact if incorporated into primary care practice for early identification of patients at highest risk.

Training and guidance on the interpretation of the CVD IRT report will be provided before study recruitment commences. The training will comprise an understanding of the CVD IRT, indications and contraindications for use and review of potential risks. For this study a training session will be delivered either in person or via video conferencing.

2.1. Assessment and management of risk

The CVD risk assessment tool currently available within primary care is QRISK®. This online tool allows HCPs to enter patient information (including some blood results) to generate a percentage risk of the patient developing CVD over the next 10 years. For the IRT, as well as generating a QRISK®2 score, the patient provides an additional blood sample for genetic analysis (PRS). In either scenario, the patient will need to provide blood samples and clinical data.

Regardless of which risk assessment score is used, the patient may experience anxiety in awaiting the report and receiving the report. A person's inability to influence genetics may cause additional distress compared to the QRISK®2 score. However, in a summary of 30 studies, predispositional genetic testing had no significant impact on psychological outcomes, little effect on behaviour, and did not change perceived risk[15]. With this in mind, it is assessed that the risk to benefit ratio of the study is acceptable, exposing the participant to limited risk similar to a QRISK®2 score.

Training of staff on understanding the influence of genetics on an individual's risk and how to interpret and present the genetic data will aim to alleviate patient anxiety.

The qualitative aspect of the study to the participant, HCP and PCCs is considered extremely low risk.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The aim of this study is to describe the operational acceptability and impact of predictive genetic testing for CVD risk within a primary health care setting.

3.1. Primary objective

The primary objective of this study is to demonstrate that an IRT combining genetic and non-genetic risk factors) for CVD can be incorporated into routine primary care.

3.2. Secondary and exploratory objectives

The secondary objectives are described as follows:

1. To explore and assess the impact of the CVD IRT on clinical decision-making.
2. To assess the magnitude of the change in risk score between QRISK®2 and CVD IRT.
3. To explore and assess to what extent HCPs and PCCs perceive the CVD IRT as operationally efficient and enhancing the service that they provide.
4. To explore and assess to what extent HCPs and PCCs perceive the CVD IRT as clinically relevant.
5. To explore and assess to what extent participants perceive the information received through the CVD IRT as informative for health and wellness.
6. To explore and assess the impact of the CVD IRT on patient engagement.
7. To identify and explore effective ways to communicate risk and genetics information about CVD IRT to patients, HCP and PCCs.
8. To evaluate the performance of saliva as compared to blood for use in the CVD IRT.
9. To monitor the study for any potential safety concerns.

The exploratory objectives are described as follows:

1. To explore and assess the perception of healthcare providers and commissioners on the usefulness of CVD IRT.
2. To collect further insights from the study which may aid in the development of clinical decision tools and products based on PRS for disease risk prediction.

3.3. Outcome measures

Outcome measures will be a combination of operational data such as report return rates and qualitative and quantitative data gathered from questionnaires, interviews and focus groups.

3.4. Primary endpoint

The primary endpoint will be measured both by operational success (report return rates), and feedback from HCPs and patients.

3.5. Secondary and exploratory endpoints

The secondary endpoints will be measured as follows:

1. Changes in patient treatment based on risk scores at Visit 2.
2. Comparison of QRISK®2 and CVD IRT scores.

3. Feedback provided by HCP questionnaire as well as focus group(s) with HCPs and PCCs.
4. Participant questionnaires will be used to understand whether receiving the CVD IRT information had an impact on their health and wellbeing. Participant interviews will build on questionnaire responses to further understand impact on health and wellbeing.
5. Participant questionnaires will be used to understand whether they were engaged with CVD IRT information. Participant interviews will build on questionnaire responses to further understand the level of engagement.
6. Feedback provided by participant questionnaires and interviews as well as HCP questionnaires and focus group(s).
7. Percentage of results available and concordance with CVD IRT scores available from blood samples.
8. Comparison of PRS derived from DNA extracted from blood and saliva
9. Number and nature of adverse events recorded.

The exploratory endpoints will be measured as follows:

1. HCP questionnaires and focus groups and a PCC focus group will be used to understand how useful they consider the CVD IRT.
2. Further insights into future development of genetic risk test tool will be gathered from all qualitative data sources, the participant questionnaires and interviews, the HCP questionnaires and focus group(s), as well as PCC focus group.

3.6. Summary of Objectives and Outcomes

The following table describes the study objectives, the measures used to assess each outcome and the time at which the outcome will be measured.

Objectives	Outcome Measures	Timepoint where outcome is measured
Primary Objective		
To demonstrate that an integrated risk tool (combining genetic and non-genetic risk factors) for CVD can be incorporated into routine primary care.	Report return rate	Last Participant, Last Visit 2
	Participant feedback via • questionnaires • interviews	• Visit 1 • Visit 3 • Visit 4
	HCP feedback via • questionnaires • focus group	• Visit 2 • As close to or just after LPLV2 • As close to or just after V4
Secondary Objectives		

1. To explore and assess the impact of the CVD IRT on clinical decision-making.	Changes in patient treatment based on risk scores	• Visit 2
2. To assess the magnitude of the change in risk score between QRISK®2 and CVD IRT	QRISK®2 and CVD IRT scores to be compared	• Visit 2
3. To explore and assess to what extent HCPs and PCCs perceive the CVD IRT as operationally efficient and enhancing the service that they provide	HCP feedback via • questionnaires • focus group(s)	• Visit 2 • As close to or just after LPLV2 • As close to or just after V4
	PCC feedback via • focus group	• As close to or just after HCP focus group(s)
4. To explore and assess to what extent HCPs and PCCs perceive the CVD IRT as clinically relevant	HCP feedback via • questionnaires • focus group(s)	• Visit 2 • As close to or just after LPLV2 • As close to or just after V4
	PCC feedback via • focus group	• As close to or just after HCP focus group(s)
5. To explore and assess to what extent participants perceive the information received through the CVD IRT as informative for health and wellness	Participant feedback via • questionnaires • interviews	• Visit 3 • Visit 4
6. To explore and assess the impact of the CVD IRT on patient engagement	Participant feedback via • questionnaires • interviews	• Visit 1 • Visit 3 • Visit 4
7. To identify and explore effective ways to communicate risk and genetics information about CVD IRT to patients, HCP and PCCs	Participant feedback via • questionnaires • interviews	• Visit 3 • Visit 4
	HCP feedback via • questionnaires • focus group	• Visit 2 • As close to or just after LPLV2 • As close to or just after V4
	PCC feedback via • focus group	• As close to or just after HCP focus group(s)

8. To evaluate the performance of saliva as compared to blood for use in the CVD IRT	Percentage of results available and concordance with CVD IRT scores available from blood samples	• Final saliva sample
9. To monitor the study for any potential safety concerns	Number and nature of adverse events recorded	• Throughout study, to study end
Exploratory Objectives		
1. HCP questionnaires and focus groups and a PCC focus group.	To understand how useful they consider the CVD IRT.	• As close or just after V4
2. Participant and HCP questionnaires and focus groups and a PCC focus group.	Further insights into future development of genetic risk test tolls	• As close to or just after V4

Table 2: Summary of Objectives, Outcome Measures and timepoints.

4. DESIGN

This is a multi-centre, prospective, single arm, interventional, pragmatic study, to be performed in the North of England.

The study is a mixed methods study combining qualitative and quantitative data, gathering information from patient participants, the HCPs conducting the study and PCCs.

This multi-centre study is to include 10-12 participating sites (excluding Patient Identification Centre (PIC) sites), incorporating clinics at areas of varying affluence and deprivation, and population diversity. The distribution of sites will aim to provide a range of participant population, in terms of sex, age and ethnicity.

In addition to this, multiple sites allow the study to demonstrate that the CVD IRT can be instigated and incorporated into clinics of various size, resources, and facilities.

QRISK®2 is a predictive tool already embedded in the primary healthcare setting. CVD IRT incorporates the QRISK®2 score and refines patient risk by including genetic analysis data. Previous work comparing QRISK®2 score and IRT has been undertaken in previous studies (biobank data), demonstrating that IRT refines the QRISK®2 score. This study will provide every participant with the QRISK®2 and IRT score (noted on the lab report as "combined risk") with no blinding.

4.1. Quantitative Design

The study will collect approximately 2000 blood samples (one sample for analysis and a second for back-up) from 1000 participants to undertake genomic testing to provide a CVD IRT score to each participant.

