Statistical Analysis Plan

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 1.0 06 May 2022

NCT05294419

STATISTICAL ANALYSIS PLAN (SAP)

PROTOCOL GEN2020-02

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

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SAP SIGNATURE PAGE

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

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SUMMARY OF REVISIONS

N/A

ABBREVIATIONS & TERMS

ADE	Adverse device effect
AE	Adverse event
BAME	Black, Asian and minority ethnic
BMI	Body mass index
CI	Confidence interval
CSR	Clinical study report
CVD	Cardiovascular disease
CVD IRT	Cardiovascular disease integrated risk tool
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
eDC	Electronic data capture form
GP	General practice
HCP	Healthcare professional
HCPQ	HCP questionnaire (for HCP responses towards end of study)
IRT	Integrated risk tool
ISO	International Organization for Standardization
IVD	*In vitro* diagnostic
NECS	NHS North of England Commissioning Support
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PCC	Primary care commissioner
PIC	Patient Identification Centre
PRS	Polygenic risk score
QC	Quality control
QRISK®2	A clinical risk assessment tool for CVD used by GPs in the UK
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation(s)

SOC	System organ class
TIA	Transient ischaemic attack
USADE	Unanticipated serious adverse device effect
V1eDC	Visit 1 electronic data capture questionnaire (for participant responses)
V2eDC	Visit 2 electronic data capture questionnaire (for HCP responses)
V3PartQ	Visit 3 participant questionnaire

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1 INTRODUCTION

This Statistical Analysis Plan (SAP) is created based on Protocol GEN2020-02 (Version 2.0, dated 06 Dec 2021) and describes in detail the statistical methodology and the statistical analyses to be conducted for the above-mentioned protocol. Any deviations to the planned analyses specified within the SAP, will be justified in writing, and presented within the final Clinical Study Report (CSR).

2 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 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 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.

2.3 Exploratory Objectives

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 STUDY OVERVIEW

3.1 Overall Study 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 healthcare professionals (HCPs) conducting the study, and primary care commissioners (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 [1]. CVD IRT incorporates the QRISK®2 score and refines patient risk by including genetic analysis data. Previous work, comparing the QRISK®2 and CVD IRT scores in the UK Biobank cohort, has demonstrated that CVD IRT refines the QRISK®2 score [2]. This study will provide every participant with the QRISK®2 and CVD IRT score (noted on the lab report as "combined risk") with no blinding.

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.

Questionnaires and interviews will be collected from the participants. In addition, the study will gather response data (questionnaires and focus groups) from the HCPs undertaking the clinical study, as well as a focus group with PCCs.

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[1] Hippisley-Cox *et al.* (2008) *British Medical Journal* 336:1475–1482, "Predicting cardiovascular risk in England and Wales: Prospective derivation and validation of QRISK2"; National Institute for Health and Care Excellence (2016) "Cardiovascular disease: risk assessment and reduction, including lipid modification (Clinical guideline [CG181])", available at https://www.nice.org.uk/guidance/cg181.

[2] Riveros-McKay *et al.* (2021), *Circulation: Genomic and Precision Medicine* 14: e003304, "Integrated Polygenic Tool Substantially Enhances Coronary Artery Disease Prediction"; Weale *et al.* (2021), *American Journal of Cardiology* 148: 157–164, "Validation of an Integrated Risk Tool, Including Polygenic Risk Score, for Atherosclerotic Cardiovascular Disease in Multiple Ethnicities and Ancestries".

3.2 Participant eligibility criteria

3.2.1 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

3.2.2 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
2. Currently prescribed and taking statins, for any indication.

The same inclusion and exclusion criteria are applied for the provision of saliva samples. To participate in an interview, the participant must have completed the online questionnaire at visit 3.

3.3 Study Duration

The recruitment period will be 30 weeks, The duration of participant involvement will be between approximately 14 and 20 weeks, from consent to completion to the final interview (if selected).

It is expected that the study will take approx 10 months to complete.

3.4 Sample Size

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 8-10 sites from areas of varying affluence and deprivation, and recruiting a high number of participants reflective of normal practice (around 100) will serve to answer the study objectives. It is planned to recruit around 1000 participants from 8-10 sites. All participants will be invited to complete an online survey. Of the participants who complete the survey a subset of 20-30 participants will be invited to take part in a telephone interview.

