Genetic Risk Testing and Health Coaching for CHD and T2D

Supported by: Duke University School of Nursing, Duke University Center for Applied Genomics and Precision Medicine (CAGPM) and USAF Research Laboratory

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Protocol Version/Date: Version 14.0: June 1, 2017

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Participating sites:

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Synopsis

Title of Study:	Genetic Risk Testing and Health Coaching for T2D and CHD
Protocol No:	Duke IRB # Pro00039569
Principal Investigator	Allison Vorderstrasse, DNSc, APRN
Co-Investigators:	Ruth Wolever, PhD Geoffrey Ginsburg, MD, PhD Susanne Haga, PhD William Scott, DNP
Coordinating Center	Duke University, CAGPM Durham, NC
Participating sites	David Grant Medical Center, Travis Air Force Base (DGMC – TAFB) McClellan Outpatient Satellite Clinic
Methodology:	Prospective, randomized controlled trial, genomic
Number of subjects:	250

AF-Genetic Risk of CHD and T2D and Health Coaching

GLOSSARY – Medical Termionology and Abbreviations

ADAF	ACTIVE DUTY AIR FORCE
AE	ADVERSE EVENT
AF	AIR FORCE
BMI	BODY MASS INDEX
CAGPM	CENTER FOR APPLIED GENOMICS AND PRECISION MEDICINE
CGSU	DUKE CLINICAL GENOMICS STUDY UNIT
CHD	CORONARY HEART DISEASE
CRC	CLINICAL RESEARCH COORDINATOR
CRF	CASE REPORT FORM
CVA	CEREBROVASCULAR ACCIDENT
CVD	CARDIOVASCULAR DISEASE
DGMC	DAVID GRANT MEDICAL CENTER
DUHS	DUKE UNIVERSITY HEALTH SYSTEM
DUMC	DUKE UNIVERSITY MEDICAL CENTER
EMR	ELECTRONIC MEDICAL RECORD
FBG	FASTING BLOOD GLUCOSE
FRS	FRAMINGHAM RISK SCORE
GCP	GOOD CLINICAL PRACTICES
GRC	GENETIC RISK COUNSELING
HbA1c	HEMOGLOBIN A1C
HC	HEALTH COACHING
HDL	HIGH DENSITY LIPOPROTEIN CHOLESTEROL
HIPAA	HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT
HT	HEIGHT
ID	IDENTIFIER
IRB	INSTITUTIONAL REVIEW BOARD
LDL	LOW DENSITY LIPOPROTEIN CHOLESTEROL
MC	MCCLELLAN
MI	MYOCARDIAL INFARCTION
NCI	NATIONAL CANCER INSTITUTE
PCP	PRIMARY CARE PROVIDER
PHI	PROTECTED HEALTH INFORMATION
PI	PRINICIPAL INVESTIGATOR

RCT	RANDOMIZED CONTROL TRIAL
REDCap	RESEARCH ELECTRONIC DATA CAPTURE
SAE	SERIOUS ADVERSE EVENT
SBAS	STANFORD BRIEF ACTIVITY SURVEY
SBP	SYSTOLIC BLOOD PRESSURE
SRA	STANDARD RISK ASSESSMENT
T2D	TYPE 2 DIABETES
TAFB	TRAVIS AIR FORCE BASE
TC	TOTAL CHOLESTEROL
TRIG	TRIGLYCERIDE
UAE	UNEXPECTED ADVERSE EVENT
USAF	UNITED STATES AIR FORCE
WT	WEIGHT

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1. Background and Rationale

Military personnel are not exempt from increasing rates of overweight and obesity; or the associated rising burden of coronary heart disease (CHD) and type 2 diabetes (T2D) seen in the U.S. population. Innovative and clinically feasible approaches to address these chronic disease risks are needed, particularly those that motivate and support sustainable, risk-reducing health behaviors.