Of the 1000 participants, 100 participants at 1 or 2 selected site(s) will also provide saliva samples. These samples do not contribute to the CVD IRT score, but will be used to assess the potential use of saliva as DNA source for genomic analysis for PRS.

4.2. Qualitative Design

Qualitative data in the form of questionnaires and interviews will be collected from the participants. In addition, the study will gather qualitative data (questionnaires and focus groups) from the HCPs undertaking the clinical study, as well as a focus group with PCCs. The content and timing of the questionnaires, interviews and focus are provided in **Figure 1**.

5. STUDY SETTING

This multi-centre study to be conducted at 10-12 GP practices plans to recruit approximately 1000 participants, divided to around 50-100 patients per site.

The GP practices are responsible for participant identification, informed consent, biosample collection and collection of study data, and discussing results and care plans with participants. The sites are also responsible for supporting the qualitative research team with distributing questionnaires, arranging interviews and participating in focus groups.

The study sites should already be participating in the NHS Health Check programme, using QRISK®2 as part of the Health Check to assess patient risk of developing CVD.

To be included in the study, GP practices must:

- have access to the internet and hardware that they can use to interact with the study solution (i.e. a computer that can run the Chrome web-browser);
- use EMIS or SystmOne to calculate the QRISK®2 score;

To boost recruitment, recruiting centres may use Participant Identification Centres (PIC)s with the prior agreement of the sponsor. A limit of 2 PICs per recruitment centre will be applied.

A list of participating sites and PICs will be held in the Study Master File (SMF).

5.1. COVID-19 Restrictions

Any patient contact for the purposes of the study must comply with COVID-19 restrictions applicable at the time of study recruitment. This includes careful adherence to guidance around blood and saliva sampling. Based on restrictions, it is anticipated that COVID-19 positive patients will ***not*** be attending the surgery and therefore additional exclusion criteria based on COVID-19 have not been included in the study design.

6. ELIGIBILITY CRITERIA

The study includes patients who are due an NHS Health Check, the inclusion and exclusion criteria are outlined in the following section (6.1).

The study also includes interviews and focus groups with HCPs and PCCs. For clarity, these groups of contributors are described in sections 6.2 and 6.3 respectively.

6.1. Participant Eligibility Criteria

The study will aim to recruit an estimated 1000 participants as defined by the inclusion and exclusion criteria.

6.1.1. Inclusion criteria

Participants must meet the following criteria to be eligible for this study:

1. Able and willing to provide written informed consent and to comply with the study protocol
2. Either male or female (biological sex)
3. Aged 45-64 years (inclusive)
4. Any ancestry or background
5. Eligible for NHS Health Check using QRISK®2 assessment

6.1.2. Exclusion criteria

Participants who meet any of the following exclusion criteria will not be eligible for this study.

1. Those excluded from NHS Health Checks; Currently prescribed and taking HMG-CoA reductase inhibitors (lipid-lowering preventive treatments or statins) for any indication.

6.2. HCP Eligibility Criteria

6.2.1. Online Questionnaire

All HCPs (physician or nurse) having received study training who are listed on the site delegation log, and have interacted with study participants, will be asked to complete the online questionnaire.

6.2.2. Focus Group(s)

Physicians for the focus group will be drawn from those who completed the online questionnaire and will be selected using standard qualitative research sampling techniques.

Depending on the number of online questionnaire responses, a focus group for nurses may also be conducted, with participants selected using standard qualitative research sampling techniques. Multiple physician and nurse focus groups may be undertaken if scheduling of only one focus group for physicians and nurses, respectively, is challenging.

6.3. PCC Eligibility Criteria

6.3.1. Focus Group

A sample of Primary Care Commissioners working within North East England Clinical Commission Groups (CCGs) will be selected for the focus group using standard qualitative research sampling techniques.

7. STUDY PROCEDURES

This section describes the activities undertaken by the patient participants (Section 7.1), HCPs (Section 7.2) and PCCs (Section 7.3). For simplicity, the Schedule of Assessments (Figure 2) includes activities for all three groups.

7.1. Patient Participants

Below is a table describing the study schedule for the patient participant, from consent through to online questionnaire and possible phone interview. The last three rows show the questionnaires and focus groups as planned for the HCPs and PCCs.

Procedures	Visit 1, Baseline	Visit 2, Results	Visit 3, Online Questionnaire	Visit 4, Phone Interview	
	Day 1	+ 5-12 weeks	+ 0-14 days after V2	up to 2 months after Visit 2	Study End
Informed consent [1]	X				
Demographics	X				
Inclusion/ Exclusion Criteria	X				
Blood sample [2]	X				
Saliva sample [3]	X				
QRISK®2 score [4]	X				
CVD IRT Results availability [4]		X			
Adverse Events [5]	X	X	X	X[6]	X[6]
Device deficiencies	X	X			
Participant Questionnaire	X		X		

Interview consent	**X**				
Participant Interview [7]				**X**	
HCP Questionnaire		**X**			**X**[8]
HCP Focus Group(s)					**X**[9]
NHS PCC Focus Group					**X**[10]

1. Signed, written informed consent obtained prior to any study specific procedure. Separate consent required for saliva samples.
2. 2x2.5ml samples for genetic analysis, the second sample as back-up in case of failure at any stage of processing.
3. A subset of participants (~100) at selected sites (1-3 sites depending on recruitment) will provide a 2ml saliva sample.
4. The QRISK®2 score will be available some days after Visit 1.The IRT score will be available up to 12 weeks after the sample collection.
5. Related adverse events (ADEs) are to be collected from the provision of written informed consent up to the completion of the online questionnaire.
6. Following the questionnaire and up till study end, only SADEs self-reported by the participants will be collected.
7. A subset of participants (20-30) who expressed an interest in participating in an interview will be invited for a 30 minute phone interview. Separate consent will be collected for the interview from all participants when approx. ⅓ enrolment completed
8. HCP questionnaires will take place at each site after at least ⅔ of that site's participants or at least ⅔ of the total study participants (whichever is first for each site) have completed Visit 2.
9. The HCP focus groups will take place after the HCP questionnaires have been completed but may take place before all of the site's participants have received their study results.
10. The PCC focus group may be scheduled at any time after the HCP questionnaires have been issued.

Table 3: Schedule of assessments; patient participant, HCP and PCC.

The following figure demonstrates the timing of participant activities in relation to HCP and PCC activities. The HCP and PCC focus groups will be undertaken towards the end of the study aiming to finish no later than the end of the patient interviews

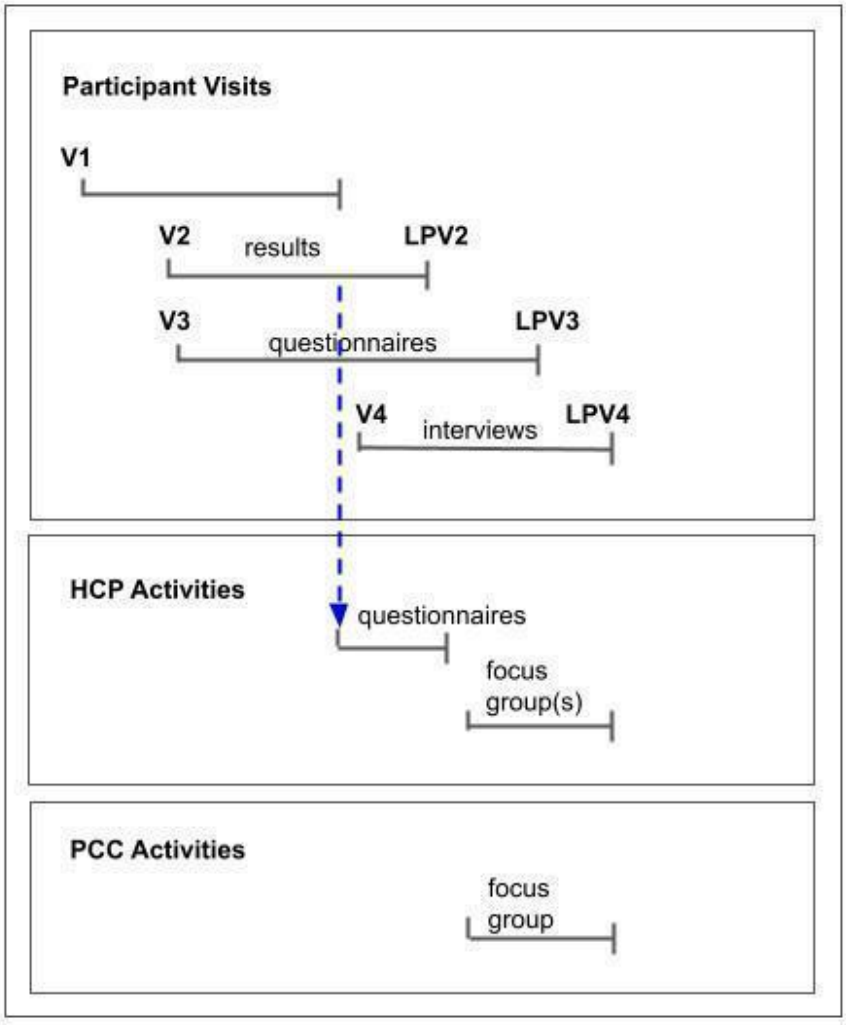

Figure 1. Schematic of study activities. The last study activity will be either the last participant interview, last HCP focus group or the PCC focus group, whichever comes last. (V - visit, LPLV - Last Participant Last Visit)

7.1.1. Participant Recruitment

The following figure demonstrates planned participant recruitment and anticipated attrition.