Approximately 30 HCPs involved in delivering the study will be invited to complete a questionnaire and take part in a focus group.

Approximately 5 representatives of the PCCs will be invited to take part in a focus group.

3.5 Randomization and Blinding

Not Applicable.

3.6 Study Assessment Schedule

The time and events schedule for the study is presented in Table 1.

Procedures	Visit 1, Baseline	Visit 2, Results	'Visit 3', Online Questionnaire	'Visit 4', Phone Interview	Focus groups
	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 (V1eDC)		X (V3PartQ)		
Interview consent	X				
Participant Interview [7]				X	
HCP Questionnaire		X (V2eDC)			X [8] (HCPQ)
HCP Focus Group(s)					X [9]
NHS PCC Focus Group					X [10]

Table 1: Schedule of assessments; patient participant, HCP and PCC.

Footnotes to Table 1 Schedule of Study Assessments

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 CVD 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.

4 STUDY VARIABLES

4.1 Safety Assessments - Adverse Events and Device Deficiency

Safety assessments include assessment of adverse events (AEs) and device deficiencies. The number and nature of these events will be recorded as safety variables.

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.

Terms and definitions relevant to safety assessments are provided in the table below.

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 2: Terms and definitions relevant to safety assessments.

Adverse Event and device deficiency collection is detailed in the protocol (Section 9.2) and listed as reported.

4.2 Performance Outcomes

4.2.1 Primary Outcome

The primary endpoint will be measured both by operational success (report return rates), and feedback from HCPs, PCCs and patients via questionnaires, telephone interviews and focus groups.

4.2.2 Secondary Outcomes

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

4.2.3 Exploratory Outcomes

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 the genetic risk test tool will be gathered from all qualitative data sources, the participant questionnaires and interviews, the HCP questionnaires and focus groups, as well as the PCC focus group.

5 ANALYSIS SETS

5.1 Enrolled Participant Analysis Set

The Enrolled Participant Analysis Set will consist of all participants who have given consent and a blood sample taken.

5.2 Visit 1 Performance Analysis Set

The Visit 1 Performance Analysis Set comprises all members of the Enrolled Participant Analysis Set who did not withdraw and who completed an eDC questionnaire (V1eDC).

The Visit 1 Performance Analysis Set will be used for the analysis of Visit 1 eDC questionnaire data.

5.3 CVD IRT Performance Analysis Set

The CVD IRT Performance Analysis Set comprises all members of the Enrolled Participant Analysis Set who did not withdraw and for whom a valid CVD IRT report was generated.

The PRS Performance Analysis Set will be used for the analysis of CVD PRS and IRT performance.

5.4 Visit 2 Performance Analysis Set

The Visit 2 Performance Analysis Set comprises all members of the Enrolled Participant Analysis Set who did not withdraw and who attended Visit 2 and received a valid CVD IRT report, and for whom a Visit 2 HCP questionnaire (V2eDC) was completed.

The Visit 2 Performance Analysis Set will be used for the analysis of Visit 2 HCP questionnaire data.

5.5 Visit 3 Performance Analysis Set

The Visit 3 Performance Analysis Set comprises all members of the Enrolled Participant Analysis Set who did not withdraw and who completed the 'Visit 3' online participant questionnaire (V3PartQ).

The Visit 3 Performance Analysis Set will be used for the analysis of 'Visit 3' online participant questionnaire data.

5.6 Visit 4 Performance Analysis Set

The Visit 4 Performance Analysis Set comprises all members of the Enrolled Participant Analysis Set who did not withdraw and who completed the 'Visit 4' telephone interview.

The Visit 4 Performance Analysis Set will be used for the analysis of 'Visit 4' telephone interview data.

5.7 Saliva Performance Analysis Set

The Saliva Performance Analysis Set comprises all members of the Enrolled Participant Analysis Set who provided saliva samples.

The Saliva Performance Analysis Set will be used for the analysis of performance of data derived from saliva.

5.8 HCPQ Performance Analysis Set

The HCPQ Performance Analysis Set comprises all HCP individuals who completed the HCP questionnaire (HCPQ).

The HCPQ Performance Analysis Set will be used for the analysis of HCPQ questionnaire data.