Risk assessment, historically based on clinical risk factors alone (e.g., blood pressure, cholesterol) is a central aspect of preventive care. In recent years, however, over one hundred genetic markers associated with increased risk for CHD have been described [1], and for T2D there are approximately 40 well-validated markers associated with increased risk [2]. While risk for both conditions remains modifiable with lifestyle changes such as diet and exercise [3], the feasibility and utility of integrating genetic risk information into primary care patients' global risk assessment for common chronic diseases remains unknown.

In addition, pairing a behavioral intervention with the provision of genetic risk information may be even more effective than the same intervention with more familiar clinical risk information alone [4]. This study will examine the impact of providing genetic CHD and T2D risk information, with or without a supportive behavioral intervention, on promoting risk-reducing behaviors and improvingclinical outcomes.

2. Trial Objectives

In short, using a 4-group (2X2) randomized controlled trial (RCT) design, this study will determine whether incorporating multiple-marker genetic testing into risk counseling for CHD and T2D [5], coupled with a health coaching intervention will lead to greater changes in physical fitness, health behaviors, risk status and clinical outcomes in active-duty Air Force (ADAF) , beneficiaries, and retiree patients. We will address the following task objectives or primary aims:

1. Determine the main and interactive effects of multiple-marker genetic risk information incorporated into standard CHD and T2D risk counseling (Standard Risk Assessment, or SRA) and an established, structured telephonic health coaching (HC) intervention on health behavior change (diet, exercise habits, smoking cessation) over 12 months, with a focus on ADAF, beneficiaries, and retiree patients.

2. Determine the main and interactive effects of genetic risk information incorporated into standard CHD and T2D risk counseling and a telephonic HC intervention on clinical outcomes (fasting blood glucose (FBG), systolic blood pressure (SBP), body mass index (BMI), Low-density lipoprotein cholesterol (LDL), triglycerides (TRIG), total cholesterol (TC), AF composite fitness scores, Framingham risk score (FRS), Diabetes risk score.

Secondarily, we will determine the effects of potential mediators of primary outcomes, including perceived risk, patient activation, stages of change for behaviors of interest, and psychosocial risk factors for CHD and/or T2D (depression, unmanaged stress, and social isolation).

3. Patient Selection

3.1. Target Population

The study population includes adult patients, 18-65 years of age, followed at AF primary care clinics with at least one risk factor for either CHD or T2D as defined in the inclusion criteria.

3.2. Inclusion Criteria

Patients will be eligible for inclusion in this study only if **all** of the following criteria apply:

1. Age 18 to 65 years
2. Willingness and ability to provide informed consent
3. Have an active email address and internet access
4. Physical exam in the last 6 months with the following documented evaluations in EMR:
    a. Blood pressure
    b. Height and weight
    c. Fasting blood glucose or Hemoglobin A1C (HbA1c)*
    d. Lipid panel (TC, LDL, HDL, TRIG)

with at least one of them outside of the normal ranges defined as:

i. BMI $\geq$ 25 kg/m2 (BMI = weight [kg] / ht $[m]^2$)

ii. FPG > 100 AND $\leq$ 125 mg/dL

iii. HbA1c > 5.7% ≤ 6.4%

iv. SBP ≥ 130 mmHg

v. TC ≥ 200 mg/dL

vi. TRIG ≥ 150 mg/dL

vii. LDL ≥ 129 mg/dL

* If a Fasting blood glucose or Hemoglobin A1C (HbA1c) and lipid panel are - documented within the last 6 months they will also be used to determine eligibility as defined above. If either of these tests have not been done in the last 6 months as part of standard care, they will be drawn after consent, either within 4 weeks prior to the baseline visit or at the baseline visit to ensure that the results are available during the baseline visit to confirm eligibility.

3.3. Exclusion Criteria

A patient will **not** be eligible for inclusion in this study if any of the following criteria apply:

1. Projected deployment in the upcoming 6 months ;
2. Diagnosed T2D;
3. Diagnosed CHD (MI, or documented CHD);
4. Inability to ambulate or participate in physical activity;
5. Serious chronic disease related complications or conditions that could significantly affect study outcomes [currently treated cancer, renal failure, cardiovascular accident (CVA) with residual effects on functioning];
6. Current participation in another research study ;
7. Spouse, partner or other household member already participating in this study protocol.