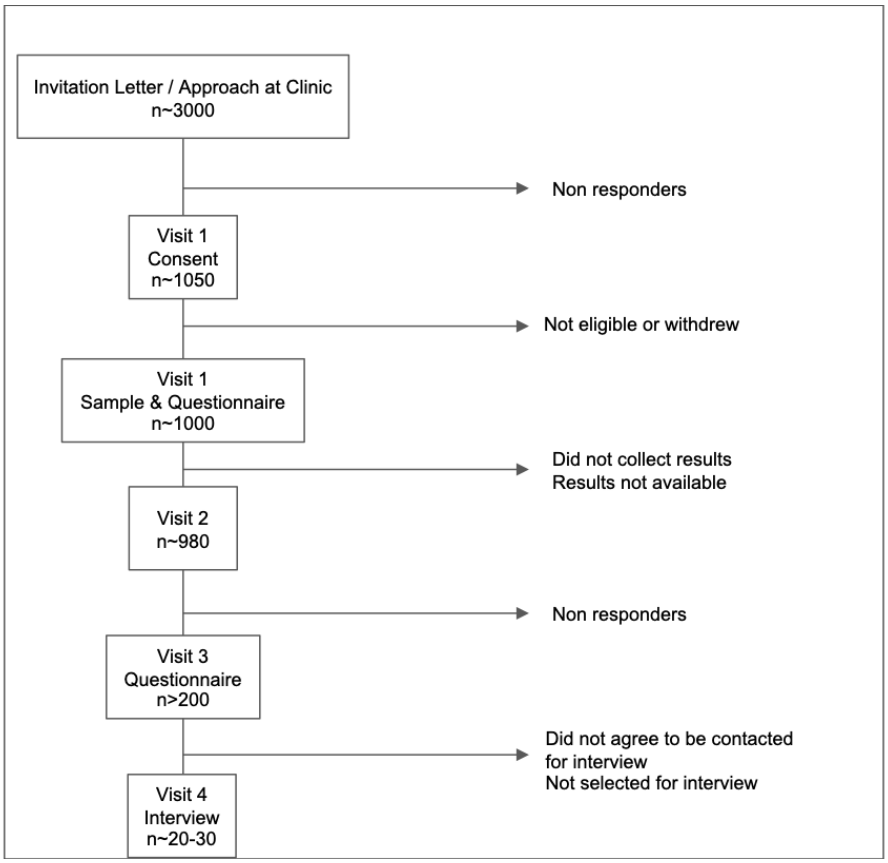

Figure 2: CONSORT diagram for patient participants. If identified participants decide not to proceed in the study, they will have the opportunity to continue with a CVD risk assessment as per standard practice (QRISK®2). If during the study, it is not possible to provide the participant with the CVD IRT score, they will receive the QRISK®2 score and continue with standard recommended treatment based on the QRISK®2 score received.

7.1.2. Participant identification

Potential participants will be identified primarily by searching the clinic database for patients due an NHS Health Check. Additionally, opportunistic recruitment during routine consultations may also take place, if they require an NHS Health Check.

7.1.3. Participant Screening

Identified potential participants who are eligible for an NHS Health Check and QRISK®2 evaluation will be considered for participation in the study, unless the investigator considers the potential participant unsuitable for the study.

The study invitation letter will be provided with a copy of the patient information sheet (PIS) and consent form (on surgery headed paper). Study sites participating in the saliva sub-study will provide the PIS and consent form for the saliva sample as well.

A screening log of those identified by search will be maintained, documenting when invites are sent, if they are not invited or if they fail to respond. For ease, this can be documented on a print out of the search results, or a separate screening log can be maintained. The screening log, in whichever format used, will be filed in the Investigator Site File (ISF).

7.1.4. Participant Payment

Participants may be reimbursed for reasonable travel expenses, but no other payments will be made.

7.1.5. Participant Consent

The Principal Investigator (PI) will retain overall responsibility for the conduct of research at their site, including the taking of written informed consent of participants at their site. They will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Physicians or practice nurses will take consent, as per delegation log.

Written informed consent will be obtained from the participant after they have been given adequate time and opportunity to discuss any study related questions with the health care team. Consent is anticipated to be provided during an appointment (in person) with the health care team, but may also be provided remotely, via telephone or video conference, and written consent will be obtained before any other study procedures (data and biosample collection) commence.

The staff member recording consent will be responsible for assessing the capacity of the interested participant to provide informed consent.

Patients will be informed that if they decline to participate in the study (without having to give a reason), that decision will not compromise their ongoing health care.

The sponsor will keep anonymised genetic data to support future research. If the participant does not wish to allow the sponsor to keep genetic data for future research, they will not be able to participate in the study.

The participant will remain free to withdraw at any time from the study without having to give a reason and without prejudicing their further management and will be provided with a contact point where they may obtain further information about the study. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.

The original signed consent form will be provided to the participant, and copies filed in the investigator site file (ISF) and participant medical notes if required by local practice.

7.1.6. Additional participant consent provisions for collection of saliva samples and interviews

Around 100 participants (at 1-2 sites) of the 1000 participant population will be asked to provide saliva samples for a subanalysis of the study, looking at the capability of using DNA extracted from saliva samples for genetic analysis. A separate information sheet and consent form will be provided for the provision of saliva samples.

Participants asked to provide saliva samples can decline to do so and still participate in the main study.

Around 20-30 participants will be invited for an interview after one third of participants have been recruited. The participants will be selected by the qualitative researcher from data provided by the sponsor on participants who have provided consent to take part in the interview as described in

7.1.6.1. The researcher will notify the relevant site clinical study team to identify and pass on contact details to the qualitative researcher.

7.1.7. Participant Study assessments, per visit

A participant's journey will include 3 visits, and potentially up to 4 visits, as demonstrated in Figure 2.

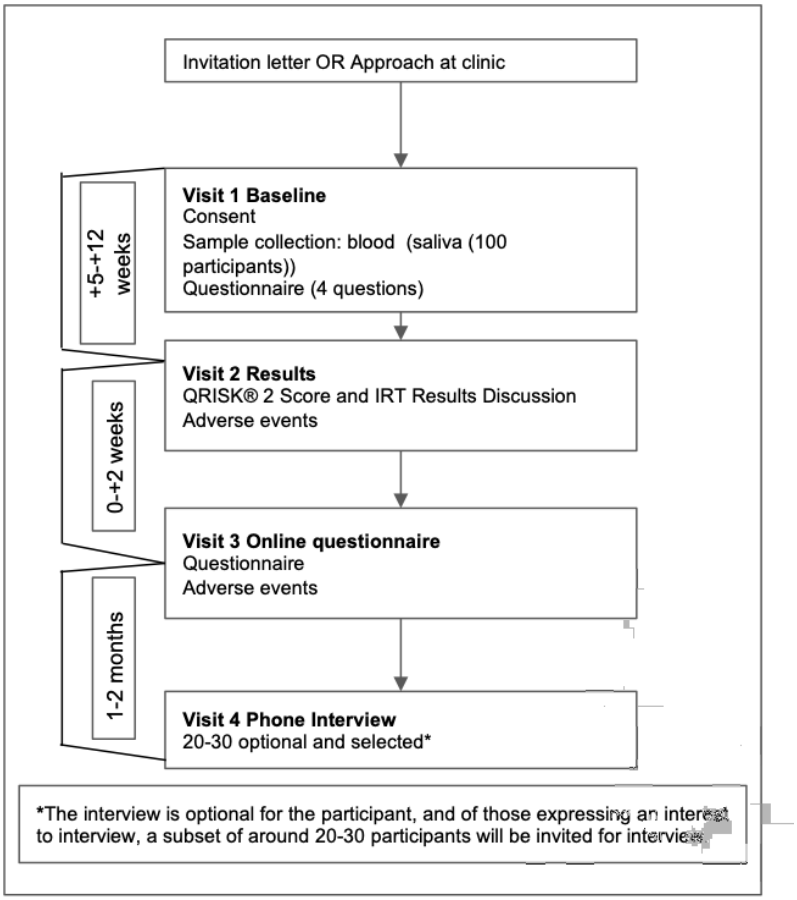

Figure 3: Patient Participant Flow Diagram. Only patient participant visits are outlined in the schedule above. The HCP questionnaires and focus groups (HCP and PCC) will be conducted in parallel with the participant Interviews where necessary.