5.9 HCP Focus Group Analysis Set

The HCP Focus Group Analysis Set comprises all HCP individuals who took part in the HCP focus group(s).

The HCP Focus Group Analysis Set will be used for the analysis of HCP focus group data.

5.10 PCC Focus Group Analysis Set

The PCC Focus Group Analysis Set comprises all PCC individuals who took part in the PCC focus group(s).

The PCC Focus Group Analysis Set will be used for the analysis of PCC focus group data.

5.11 Per Protocol Analysis Set

The Per Protocol Analysis Set comprises all Participants in the Performance Analysis Set who had no major protocol violation and either:

- Completed their Survey or
- Withdrew before PRS delivered

All criteria for major protocol violations and patient evaluability for Per Protocol Analysis Set will be established by the study team prior to the database lock and will be documented in a memo by the study team. Supportive performance analyses will be performed for selected performance endpoints using the Per Protocol Analysis Set.

6 GENERAL STATISTICAL CONSIDERATIONS

Descriptive statistics on continuous variables will include the number of observations (n), mean, standard deviation (SD), 95% confidence interval, minimum, first quartile (Q1), median, third quartile (Q3), and maximum. Categorical variables, including categories which are created by combining sub-categories, will be summarised using the frequency count and percentage in each category, together with a 95% confidence interval.

All analyses will be performed using the R statistical software environment (version 4.1.2 or higher).

7 STATISTICAL ANALYSIS

Quantitative statistical analysis will be performed by Genomics plc. Qualitative summaries of focus group discussions will be provided by NECS.

7.1 Patient Disposition

Patient disposition information will be summarised for all enrolled Participants for the following disposition categories:

- Participants who were enrolled
- Participants who provided a sample
- Participants who completed a V3PartQ questionnaire
- Participants who completed a Visit 4 telephone interview

Participants who formally withdrew from the study
The primary reasons for terminating will be tabulated. The primary reason for early withdrawal from the study will also be tabulated.

In addition, the number and percentage of participants in each analysis set will be presented. All disposition data will be listed by patient.

7.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarised descriptively for all analysis sets. These include age (in years), biological sex (male / female), age group (5-year age groups: 45-49 / 50-54 / 55-59 / 60-64), self identified ethnicity, and education level.

Self- identified ethnicity is reported in the following categories:
White: English, Welsh, Scottish, Northern Irish or British / Irish Gypsy or Irish Traveller / Other
Mixed/Multiple: White and Black Caribbean / White and Black African / White and Asian / Any other mixed ethnicity
Asian or Asian British: Indian / Pakistani / Bangladeshi / Chinese / Other Asian background
Black African, Black Caribbean or Black British: African / Caribbean / Other Black background
Other ethnic group: Arab / Other

Education level is reported in the following categories:
Early education: No formal qualifications / GCSE attained / EBacc
Further education: Vocational Training / Apprenticeship / BTech L3 / A Levels
Higher education: Undergraduate Degree / Postgraduate Degree

Categorical baseline variables (e.g., biological sex, age group, self identified ethnicity, education level), will be summarized by the number and percentage of participants in corresponding categories. Continuous baseline variables (e.g age at informed consent) will be summarised by descriptive statistics (number of observations, mean, standard deviation, median, Q1, Q3, minimum, and maximum).

All demographic and baseline characteristics data will be listed by patient.

7.3 Disease History, Medical History and Prior and Concomitant Medications

No information on disease history, medical history and prior and concomitant medications will be recorded as part of this study, unless recorded as part of interview and focus group feedback, and except for the implied lack of certain conditions (e.g. CVD-free) that arise from the study entry criteria. The underlying variables that make up the QRISK®2 score will not be recorded as part of this study.

7.4 Protocol Deviations

Protocol deviations will be categorised as 'major' or 'minor' at a data review meeting convened by the sponsor. All major deviations and selected minor deviations (including but not limited to violation of entry criteria) will be listed.

7.5 Performance Analyses Summary Table

The study objectives will be met from a combination of quantitative analyses (e.g. on risk scores, report generation times, and fixed-category questionnaire responses) and qualitative assessments (e.g. free-text questionnaire responses, interview responses, and focus group responses).