The cardio-metabolic risk factors used for inclusion are those identified by the FRS and national guidelines (National Cholesterol Education Program, AHA, ADA). Because we are targeting those at risk for CHD and/or T2D, participants must have at least one factor in the risk ranges listed. Patients with diagnosed CHD or T2D are excluded because this study is targeted toward prevention of these conditions in those at risk. Those with physical activity limitations or other serious co-morbidities are excluded due to potential effects on participation and study outcomes. The age limit of 18-65 years was designated as much of the risk of T2D or CHD in older adults is due to

age; not modifiable risk factors. Therefore, many intervention studies aimed at risk reduction limit participation to those at age 65 or younger.

3.4. Inclusion of Minorities

Adult patients of all races and ethnic groups will be considered for study participation.

4. Registration Procedure

All patients who have signed informed consent and met the eligibility criteria will be registered in the Research Electronic Data Capture (REDCap) system and will be issued a study specific ID number.

4.1. Institutional Registration

Patient registration at each study site/institution will be conducted according to the institution's established policies. Prior to registration, patients will be asked to sign and date an Institutional Review Board (IRB)-approved consent form.

4.2. Informed Consent

Authorized study personnel should fully explain the scope of the study to each patient before obtaining informed consent. When obtaining informed consent, study personnel should:

First: Confirm that the patient is a potential candidate for study participation.

Next: Obtain dated and signed informed consent document.

Finally: Confirm that the patient is eligible as defined in Sections 3.2 and 3.3 (Inclusion/Exclusion Criteria).

5. Study Design

This trial will recruit primary care patients at David Grant Medical Center (DGMC) that have at least one risk factor for CHD or T2D. Enrolled subjects will be randomized to one of four groups:

1. Standard Risk Assessment (SRA) only;
2. SRA plus Health Coaching (SRA+HC);
3. SRA plus Genetic Risk Counseling (SRA+GRC); ***or***
4. SRA+HC+GRC

The primary outcomes of this study are behavioral (diet and exercise/fitness), collected at 6 weeks, and 3, 6 and 12 months. At 12 months, clinical outcomes will be measured at the clinic (blood pressure, weight, and waist circumference). And at 12 months, clinical outcomes will be documented from the electronic medical record (EMR) (glucose, lipid panel, change in risk status, AF fitness scores*) from the subjects' annual visit results.

*Note: AF fitness scores are provided following required annual fitness evaluations for all ADAF only (not beneficiaries, retirees) and are age and gender based. The variables considered with points for level of performance in each category are: Cardiorespiratory endurance (run time); Body composition (abdominal circumference); and Muscle fitness (push-ups). A composite score derived from adding points in all categories must be >75. Ranges are defined for Unsatisfactory; Satisfactory and Excellent.

5.1. Expected Enrollment

Total of two hundred fifty (250) subjects will be enrolled in two primary care clinics, at two sites as follows:

1. David Grant Medical Center ,Travis Air Force Base, Solano, California
2. McClellan Outpatient Satellite Clinic, McCllelan Air Force Base, Sacramento County, CA

5.2. Recruitment

Ascertainment of potential subjects will be obtained by physician referral, patient self-referral or EMR chart review (Appendix I. and J.) The study coordinator will mail a letter, signed by the subjects' primary care physician, to those individuals identified by EMR chart review, introducing the study. After 2 weeks, the CRC will follow-up with a brief phone call to assess subjects' interest in study participation. (Appendix G. and H.). If the potential subject is interested in participation, consent and baseline visit will be scheduled. Patients identified by physician referral may be consented at time of physician referral or contacted later by phone to arrange consent and/or baseline visits. For

self-referred patients the initial phone conversation will be followed by consent/baseline visit in the clinic. Since a major target population for this study is ADAF, beneficiaries, and retiree patients, we will be placing flyers/advertisements/recruitment staff in locations on base to reach this audience including gymnasiums, annual fitness evaluation centers and annual exam clinics on base.