7.1.7.1. Visit 1, Baseline

Before (remotely) or During Visit 1, the participant will have the opportunity to further review the information sheet and have any questions answered before signing a consent form. The participant should only sign and date the consent form if they wish to participate in the study. If for any reason they are unwilling or unable to sign the consent form, they cannot participate in the study.

After approximately ⅓ of participants are enrolled, subsequent participants will be asked if they are willing to consent for selection to take part in an interview, consisting of a 30 minute telephone interview about the study, approximately 1-2 months after receiving their results. If the participant

agrees to take part they are asked to sign the interview consent form at Visit 1. Information to be collected at Visit 1 after written informed consent has been obtained will comprise:

- date of visit
- date of consent
- confirmation of eligibility
- date of blood sample
- age at time of sample
- biological sex
- self identified ethnicity
- educational level
- date of consent for saliva sample (if applicable)
- date of saliva sample (if applicable)
- QRISK®2 score (when available)
- questionnaire (4 questions to participants).

Since the study requires the participant to receive an online questionnaire, the site will require the participant's email address. This will be documented in the enrolment log.

Study eligibility will be confirmed by a member of the study team (as per delegation log) using participant medical notes and questioning the participant, and eligibility will be documented in the Case Report Form (CRF), but no details of the medical history will be collected for the purposes of the study.

When eligibility has been confirmed, the participant will be added to The HEART Application using their age and biological sex. The study staff will be trained on the use of The HEART Application and receive instruction for use (IFU), electronic Case Report Form (eCRF) and sample handling and posting and their site responsibilities. The system will generate a participant ID, which is used to identify the participant in all study documentation and added to the enrolment log, participant medical notes, sample shipping logs, adverse and serious adverse device event in the eCRF.

Since all participants are attending for a CVD risk assessment, they will be providing a blood sample as part of the process. The study requires blood to be taken using a butterfly and vacutainer holder, which will allow all blood samples (standard care and study) to be obtained via a single venepuncture.

The study samples will be prepared as described in the 'Sample Handling and Shipping Instructions Manual'. To ensure tracking, the samples will be labelled with a barcode and its human readable form (a six-digit number (XX-YYY-Z). The six-digit number is entered into The HEART Application. Spare labels are provided.

Before the participant leaves Visit 1, they will be asked to complete a short questionnaire (4 questions) on paper, with their participant ID and date of visit completed on the questionnaire. Participants hand the completed form to the study staff before they leave. Study staff enters questionnaire answers to the participants data in the eCRF.

When the QRISK®2 score is available, this will be added to The HEART Application as it is required to calculate the CVD IRT.

QRISK®2 score will be provided to the participant at the same time as the CVD IRT to simplify the process for the participant (unless physician intervention based on the QRISK 2 is needed before the

CVD IRT is available), so as not to receive two separate scores for the risk of developing CVD at different times.

In the event that a CVD IRT score cannot be provided to the participant, a replacement sample will not be sought and the participant's QRISK*2 score will be used to determine the standard of care. This may be due to loss of sample in transit to the laboratory or under the quality controls for sample processing, the sample integrity does not yield adequate DNA or the PRS score cannot be generated.

7.1.7.2. Saliva Samples

If the participant is attending a clinic recruiting for the saliva subanalysis, they will be asked to provide a saliva sample. They will be given the opportunity to review a separate information sheet and sign a separate consent form. They may decline the substudy while still participating in the main study. They will provide a 2ml sample, which will be labelled and packaged according to the instructions, and sent to a separate laboratory for DNA extraction.

There is a small possibility that saliva samples go missing in transit to the laboratory, despite processes in place to mitigate the risk. If this is the case, there will be no impact to the participant and they will not be asked to provide a replacement sample.

Saliva samples are for research purposes only. The CVD IRT will be based on blood samples not saliva samples.

7.1.8. Visit 2, Receiving CVD IRT results and study participant management

Approximately 5-12 weeks after the blood sample collection, the CVD IRT result will be available. The study staff will be notified of its availability by email and will be able to download the CVD IRT report from The HEART Application. Study personnel will be trained on the content of the report and best practice on sharing genetic information. Only those trained and listed on the delegation log will be permitted to share the CVD IRT results with the participants.

Current NICE guidance recommends intervention if the ten-year risk of CVD is greater than 10%. Both QRISK®2 and CVD IRT produce estimates of 10-year CVD risk, therefore, where the QRISK®2 and / or the IRT score exceeds 10%, NICE guidance is recommended to be followed.

The IRT report will be available up to 12 weeks after the sample is taken. If QRISK®2 indicates intervention is needed within this timeframe, the physician's discretion should be used.

The HCP will determine the best method of sharing the results (QRISK®2 and CVD IRT) as per standard practice. Participants may be contacted by phone or videoconference or may be asked to attend the clinic in person.

At Visit 2 the following data will be collected:

- date of visit
- the method of sharing results, e.g., phone, videoconference or clinic visit
- who shared results, e.g., GP or nurse
- whether QRISK®2 score required change in treatment (e.g., statin, life style, both or none influenced the change)
- any change in treatment (e.g. statin)

- if the participant's CVD IRT score was higher than their QRISK score, whether the CVD IRT score influenced (or informed on) a change in treatment (e.g. statin. lifestyle, both or none)
- what treatment was changed
- the participant will be asked about any potential adverse events since the previous visit.

The report is intended for HCP use to share results, but if requested by the participant a copy can be provided. The participant should be reminded of the online questionnaire and its importance to the study which will be sent to their email address in around 0-14 days' time. The study staff should also ensure that the participant's personal email address is available and correct on the enrolment log, for the above purposes and for participation in Interviews, if required by NECS .

7.1.9. Visit 3, Online questionnaire

Each participant will be emailed a link to a questionnaire by the study team. The individualised link for the questionnaire can be copied from The HEART Application, which will be available when the report is available for download. It is essential that the link copied from the correct participant ID is sent to the correct participant.

Responses are anonymous and each questionnaire should take around 20 minutes to complete.

If the questionnaire is not completed within 2 weeks, the participant will be reminded of the questionnaire either by re-sending the link by email or by phone contact from the clinical study team. If the questionnaire is still not completed, a further reminder can be sent. One reminder will be the maximum number of reminders allowed per participant. The questionnaire link will be disabled no earlier than 4 weeks after the link was first sent, therefore, each participant is allowed at least 4 weeks to complete the online questionnaire.

The following information will be collected:

- date questionnaire link sent to the participant
- dates of reminders, if applicable
- date of completion
- anonymised questionnaire responses.

7.1.10. Visit 4, Phone interview

To participate in an interview, the participant must have signed the relevant focus group consent form at visit 1 and completed the online questionnaire at Visit 3. The participant will be informed that they may not be selected as only a small number of interviewees are required. If they are selected, they will be contacted by the study team conducting the Interview to arrange a suitable time. If they are not selected, there will be no further communication.

If a participant is selected for a phone interview, they will be contacted by the qualitative research team.

Consent procedures will be followed as described in section 7.1.5.

With consent, their details will be passed to the qualitative research team to arrange a convenient time for the interview. A discussion guide will be used for the interview.

The following information will be collected:

- consent date
- interview date
- audio recording, transcribed

If the interviewee does not attend the interview, a single attempt will be made to reschedule. Non-attendees will be replaced as required until approx 20- 30 participants are interviewed

7.1.11. Withdrawal criteria

Participants may be withdrawn from the study at any time for any reason.

Reasons for withdrawal from the study may include, but are not limited to, the following:

- Participant's withdrawal of consent at any time.
- Investigator or Sponsor determines it is in the best interest of the patient.