The following table describes the study objectives, and summarises the ways in which each objective will be met. Each objective will be met from a holistic assessment of a series of quantitative and qualitative analyses. Please refer to the appended Excel files "TFLs_TOC_HEART.xlsx" and "TFLs_TOC_HEART_Example_layouts" for further details on table layouts referred to below.

Objectives	Data type	Key Tables/Metrics	Supporting Tables/Figures
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	"TFLs_TOC_HEART_Example_layouts/DT1 1ry"	"TFLs_TOC_HEART_Example_layouts/T1 Participant" "TFLs_TOC_HEART_Example_layouts/T15 Timings" Histogram of days til report returned
	Participant feedback via questionnaires (quantitative responses)	"TFLs_TOC_HEART_Example_layouts/DT1 1ry" (V1eDC-Q1, V3PartQ-Q9)	"TFLs_TOC_HEART_Example_layouts/T3 V1eDC" "TFLs_TOC_HEART_Example_layouts/T7 V3PartQ"
	Participant feedback via interviews and questionnaires (qualitative responses)	"TFLs_TOC_HEART_Example_layouts/T9 PartQual" (Comments relevant to objective compiled from free text responses in V3PartQ-Q3 and from telephone interviews)	N/A
	HCP feedback via questionnaires	"TFLs_TOC_HEART_Example_layouts/DT1 1ry" (V2eDC-Q6, HCPQ-Q3, HCPQ-Q5, HCPQ-Q14)	"TFLs_TOC_HEART_Example_layouts/T4 V2eDC-1" (HCP views summed over all participants processed) "TFLs_TOC_HEART_Example_layouts/T5 V2eDC-2" (HCP views at start of study) "TFLs_TOC_HEART_Example_layo

			uts/T6 V2eDC-3" (HCP views at end of study) "TFLs_TOC_HEART_Example_layouts/T8 HCPQ"
	HCP and PCC feedback via focus groups and questionnaires (qualitative responses)	"TFLs_TOC_HEART_Example_layouts/T10 HCPQual" "TFLs_TOC_HEART_Example_layouts/T11 PCCQual" (Comments relevant to objective compiled from free text responses to HCPQ-Q4, HCPQ-Q8, HCPQ-Q10 and HCPQ-Q15, and from HCP and PCC focus groups)	N/A
Secondary Objectives			
. To explore and assess the impact of the CVD IRT on clinical decision-making	HCP feedback via questionnaires and focus groups	"TFLs_TOC_HEART_Example_layouts/DT2 2ry-1" (V2eDC-Q4, V2eDC-Q3, V2eDC-Q5, HCPQ-Q6, HCPQ-Q7, HCPQ-Q9, HCPQ-Q19, HCPQ-Q20) "TFLs_TOC_HEART_Example_layouts/T10 HCPQual" (Comments relevant to objective compiled from free text responses to V2eDC-Q4, HCPQ-Q8, HCPQ-Q10, HCPQ-Q12, HCPQ-Q15 and HCPQ-Q24, and from HCP focus group discussions)	"TFLs_TOC_HEART_Example_layouts/T4 V2eDC-1" (HCP views summed over all participants processed) "TFLs_TOC_HEART_Example_layouts/T5 V2eDC-2" (HCP views at start of study) "TFLs_TOC_HEART_Example_layouts/T6 V2eDC-3" (HCP views at end of study) "TFLs_TOC_HEART_Example_layouts/T8 HCPQ"
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	"TFLs_TOC_HEART_Example_layouts/DT3 2ry-2"	"TFLs_TOC_HEART_Example_layouts/T12 Risks" "TFLs_TOC_HEART_Example_layouts/T13 Risk classification" "TFLs_TOC_HEART_Example_layouts/T14 Deltas freq" Ordered plot of deltas (CVD IRT minus QRISK®2) across individuals.