5.3. Schedule of Events

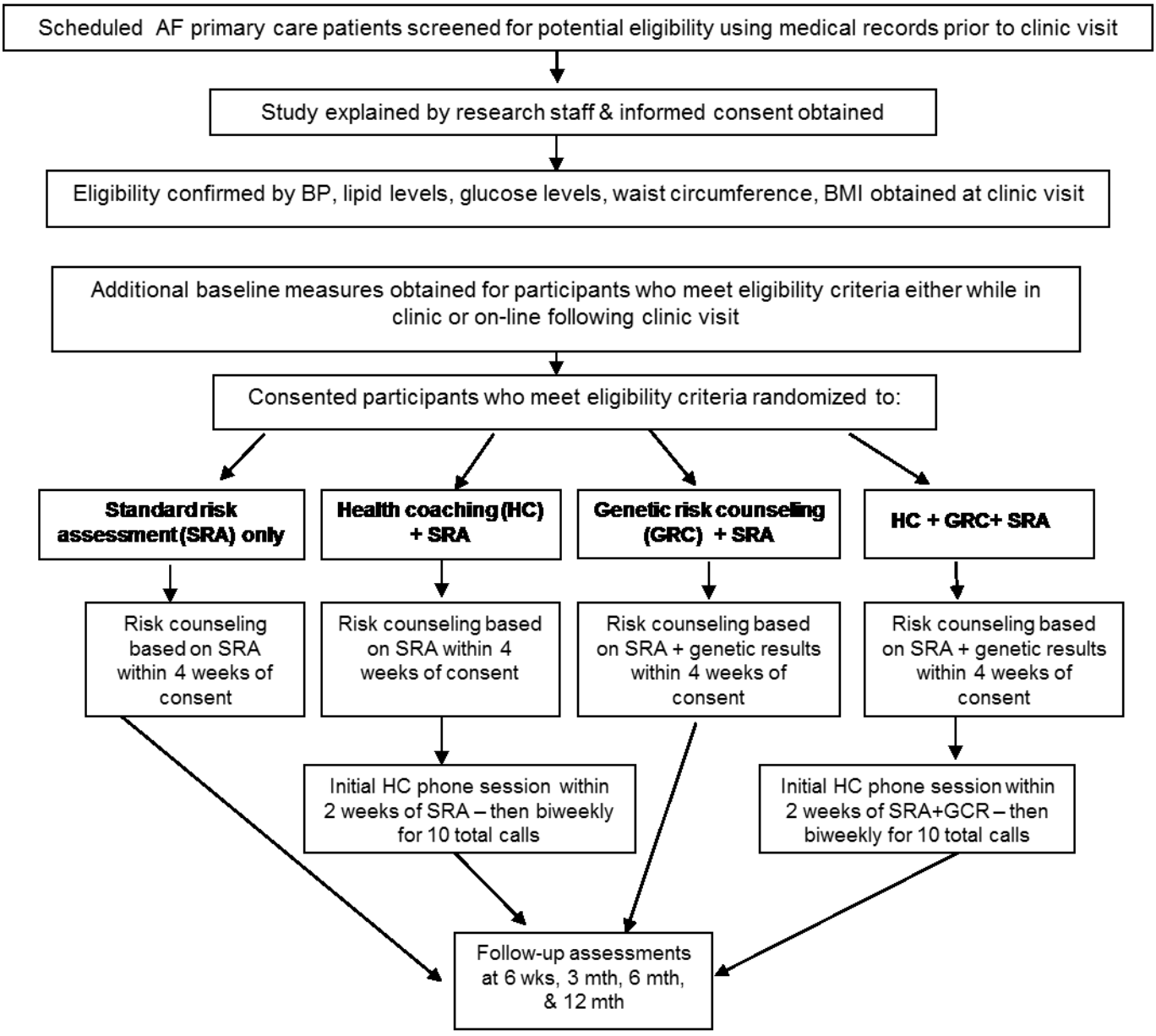
5.3.1. Visit Overview

Baseline visit:

Informed consent will be obtained and documented. Inclusion and exclusion criteria will be verbally verified with participant and date of consent will be documented on the Case Report Form (CRF, Appendix A.). Height, weight, waist circumference, and blood pressurewill be measured by CRC and documented on CRF. Refer to section 5.3.2. Study Specific Tests and Procedures for methods of obtaining height, weight, waist circumference, and blood pressure.