Participants who wish to withdraw from the study can inform the investigator or study team at any time during the study. Participants who withdraw and who have had specimen samples taken for genetic analysis will not receive their results but their results will be used in the study analyses. A participant that wishes to withdraw before receiving the CVD IRT score will continue to receive their QRISK®2 score as per standard practice.

Reasonable effort will be made to obtain information about participants who withdraw from the study, and the primary reason for withdrawal/discontinuation documented.

The CRF will collect:

- date of withdrawal
- reason for withdrawal if the participant is willing to share.

As described in section 9.2, if a participant has an ongoing serious adverse device effect (SADE) or unanticipated SADE (USADE) at their final visit, follow-up to resolution should be attempted.

Patients who withdraw from the study will not be replaced.

7.2. HCP participation

7.2.1. Screening

The Sponsor representative will work with qualitative researchers to identify HCPs that are eligible to complete the questionnaire (see section 6.2.1).

7.2.2. Consent

The online questionnaire includes a preamble to inform the HCP that by completing the questionnaire they are providing consent for the use of their data and responses.

The focus group will require separate and written consent prior to focus group participation.

7.2.3. Schedule

There will be two questionnaires for HCPs to complete -

1) At Visit 2 - When the CVD IRT report has been received and discussion with the participant has taken place, the HCP will be required to complete a focused questionnaire in the eDC.
2) When at least ⅔ of the site's participants or at least ⅔ of the total study participants (whichever is first for each site) have completed Visit 2, the clinical study team will be provided with a link to an online questionnaire, designed specifically for the physicians and nurses who have participated in the clinical study. The questionnaire will take approximately 20 minutes to complete.

   The HCPs will be reminded to complete the questionnaire a maximum of two times.

   When no more questionnaire responses are anticipated, focus groups will be arranged selecting HCPs from those that have completed the questionnaire.

The timeline of the focus groups will be towards the end of participant participation at site, and the completion of the HCP questionnaires. It is intended that focus groups may be conducted in parallel with the participant Interviews . It is anticipated that the interviews will be conducted as close to or just after all participants have completed Visit 2.

7.3. PCC participation

7.3.1. Screening

The qualitative researcher will identify approximately five PCCs from the North East England Clinical Commissioning Groups (CCGs).

7.3.2. Consent

The focus group will require written consent prior to focus group participation.

7.3.3. Schedule

The PCC focus group will be conducted at any time after the HCP questionnaires have been sent out and maybe conducted in parallel with the participant interviews and HCP focus groups. .

7.4. End of study

The end of the study is taken as the date of the last participant, last interview (Visit 4). Focus groups with HCPs and PCCs may take place before or after the end of the study .

The end of the study for an individual participant is defined as the date when the participant has completed the online questionnaire, OR for a participant being interviewed as soon as that interview has taken place, unless they have been withdrawn from the study earlier.

The end of the study for an individual GP practice is defined as the date that the last participant has completed Visit 2, the HCPs have completed the online HCP questionnaire OR for a practice participating in the HCP focus group, as soon as that focus group meeting has taken place.

When recruitment is complete, the function to add new participants will be removed from all sites. The HEART application will be kept live until the final reminder for the questionnaire has been

submitted, to allow access to the questionnaire link. Access will be removed on a site by site basis as each site completed study activities.

The final activity of the study is either the final participant Interview, the final HCP focus group of the PCC focus group, whichever comes last.

7.5. Storage, analysis and destruction of clinical samples

A 'Sample Handling and Shipping Instructions Manual' will be provided for sites to instruct on the samples required and how to package for delivery. No sample processing will take place at site and no blood or saliva samples will be stored at site and all samples will be packaged on the day of collection and sent for analysis within 24 hours. No patient identifiable information will be provided with the samples; only the participant ID and sample number/barcode linked to the samples. Samples will be tracked and monitored through to destruction.

7.5.1. Biosample processing

Biosample processing and the generation of the genetic data will take place in contracted research laboratories following laboratory standard operating procedures (SOPs) and Sponsor's instructions.

Anonymised samples collected from consenting participants will be transported to separate UK laboratories (one for blood, one for saliva) where DNA will be extracted from the samples. Blood and saliva DNA, only sufficient for analysis and no more, will be transported to a single genotyping laboratory in the US for genetic analysis. The resulting DNA sequences (electronic files) will be returned to Genomics plc in the UK.

Anonymisation of samples will be maintained throughout sample processing.

7.5.2. Genetic data analysis

Blood samples

On receipt of the individual genetic results, analysis of genetic data will take place at Genomics plc. Individual level CVD IRT reports will be generated for each participant and returned to the GP practice.

Saliva samples

DNA extracted from the saliva samples will be used for exploratory purposes only to understand whether DNA extracted from saliva can provide comparable results.

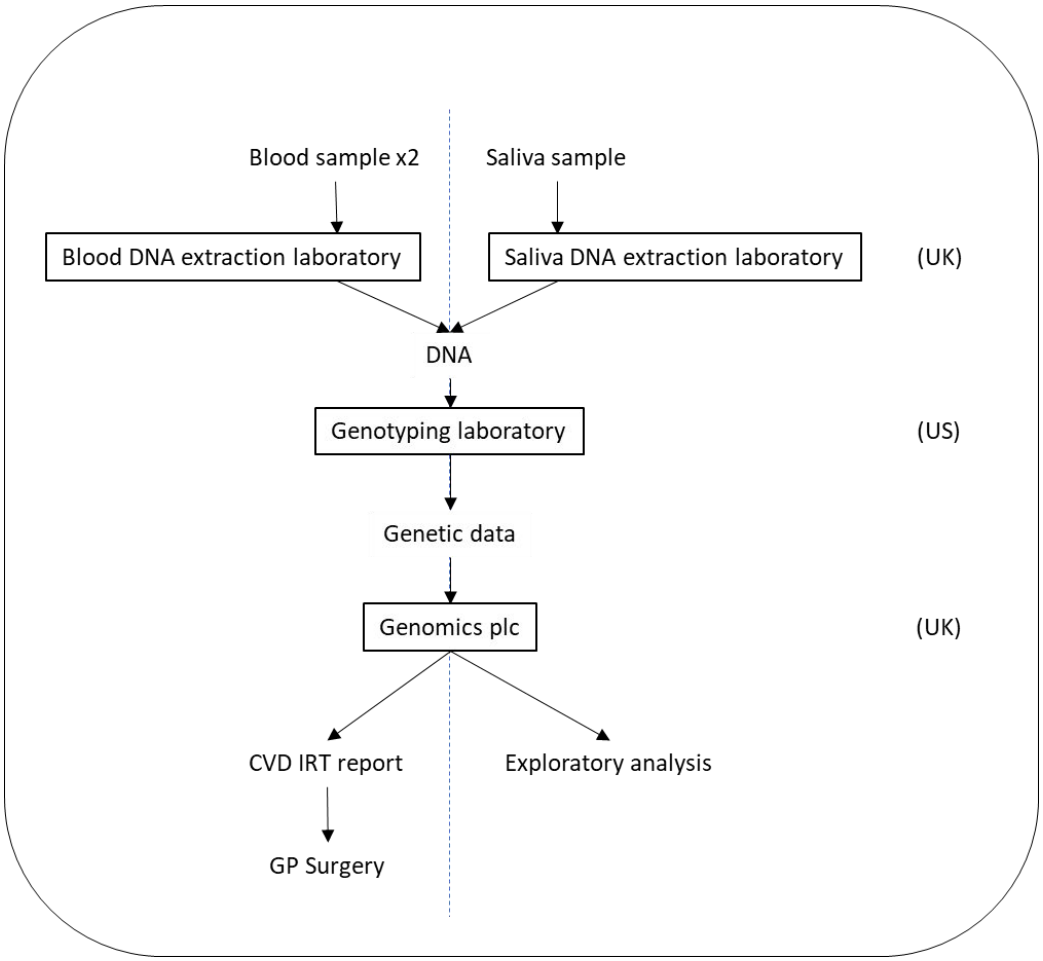

Figure 4: Transport and processing of study samples.

7.5.3. Sample destruction

The DNA will be extracted from one of the blood samples and the saliva sample at the respective DNA extraction laboratories. The second blood sample will be stored in case of quality failure with the initial blood sample.

The DNA will be stored at the extraction lab, with only sufficient DNA for analysis sent to the Genotyping laboratory in the US. Excess DNA will be stored at the UK DNA extraction laboratories in case replacement samples are required. At the end of the study, any and all unused DNA and remaining blood and saliva samples will be destroyed when genetic analysis for the study is complete, on the sponsor's instructions.