			Histograms of CVD IRT and QRISK®2 distributions, overall and split by age group, by sex, by ethnicity and by education level.
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 and focus groups	"TFLs_TOC_HEART_Example_layouts/DT4 2ry-3" (V2eDC-Q6, HCPQ-Q3, HCPQ-Q5, HCPQ-Q11, HCPQ-Q14, HCPQ-Q16, HCPQ-Q17) "TFLs_TOC_HEART_Example_layouts/T10 HCPQual" (Comments relevant to objective compiled from free text responses in V2eDC, HCPQ and from HCP focus group discussions)	"TFLs_TOC_HEART_Example_layouts/T4 V2eDC-1" (HCP views summed over all participants processed) "TFLs_TOC_HEART_Example_layouts/T5 V2eDC-2" (HCP views at start of study) "TFLs_TOC_HEART_Example_layouts/T6 V2eDC-3" (HCP views at end of study) "TFLs_TOC_HEART_Example_layouts/T8 HCPQ"
	PCC feedback via focus group	"TFLs_TOC_HEART_Example_layouts/T11 PCCQual" (Comments relevant to objective compiled from PCC focus group discussions)	N/A
To explore and assess to what extent HCPs and PCCs perceive the CVD IRT as clinically relevant	HCP feedback via questionnaires and focus groups	"TFLs_TOC_HEART_Example_layouts/DT5 2ry-4" (HCPQ-Q3, HCPQ-Q6, HCPQ-Q7, HCPQ-Q11, HCPQ-Q19, HCPQ-Q20, HCPQ-Q21) "TFLs_TOC_HEART_Example_layouts/T10 HCPQual" (Comments relevant to objective compiled from free text responses in HCPQ and from HCP focus group discussions)	"TFLs_TOC_HEART_Example_layouts/T8 HCPQ"
	PCC feedback via focus group	"TFLs_TOC_HEART_Example_layouts/T11 PCCQual" (Comments relevant to objective compiled from PCC focus group discussions)	N/A
5 To explore and assess to what extent participants	Participant feedback via questionnaires and interviews	"TFLs_TOC_HEART_Example_layouts/DT6 2ry-5" (V1eDC-Q4, V3PartQ-Q1, V3PartQ-Q2,	"TFLs_TOC_HEART_Example_layouts/T3 V1eDC"

perceive the information received through the CVD IRT as informative for health and wellness		V3PartQ-Q6, V3PartQ-Q9, V3PartQ-Q14) "TFLs_TOC_HEART_Example_layouts/T9 PartQual" (Comments relevant to objective compiled from free text responses in V3PartQ and from telephone interviews.)	"TFLs_TOC_HEART_Example_layouts/T7 V3PartQ"
6 To explore and assess the impact of the CVD IRT on patient engagement	Participant feedback via questionnaires and interviews	"TFLs_TOC_HEART_Example_layouts/DT7 2ry-6" (V1eDC-Q4, V3PartQ-Q1) "TFLs_TOC_HEART_Example_layouts/T9 PartQual" (Comments relevant to objective compiled from free text responses in V3PartQ (in particular V3PartQ-Q13) and from telephone interviews)	"TFLs_TOC_HEART_Example_layouts/T3 V1eDC" "TFLs_TOC_HEART_Example_layouts/T7 V3PartQ"
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 and interviews	"TFLs_TOC_HEART_Example_layouts/DT8 2ry-7" (V1eDC-Q3, V1eDC-Q4, V3PartQ-Q4, V3PartQ-Q5, V3PartQ-Q6, V3PartQ-Q9, V3PartQ-Q14) "TFLs_TOC_HEART_Example_layouts/T9 PartQual" (Comments relevant to objective compiled from free text responses in V3PartQ and from telephone interviews)	"TFLs_TOC_HEART_Example_layouts/T3 V1eDC" "TFLs_TOC_HEART_Example_layouts/T7 V3PartQ"
	HCP feedback via questionnaires and focus groups	"TFLs_TOC_HEART_Example_layouts/DT8 2ry-7" (V2eDC-Q1, HCPQ-Q11, HCPQ-Q13, HCPQ-Q14, HCPQ-Q16, HCPQ-Q17, HCPQ-Q18) "TFLs_TOC_HEART_Example_layouts/T10 HCPQual" (Comments relevant to objective compiled from free text responses in HCPQ and from HCP focus group discussions)	"TFLs_TOC_HEART_Example_layouts/T4 V2eDC-1" (HCP views summed over all participants processed) "TFLs_TOC_HEART_Example_layouts/T8 HCPQ"
	PCC feedback via focus group	"TFLs_TOC_HEART_Example_layouts/T11 PCCQual" (Comments	N/A