Most recent lab results (FBG or HbA1c, TC, TRIG, HDL, LDL, last PHA,) and current medications will be obtained from the EMR. Last fitness score will be obtained from a separate database, outside of the EMR. Participants who are not active duty will not have PHA with fitness scores. All variables measured directly or obtained from EMR will be entered into REDcap by CRC. Subjects randomized to the two genetic arms will have blood collected and sent for testing at Duke University Clinical Molecular Diagnostics Laboratory. Female subjects will be asked if they are currently pregnant and this will be documented (Note: the purpose of collecting pregnancy information is to account for potential confounders later in analysis; not for exclusion criteria). Participants will be registered in REDCap database. They will complete the baseline survey during their clinic visit (at a clinic computer).

Fig.1. Study Schema



Randomization:

Randomization will take place to *one* of the following:

1. Standard Risk Assessment (SRA) only;
2. SRA plus Health Coaching (SRA+HC);
3. SRA plus Genetic Risk Counseling (SRA+GRC); ***or***
4. SRA+HC+GRC

Random assignments will be generated using a standard random number generator with uniform distribution to the four groups by the Clinical Genomics Study Unit (CGSU) data manager. The research staff (CRC at site) will use this randomization schema to inform participants of their group assignment.

Follow up visits:

6-week and 3-month – At 6 weeks and 3 months after the baseline visit, participants will be asked to complete selected surveys online (Table 1). The 6 week survey must be completed after the counseling visit and before Health Coaching begins.

6-month – Six months from the baseline visit, participants will return to the clinic to have weight, BP and waist circumference measured (same procedures as baseline visit). Medications will be reviewed and AE's assessed. Female subjects will be asked if they are currently pregnant and this will be documented.

They will also complete the required surveys as listed, either before their scheduled visit or during their visit at the clinic.

12-month- Twelve months from the baseline visit, participants will return to the clinic for a final visit to have weight, BP and waist circumference measured (same procedures as baseline visit). Medications will be reviewed and AE's assessed.

Lab values from the EMR will be documented for fasting glucose, TC, HDL, LDL, TRIG CRC will check in EMR prior to each subject's 12-month visit. If lab values as stated above are not available from the last 6 months of study participation , then a lipid panel (TC, HDL, LDL, TRIG) and either a FBG or HbA1c will be ordered. Female subjects will be asked if they are currently pregnant and this will be documented.

They will also complete the required surveys as listed, either before their scheduled visit or during their visit at the clinic.

Window of ±one week were allowed for all follow up visits. In order to maximize power and considering

recent findings on the stability of metabolic clinical markers absent behavior change, statistical analyses will employ extended inclusion windows for study time-points. Statistical analyses will include: +/-3 weeks for the 6 week survey, +/-7 weeks for the 3 month survey, and +/-11 weeks for the 12 month survey.

Table 1.