The DNA sequence (now electronic data) will be sent to Genomics plc to calculate the PRS, and to determine the CVD IRT score.

7.5.4. Future research

The anonymised genetic data (electronic only) will be kept for future research, and this will be clearly set out in the participant consent forms. If the participant does not agree to their genetic data being kept for future work, they will not be able to participate in the study.

7.6. Qualitative assessments

The study uses questionnaires, interviews and focus groups as qualitative assessments.

7.6.1. Questionnaires

Visit 1 (baseline): Participants will be asked to complete a paper questionnaire consisting of four questions. Participants will complete after the study procedures have been completed and just prior to leaving the GP Surgery. The study staff will enter the data into the eCRF and keep the questionnaires filed in the site file as source data.

Visit 2: HCPs will be asked to complete a focused questionnaire via the eDC.

Visit 3: An online questionnaire (using SurveyMonkey) will be sent to study participants and HCPs to complete. The questionnaires, different for participants and HCPs, are mixed qualitative and quantitative questionnaires designed to capture their understanding and perception of the CVD IRT as well as its usefulness and impact.

All participants who completed Visit 2 will be requested to complete an online mixed quantitative and qualitative questionnaire. A link will be emailed by the site staff to the patients' personal email address up to 14 days after the receiving test results, and patients will be reminded once to complete the questionnaire. If there is no response after 4 weeks, the questionnaire will be closed to the participant. The target minimum response rate is 20%.

All HCPs involved in the study will be emailed a link to the HCPs' work email address after at least ⅔ of that site's participants or at least ⅔ of the total study participants (whichever is first for each site) have completed visit 2. HCPs will be reminded to complete the questionnaire no more than twice. HCPs are expected to respond to the questionnaire within three weeks of issue. The target response rate is 50%.

7.6.2. Interviews

From the questionnaire respondents, a sample of participants will be selected by NECS for semi-structured individual telephone interviews (which will be recorded) lasting approximately 30 minutes in length.

The interview process will take place 1-2 months after a participant has completed their survey Participants who consent to participate in these interviews will be selected to represent a purposive sample from a variety of practices and areas within the study. A total of 20-30 participants will be interviewed (the final number will be dependent upon total interview recruitment figure) via telephone with the aim of undertaking up to 2 months after test results are returned.

Interview topics will be structured around the relevant outcome measurements of the key study objectives. Detailed interview questions will be developed and guided by the data received from online questionnaires and agreed with the Sponsor before the interviews take place.

For example, patients may be asked about:

- Study process - Level of satisfaction in experience
- Study report results - Level of satisfaction in outcome

- Communication – Before and during the testing and results process

The interviews will be recorded. The content will be analysed using thematic analysis. These findings will present anonymised patients' perspectives and experiences and will be triangulated with the online questionnaire and quantitative data collection.

NECS will provide anonymised typed transcripts from the recordings of the interviews and thematic analysis will be provided to Genomics plc Audio recordings will be destroyed once transcriptions have been analysed.

7.6.3. Focus Groups

7.6.3.1. HCP

The HCP focus groups will follow the completion by HCPs of the online questionnaire. HCPs will be asked to provide and sign consent for the release of typed anonymised transcripts from the recordings of the focus groups to NECS and thematic analysis provided to Genomics plc.

NECS will run an online focus group(s) of around 15 HCPs from a number of practices. The number is dependent upon the total recruitment figure and will be run until saturation is reached). The focus groups will last 45 - 60 minutes in length and be held online (e.g. Zoom/Teams) after the majority or all of the HCP questionnaires have been returned. There may be an option to incorporate this into a weekly practice meeting for HCP convenience. Dependent on recruitment, and subject to responses, a separate focus group(s) may be organised for nurses involved in the study.

Interview topics will be structured around the relevant outcome measurements of the key study objectives. Detailed interview questions will be developed and guided by the data received from online questionnaires and patient interviews, and agreed with the Sponsor before the interviews take place.

For example, HCPs may be asked about:

- Set-up - Incorporating the test into practice systems and initial approach to patients
- Communication – Exchanges with patients and Genomics plc
- Results - Level of satisfaction and perception of the process of obtaining and communicating results to patients
- Implementation - Consideration of genetics as a risk factor in primary care
- Usefulness - Value of genetics as a risk factor for cardiovascular disease

The focus groups will be recorded. The content will be analysed using thematic analysis. These findings will present HCPs anonymised perspectives and experiences and will be triangulated with the online questionnaire and quantitative data collection.

7.6.3.2. PCCs

Primary Care Commissioners (PCCs) (<5) will be recruited from Northeast England Clinical Commissioning Groups (CCGs) to understand their views on potential implementation. They will be invited to a separate focus group 45-60 minutes in length. The session will take place in parallel with the HCP focus groups.

Attending PCCs will be asked to provide and sign consent for the release of typed anonymised transcripts from the recordings of the focus groups.

Interview topics will be structured around the relevant outcome measurements of the key study objectives. Detailed interview questions will be developed and guided by the data received from online questionnaires, patient interviews and HCP focus groups, and agreed with the Sponsor before the interviews take place.

For example, Primary Care Commissioners may be asked about:

- Acceptability of the test in the current primary care setting
- Implementation of genetics as a risk factor in primary care
- Usefulness of genetics as a risk factor.

Audio recordings will be analysed using thematic analysis. These findings will present PCCs' anonymised perspectives and experiences.

8. CONCOMITANT MEDICATIONS

No data on participant concomitant medications will be collected for this study.

Participants who are required to start statin treatment based on the CVD risk assessment score provided at visit 2 will be able to do so.

9. SAFETY MONITORING

9.1. Definitions

9.1.1. Adverse Events and Device Deficiency

The adverse event and device deficiency definitions are aligned to those in the international standard ISO 20916: 2019 for in vitro diagnostic medical devices, allowing for CVD IRT being a risk assessment tool rather than a diagnostic tool.

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, inappropriate patient management decision, unintended disease or injury, or untoward clinical signs, whether or not related to the IVD or study procedures.
Serious Adverse Event (SAE)	AE that led to any of the following a) death b) serious deterioration in the health of the participant as defined by one or more of the following i) a life-threatening illness or injury, or ii) a permanent impairment of a body structure or a body function including chronic diseases, or iii) in-patient of prolonged hospitalisation, or iv) medical or surgical intervention to prevent life-threatening

	illness or injury or permanent impairment to a body structure or a body function c) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment
Adverse Device Effect (ADE)	AE related to the use of an IVD.
Serious Adverse Device Effect (SADE)	ADE that has resulted in any of the consequences characteristic of a SAE
Unanticipated Serious Adverse Device Effect (USADE)	SADE which by its nature, incidence, severity or outcome has not been identified in this protocol.
Device deficiency	A device deficiency is an inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety, or performance, such as malfunction, misuse or use error or inaccurate results and inadequate labelling.

Table 4: Definitions of AEs and device deficiency.

The following should not be considered an AE: a condition requiring a pre-planned procedure unless the condition worsened since screening or a pre-existing condition found as a result of screening, unless the condition has worsened since enrolment.

9.1.2. Adverse Event Severity Classification

An AE can be classified as severe and not deemed a SAE. Similarly, a SAE is not automatically severe in nature.

Severity will be defined according to the following criteria:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or perform normal daily activity

Table 5:Severity Classification

9.1.3. Adverse Event Relationship Classification

Each Adverse Event will be assigned a relationship to the study tool or study procedures. Relationships will be assessed as follows:

Not related	Relationship to the device or procedures can be excluded when there is no temporal relationship, the event is not known for the type of device or procedure, is implausible and other more reasonable explanations are available.
Unlikely	The relationship with the use of the device or procedures seems not relevant and/or the event can be reasonably caused by another cause.
Possible	The relationship with the use of the device or procedures is weak but cannot be ruled out.
Probable	The relationship with the use of the device or procedures cannot be reasonably explained by another cause.
Causal relationship	The event is associated with the device or procedures when there is a temporal relationship, the event is known for the type of device or procedure, and no other reasonable explanation is available.

Table 6: Definitions of relationship to device or procedure

9.1.4. Adverse Event Outcome Classification

Outcome of the event will be defined according to the following:

Resolved:	The event was fully resolved at the end of the study.
Resolved with sequelae:	The event has resolved, but retained pathological conditions resulting from the results and presentation.
Continuing:	The event is ongoing at the end of the study.

Death:	This event is determined to be the cause of death.

Table 7: Event outcomes.