		relevant to objective compiled from PCC focus group discussions)	
8 To evaluate the performance of saliva as compared to blood for use in the CVD IRT	QC data from saliva and blood samples (from the same individuals)	"TFLs_TOC_HEART_Example_layouts/DT9 2ry-8"	Additional analyses will be contained in the separate sample QC report. Ordered plot of deltas (CVD-IRT-from-saliva minus CVD-IRT-from-blood) across individuals in the Saliva Performance Analysis Set.
9 To monitor the study for any potential safety concerns	Number and nature of adverse events recorded	"TFLs_TOC_HEART_Example_layouts/T16 Safety data"	
Exploratory Objectives			
1 To explore and assess the perception of healthcare providers and commissioners on the usefulness of CVD IRT.	HCP and PCC feedback via questionnaires and focus groups	"TFLs_TOC_HEART_Example_layouts/T10 HCPQual" "TFLs_TOC_HEART_Example_layouts/T11 PCCQual" (Comments relevant to objective compiled from free text responses in V2eDC and HCPQ questionnaires, and from HCP and PCC focus group discussions)	N/A
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.	HCP and participant feedback via questionnaires, interviews and focus groups	"TFLs_TOC_HEART_Example_layouts/T10 HCPQual" Comments relevant to objective compiled from free text responses in V2eDC, V3PartQ and HCPQ questionnaires, and from interviews and focus group discussions.	N/A

Table 3: Performance analyses summary table.

7.6 Additional Information on Performance Analyses

7.6.1 Subgroup Performance Analyses

Response in participants will be analysed overall and for the following subgroups:

- Biological sex (male or female)
- Age group (5-year age groups: 45-49, 50-54, 55-59, and 60-64)
- Ethnicity (White / Mixed / Asian or Asian British / Black African, Caribbean or Black British / Other)
- Education level (Early Education / Further Education / Higher Education)

Response in HCP individuals will be analysed overall and for the following subgroups:

- Practice role (GP / nurse / other)
- Study role (making decisions on care plans / not making decisions on care plans)
- By study site

Additional subgroup analyses may be performed if deemed necessary.

7.6.2 Further Exploratory Performance Analyses

Further exploratory analyses of Performance may be performed at the Sponsor's discretion.

All exploratory analyses will be described as such in the CSR.

7.7 Safety Analyses

Safety assessments include treatment emergent adverse events and device deficiencies as per protocol.

All safety analyses will be performed by cohort and overall based on the Enrolled Participant Analysis Set.

7.8 Interim Analysis

An interim performance analysis will be performed when approximately half of the participants have been recruited, and approximately 100 V3PartQ questionnaires have been completed. Importantly, the interim analysis will not be used to deviate from the study protocol, nor will the results be used to compete with or contradict the final analysis. Once performed, the final analysis will be the source of truth for all questions relating to the study objectives.

The interim analysis will serve two purposes:

- To check for demographic balance across sex, age and ethnicity groups. If imbalances are found, steps will be taken to redress the imbalance, in order to adhere to Protocol specifications.

- To check the integrity of the HEART study reporting mechanisms. For this purpose, all endpoints described in the table in Section 7.5 will be analysed to check that reports are correctly generated.

7.9 Timing of Analyses

The final analysis of the study will be performed after all participants have completed their final visit and the subgroup have completed interviews or have withdrawn before then.

The interim analysis will be carried out once approximately half of the participants have been enrolled.

7.10 Data Review Meeting

A data review meeting will be convened by the Sponsor at the following timepoints

- Before any administrative analyses
- Before the final analysis
- Before the follow-up analyses.

Each data review meeting will take place after the data have been cleaned but prior to the database being locked for analysis.

The terms of reference of the Data Review Meeting before the final analysis shall include but not be limited to:

- The determination of whether protocol deviations / violations are 'major' or 'minor', or not a protocol violation at all
- The allocation of subjects to analysis sets
- A review of missing data and of outliers
- A decision on whether centres need to be combined
- A review of the distribution of the Performance variables, considering any implications for the proposed method of statistical analysis
- A review of whether additional covariates need to be included in the analyses
- The finalisation of the SAP

The Data Review Report will be an Appendix to the CSR.

7.11 Changes from Analyses Specified in the Protocol

No changes have been issued or planned.