STUDY VISITS	**GROUP 1** Risk Assessment Only	**GROUP 2** Risk Assessment +Health Coaching	**GROUP 3** Risk Assessment +Genetic Test	**GROUP 4** Risk Assessment +Health Coaching +Genetic Test
CONSENT/** **BASELINE VISIT**	Consent Survey Height, Weight, Waist, BP	Consent Survey Height, Weight, Waist, BP	Consent Survey Height, Weight, Waist, BP Blood Draw	Consent Survey Height, Weight, Waist, BP Blood Draw
RISK ASSESSMENT VISIT	Risk Assessment	Risk Assessment	Risk Assessment + Genetic Result	Risk Assessment + Genetic Result
6 WEEK SURVEY	On-line survey	On-line survey	On-line survey	On-line survey
3 MONTH SURVEY	On-line survey	On-line survey	On-line survey	On-line survey
6 MONTH VISIT	Survey Weight, Waist, BP Meds, Assess AE	Survey Weight, Waist, BP Meds, Assess AE	Survey Weight, Waist, BP Meds, Assess AE	Survey Weight, Waist, BP Meds, Assess AE
12 MONTH VISIT	Survey Weight, Waist, BP Meds, Assess AE, Labs	Survey Weight, Waist, BP Meds, Assess AE, Labs	Survey Weight, Waist, BP Meds, Assess AE, Labs	Survey Weight, Waist, BP Meds, Assess AE, Labs

**Consent may be obtained at a separate visit if HbA1c and/or lipid panel labs need to be performed for eligibility confirmation. If done separately Baseline visit should ocurr within 4 weeks of consent.

5.3.2. Study Specific Tests and Procedures

Measurements

Height

Height will be measured in centimeters to the nearest centimeter using a stadiometer, without shoes, and facing away from the wall.

Weight

Weight will be obtained using a zeroed electronic scale. Participants will be weighed without shoes or outer garments (sweaters, coats off) at this visit and all subsequent follow-up visits to the nearest tenth of a kilogram.

Waist circumference

Waist circumferencewill be measured after subject removes shoes and places feet hip distance apart. This will be taken against the skin, not on top of clothing. The point of measurement will be determined by locating a bony landmark, the right iliac crest. The CRC will make a horizontal mark with a pen or marker above their fingers to indicate the spot directly above the top of the iliac crest. The CRC will place the tape around subject's midsection at the level of the mark, maintaining a horizontal plane around the abdomen. This measurement will be taken and recorded 3 times and averaged. The tape measure will be released between each measurement.

BMI

Body mass index (BMI) will be calculated from these measurements (BMI = weight [kg] / ht [m]2)

Blood Pressure

Blood pressure measurements will be taken on the right arm (unless contraindicated) with an appropriate size cuff while participants are seated with the right arm supported at mid-atrial level. Participants are asked to refrain from eating, smoking, and exercise for at least 30 minutes prior to blood pressure measurements, and to sit quietly for at

least 5 minutes before the blood pressure measurement. Two measurements of BP will be taken with a two minute rest period between the measures, and averaged.

Blood collection for genetic testing

Participants in each of two genetic testing arms will complete venipuncture for peripheral blood sample collection for genetic testing of validated CHD RS10757274 and T2D RS7903146, RS1801282, RS5219 risk variants. Samples will be sent to Duke University Clinical Molecular Diagnostics Laboratory, which is CLIA-certified. DNA extraction will be performed as well as real time PCR allelic discrimination assays for RS7903146, RS1801282, RS5219, and RS10757274 (Appendix P.). Results (genotyping of alleles for SNPs of interest) will be returned by subject studyID number to the site research staff for entry into the REDCap database. Remaining blood samples will be retained by the lab until the end of the study, at which time they will be discarded.

Standard Risk Assessment (SRA) for CHD and T2D (need to take place no later than 4 weeks post randomization)

The SRA has been developed for this study based on the Framingham risk assessment and other known risk factors for CHD and T2D. The SRA consists of: FBG, age, gender, BMI, total cholesterol, HDL, BP, family history (number of first-degree relatives who have CHD (and age at diagnosis) or T2D, self-reported), and smoking (self-reported). A Framingham Risk Score and Diabetes Risk Score will be calculated for each patient along with other well-validated CHD and T2D risk factors, and all will be reviewed at the risk counseling visit. This method of presenting genetic risk data to patients has successfully been used for over 400 clinical study patients to be used by the provider (Appendix K., L., M., N.).