9.2. Adverse Event Recording

Adverse event monitoring outlined in this protocol is reflective of the risk/benefit ratio of participating in the study to the patient. Intervention is minimal; an additional blood sample and saliva sample for a subgroup, the participant will receive a second CVD risk score in addition to the standard CVD QRISK®2 score, followed by an online questionnaire (and possible interview). All these activities are considered low risk.

To this end, the study will only collect adverse events considered related to study procedures or the risk assessment tool (CVD IRT). In addition, since all participants will provide a blood sample as part of standard practice (for QRISK®2), the study is requesting that study blood samples be collected using the same venepuncture. Therefore, mild events such as the following which are common when giving blood samples will not be collected for the study safety database:

- Pain
- Feeling faint
- Bruising
- Minor bleeding
- Haematoma
- Site infection

However, adverse events due to the process of blood sampling that are not common or are severe in nature will be collected. The WHO Best Practices for Injections and Related Procedures Toolkit can be referred to minimise adverse events[16].

From point of consent to collection of results at visit 2, all AEs considered related to the risk assessment tool or study procedures will be collected during visit 2 by the clinical team. At visit 3, the online questionnaire will be reviewed by the qualitative research team to identify related AEs and reported to the clinical team for documentation.

Similarly, during interviews, the qualitative research team (interviewer) will again identify related adverse events, but in this instance only those meeting the criteria of 'serious' will be collected. All SADEs will be forwarded to the clinical team for documentation.

Throughout the study, the participant will be invited to contact the study team at any time to discuss any concerns and issues raised by the study, and any related AEs identified will be collected as described above. Up to the point of online questionnaires, self-reported related adverse events will be collected and after the online questionnaires, self-reported related adverse events meeting the criteria of 'serious' will be collected until study end. Related SAEs should be followed to resolution if possible.

All adverse events must be recorded in the eCRF as soon as possible.

9.2.1. Anticipated Adverse Events

Low numbers of adverse events are thought to occur in this clinical study. However, it is possible that providing participants with a risk score for their likelihood of developing CVD in the next 10 years, may cause anxiety to the participant, both in anticipating the score and after receiving the score. In addition, the genetic component may cause additional concerns, due to the immovable nature of the genetic component. As such, the following events and those with similar meaning that are **mild** in nature, are anticipated for CVD IRT.

- Anxiety
- Nervousness
- Distress
- Unease

However, adverse events of this type, but that are considered moderate or severe, will not be considered anticipated for the purposes of this clinical study for patients that previously did not experience such events.

For participants who already experience mild anxiety for example, an increase to moderate anxiety would be considered anticipated. Similarly, an increase from moderate to severe anxiety would be considered anticipated.

The sponsor (or delegate) has the final responsibility of assigning whether AEs are anticipated.

9.3. Device Deficiency Recording

All device deficiencies, such as failure to log on, inability to create new participants or error messages will be documented and reported to << [redacted] >>.

Adverse events that resulted from a device deficiency (which would by definition be related to the CVD IRT) will be recorded as outlined in section 9.2.

9.4. Recording and Reporting Responsibilities

9.4.1. Investigator Responsibilities

The investigator and study team are responsible for collecting AEs as described in section 9.2 using the eCRFs (AE log and SAE page) within 24 hours of learning of the event. The investigator is responsible for reviewing all AEs and SAEs.

AEs will also be recorded in the participant medical notes.

The investigator is responsible for assigning seriousness and relationship to the risk assessment tool or study procedures and document this in the eCRF. If this is not available immediately, the initial report using the paper backup should be submitted to [redacted] and follow-up information reported as soon as possible, in a timely manner.

9.4.2. Qualitative Researcher Responsibilities

ADEs and SADEs identified by the qualitative research team will be collected and shared with the clinical study team at site immediately upon identification to then be entered into the eCRF The qualitative research team will review questionnaires on a regular basis to ensure appropriate and timely reporting.

9.4.3. Chief Investigator (CI) Responsibilities

The CI has clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.

9.4.4. Sponsor Responsibilities

- Central data collection and verification of AEs, ADEs, SAEs, SADEs and USADEs according to the study protocol onto a database.
- Expedited reporting of USADEs to REC within required timelines.
- Notifying Investigators of SAEs/SADEs and USADEs that occur within the trial.
- Update Reference Safety Information for the trial annually and share with investigators.

9.5. Reporting urgent safety measures

If any urgent safety measures are required during the clinical study to protect participants against immediate hazard to their health or safety, the investigator shall immediately inform the sponsor so as to inform the REC within set timelines, 3 working days.

9.5.1. Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial.

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

The sponsor of a clinical study will notify the REC, as appropriate.

10. STATISTICS AND DATA ANALYSIS

10.1. Sample size justification

The aim of this study is to demonstrate that predictive genetic testing can be incorporated into primary health care.

This study is adding genetic testing to a tool that is already available; QRISK®2 predicts the likelihood of developing CVD over the next 10 years by assessing clinical data. It is intended that the addition of a genetic component to the test should not complicate the process, maintaining ease of use.

To this end, it is planned to select sites of different size, capacity and resource to test assimilation of the genetic component into their varying processes. Additionally, the addition of the genetic component should not hinder the number of assessments normally undertaken, therefore high throughput is essential.

Also of interest to the study is a diverse population. The study will aim to recruit an equal number of male and female, even numbers across the 5 year age brackets (e.g., 45-49 years), and also aim to include 10-15% black, asian and minority ethnic (BAME) participants.

It is considered that 10-12 sites from areas of varying affluence and deprivation, and recruiting a high number of participants reflective of normal practice (50-100) will serve to answer the study objectives. It is planned to recruit around 1000 participants from 10-12 sites.

This number will also be sufficient to answer the secondary and exploratory objectives.

100 saliva samples are required to demonstrate comparability of risk scores with those achieved with blood derived DNA.

10.2. Planned recruitment rate

It is planned that each of the 10 to 12 sites recruit between 5 and 10 participants per week. Based on this, and allowing for staggered site initiations, it is anticipated that recruitment will take between 5 and 7 months.

10.3. Description of Methods of Analysis

Analysis will be undertaken as outlined in the Statistical Analysis Plan (SAP).

10.3.1. Operational analysis

Analysis of the primary objective includes a calculation of the return rate of reports. In addition, an in depth analysis of the operational process of returning reports to the surgery will be undertaken.

A comparative analysis will be undertaken to explore incidences of reclassification between a patient's QRISK®2 score and their combined risk score.

The analysis will explore and assess the impact of the CVD IRT on clinical decision making where the addition of genetic information shows an increase in risk.

A comparative analysis will be undertaken of PRS derived from DNA extracted from blood and saliva.

Further analysis may be undertaken, guided by the interpretation and understanding of study results.

10.3.2. Feedback analysis

Feedback from the Visit 1 Participant and Visit 2 HCP questionnaires entered into the eCRF will be analysed by Genomics plc as set out in the statistical analysis plan.

SurveyMonkey will be used to gather online mixed quantitative and qualitative data from an online questionnaire. This will be a formal sample of participants (both HCPs and patients). Tables and charts as well as basic statistics are created by SurveyMonkey for closed questions. Charts include bar, line and pie charts, and trend lines can be included where appropriate. Basic statistics vary depending on question type, but will include minimum, maximum, mean, median and standard deviation. Responses will be filtered to compare results from different responders.

In addition to the questionnaire data thematic analysis will be conducted on participant one to one interviews and HCP and PCC focus group discussions.

Descriptive statistics will be used to initially assess the data, with consideration to using further statistical tests depending on the initial finding, if further analysis is required. Presentation of the results will be charts and graphs.

11. DATA MANAGEMENT

A Data Management Plan (DMP) will describe how data will be acquired and how it will be handled, stored, checked for consistency and made available for final analysis.

11.1. Data collection tools and source document identification

Data will be collected electronically via the CVD IRT, as well as via CRFs by Genomics plc.

The anonymised online survey data (managed by NECS) for both study participants and HCPs will be downloaded and presented as part of the thematic analysis. The patient interviews will be audio recorded by NECS for their evaluation. Thematic analysis will be made and will be shared with Genomics plc. Audio recordings of any interviews conducted as part of the qualitative feedback will be destroyed once transcripts have been analysed by the qualitative researchers.

The HCP and PCC Focus Groups will have audio recordings made and transcribed by NECS. Written copies of the transcripts will be used for thematic analysis. Audio recordings of the focus groups will be destroyed once transcripts have been analysed by the qualitative researchers.

11.2. Data handling and record keeping

The personal details and consent form will only be accessible to appropriate staff members at the GP practice and, if requested, by monitors from the study Sponsor for monitoring, or for audit purposes.

Each biosample will be assigned a unique identifier, and only the GP practice will hold the source data to link back the sample identifier to the participant.

The Sponsor will implement and ensure that GP practices implement appropriate measures to ensure that all personal data is collected, stored, used, and otherwise processed according to all applicable data protection laws including the UK GDPR, the UK Data Protection Act 2018, and any successor legislation.

All clinical study findings and documents will be regarded as the Sponsor's confidential information. Study documents (protocols and other material) will be stored appropriately to ensure their confidentiality. The Chief Investigator and members of their research team (including the REC) must not use or disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study or to comply with regulatory requirements.

Genetic information extracted by contract research laboratories will be handled and held by those laboratories strictly in accordance with the Sponsor's instructions, before being transferred to the Sponsor using secure and encrypted methods. The contract research laboratories will be directed to destroy all of the study samples, DNA and the genetic data in their possession once they have completed the contracted services.

11.3. Access to Data

Study data stored and used by the Sponsor will be encrypted and access will be limited to authorised and authenticated users. The Sponsor's information security practices have been independently certified to meet international standards (ISO 27001: 2013).

Direct access to study data will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-trial-related monitoring, audits and inspections.

11.4 Archiving

Anonymised data generated as part of this study, including both genetic and other study data, will be retained indefinitely and may be used for future research and validation purposes and product development.

Records and documents pertaining to the conduct of this study, including participant generated information, ePRO data, ICFs, laboratory test results, and the study report, must be retained by the Principal Investigator for at least 10 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

NECS will keep questionnaire responses and transcripts of interviews and focus groups as per NECS processes, for a minimum of 10 years, and only be destroyed with agreement from the sponsor.

12. MONITORING, AUDIT AND INSPECTION

Study monitoring will be undertaken according to the Study Monitoring Plan (SMP) which will at a minimum include the following:

- The anticipated frequency and scheduling for monitoring.
- Mode of monitoring, remote or in-person.
- Identification of source data.
- Percentage of source data verification
- Protocol deviation reporting and capture
- Safety reporting requirements and timelines
- Device deficiency reporting requirements and timelines.

The investigator is not permitted to deviate from this protocol, except when a deviation is necessary to protect a participant's rights, safety and well-being, or the scientific integrity of the clinical performance study. Accidental protocol deviations can happen at any time. Any deviation from the protocol will be reported by the study site to the Sponsor, which will keep a record of these deviations, and as appropriate, reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable and will require immediate action that could potentially be classified as a serious breach. These will be mitigated in the first instance by re-training and increased monitoring, but if persistent, the site can be excluded from the study as a last resort.

12.1. Internal audits

Internal audit procedures are in place and will be applied to The HEART Study.

12.2. External inspections

Genomics plc will comply with the requirements of external inspections.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Research Ethics Committee (REC) Review and Reports

This study will be conducted in accordance with ethical principles set out in the Declaration of Helsinki and principles of GCP.

Before the start of the study, a favourable opinion will be sought from the UK Health Departments Research Ethics Service (NHS REC) and HRA for the study protocol, informed consent forms and other relevant documents e.g. invitation letters, advertisements if to be used. Substantial amendments that require review by NHS REC will not be implemented until review is complete and amendment approved.

REC will be notified of the end of the study, whether premature or as planned, as per REC requirements.

Within one year after the end of the study, the Sponsor will submit a final report with the results, including any publications/abstracts, to the REC.All correspondence with the REC will be retained in the Study Master File

13.2. Research Ethics Committee (REC) Review and Reports

The CVD IRT is a device for performance evaluation under Directive 98/79/EC (EU IVDD).

The protocol and study conduct will follow the applicable clauses of the UK Medical Device Regulations 2002, giving effect to Directive 98/79/EC (EU IVDD) and ISO 20916, and any relevant amendments.

13.3. Peer review

The study design process has involved pre-study scoping focus sessions with healthcare professionals to ensure the feasibility and acceptability of the study design. Six GPs, two nurses, and four practice managers from a range of practices and locations in the North East of England were consulted.

In addition, this protocol has been reviewed by the following clinical peers:

Two independent reviewers, [redacted] and [redacted] reviewed the protocol before its finalisation.

13.4. Public and Patient Involvement

At the protocol design stage, a focus group involving three patient representatives, identified via the NIHR CRN, provided input into the study design and patient facing material.

13.5. Indemnity

The Sponsor will hold appropriate insurance to cover all of its legal responsibilities and liabilities as study sponsor and will indemnify the participating sites against liabilities and claims arising from the trial, except for claims that arise from their malpractice and/or negligence.

The sponsor's policies and procedures will address the costs of treatment of study participants in the event of study-related injuries in accordance with the applicable regulatory requirement(s).If study participants receive compensation, the method and manner of compensation will comply with applicable regulatory requirement(s).

13.6. Post study care

Post-study care will be assured by the HCPs who enrolled the participants into the study. Any changes to patient treatment or management will be instituted at the decision of the treating doctor or health care professional. If changes in medication are instituted, these will be at the cost of the participant and prescribing physician.

14. DISSEMINATION AND PUBLICATION

14.1. Data sharing

The output of the study will be analysed, tabulated and presented in a Final Clinical Study Report (held on file at Genomics plc).

ummary data will be presented as per public registry guidelines.

14.2. Publication Plan

The results generated by this study will be owned by Genomics plc. The right to publish the findings of this study in the scientific literature will belong to, and will only be granted by, Genomics plc.

The output of the study will be analysed, tabulated and presented in a Final Clinical Study Report (held on file at Genomics plc).

It is anticipated that a study summary report will be made available to all participating practices.

Participating patients who are interested in the results will be directed to the public registry for a summary of the study.

Publications in peer-reviewed journals will be authored by a combination of the CI, NECS stakeholders, and the Genomics plc research team. NECS will be acknowledged as a partial funder of the study and a contributor to the protocol.

No participants will be identified by any of the reports or publications resulting from this research.

14.3. Authorship eligibility guidelines and any intended use of professional writers

Authorship of the final report will reflect the contribution of investigators at the design and analysis stages.

In the case a scientific publication is agreed, the standard guidelines of the International Committee of Medical Journal Editors will be followed.

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16. PROTOCOL AMENDMENT HISTORY

Any substantial amendments will be submitted to the REC and HRA for review. No changes will be implemented at any site until any required approvals for amendments have been obtained.

Protocol Version	Section	Summary of changes
1.0 to 2.0	1.3 7.1.9	Clarification of title to 'management of report for participant discussions' Clarification of NICE guidance for use when both QRISK and CVD IRT are available and one risk calculation exceeds 10%
	3.5	Endpoint relating to saliva added to reflect the list of objectives
	3.6	Amendment of timepoints when endpoint will be collected for Participant interview, HCP and PCC focus groups
	6.1.2	Matching of synopsis and protocol exclusion criteria.
	6.2.2	Clarification on scheduling of the focus groups for singular to multiple, if needed
	7.1	Clarification for collection of participant interview consent at visit 1 for participant convenience. Acknowledgement of the HCP questionnaire at visit 3, following the results discussion with participants. Clarification to the footnotes to acknowledge the change in timing for the participant interviews, HCP and PCC questionnaires
	7.1 Figure 1	Redrawn to align with the changes in the timings of the participant interviews, HCP and PCC questionnaires
	7.2 Figure 2 7.1.3	Redrawn to incorporate the participant questionnaire at Visit 1. Clarification on participant screening for eligibility to the HeathCheck and QRISK evaluation before invitation to the study
	7.1.7 Figure 3	Redrawn to update the timing of the questionnaire at Visit 3
	7.1.6 7.1.7.1	Additional wording explaining the timing for when the recruitment for participant interviews will take place
	7.1.7.1	Re-wording of paragraph for when a sample does not provide a

		CVD IRT score
	7.1.8	Clarification to the data collected at Visit 2
	7.1.10	The consent to participate in an interview is moved to Visit 1. The paragraph relating to consent at visit 4 has been removed and instruction that not all participants would be interviewed
	7.2 7.3 7.4	Additional information on when the questionnaires would be administered to HCPS added and the timings of the Change in HCP and PCC interview timings to occur as close together as possible
	7.6 10.0 11.0	Clarification to the transfer of thematic results to Genomics and not transcripts.
	10.0	Additional wording on the impact of the participants QRISK and CVD IRT score where the genetic information shows an increased risk.