Health Coaching(HC) Intervention. Upon completion of their individual SRA Visit, participants in the two groups that include health coaching will be assigned to a trained health coach for a period of 5 months (n=200). At the SRA, the participant will fill out a "Current & Desired States Form" (Appendix C.). Then the participant will be given a folder containing information about what HC is, how the calls will be structured, and preparation materials for the calls (Appendix E.). An initial telephone call (60-75 minutes in length) with the coach will consist of a discussion on the role of the health coach and participant, the logistics of the sessions, and a discussion about the participant's self-assessment of health perceptions and goals. This self-assessment creates the foundation for the personalization of the behavioral intervention. From this point, the

participant schedules the remaining 9 biweekly sessions (30-45 minute in length) , for a total of 10 coaching calls over 5 months. All 10 telephone calls will be recorded for quality control and qualitative analysis purposes.

Self-discovery (initial) session. In the first HC call, participants are led through a process of self-discovery wherein they create a vision of health. The coaches assist participants in a self-assessment process to compare their personal goals to their current satisfaction in multiple domains of their lives. Areas that are discrepant (Appendix C.) are further explored for readiness to change. Participants then prioritize where to begin. They are encouraged to make skillful decisions that are congruent with their individual values, long-term vision and sense of purpose. Heavily supported by theory, participants are more likely to create self-sustaining agendas for themselves when they have considered the greater perspective of their lives. The coaching agenda, priorities and specific goals will be set by the participant; however the coach will regularly ask participants about self-assessment in terms of risk reduction via diet and exercise. Committing to small action steps on a biweekly basis, participants move toward self-identified health goals. Results of the self-assessment provide initial motivation for lifestyle behavior change.

During the initial call, participants are taught how to prepare for the HC sessions. They previously had received tools and information for preparation, including a "coaching prep-form", contained in the HC Packet (Appendix E.). The form is optional for the participant to use, and is organized to assist clients in briefly noting discussion points for the call including: successes since last call; obstacles encountered; problem-solving approaches tried; outcomes; upcoming potential obstacles; resources needed; small action-step commitments to be accomplished before the next call. While the general process is the same for all participants, the coaching content is highly tailored and personalized according to the individual's needs, readiness to change, and personal vision of health.

Additional biweekly calls. HC calls then follow the general template of the coaching prep form. All HC sessions begin with a brief check-in, reporting on specific action steps from the preceding week(s). Participants are trained to note success first, then to problem-solve and explore solutions for upcoming obstacles. Importantly, they learn from failed problem-solving attempts, which are non-judgmentally framed as "experiments" necessary for true learning. Non-judgmental framing is essential to maintaining rapport and encouraging clients to experiment with solutions without fear of failure. Participants then commit to new action steps toward their goals to be accomplished before the next call, and clarify what resources they will need to accomplish them. Of note, the health coaches will be blinded to the participants' genetic risk results; however, participants may choose to disclose them to the coaches, mimicking actual utilization of this information (Appendix D.).

Table 2. **Study Measures**	***Baseline***	***6 wks***	***3 mos***	***6 mos***	***12 mos***
Eligibility Screen & Informed Consent	X				
Demographic Questionnaire	X				
Family history of CHD & T2D	X				
Blood collection for genetic testing	X				
Primary Outcomes: Behavioral					
Wheel of Health	X	X		X	
Dietary Intake (NCI Multifactor Screener)	X		X	X	X
Physical Activity (SBAS)/Wellness Programs	X		X	X	X
Smoking Status	X		X	X	X
Medication Adherence (Morisky 4)	X	X		X	X
Primary Outcomes: Clinical					
Height for BMI calculation	X				
Weight	X			X	X
Waist Circumference	X			X	X
Blood pressure	X			X	X
Medications	X			X	X
Lab tests (fasting glucose, total cholesterol, HDL, LDL, triglycerides)	X				X
Fitness Status (Air Force Fitness Score)	X				X
Risk Status (FRS and T2D Risk Score)	X				X
Adverse Events Assessed				X	X
Potential Mediators					
Perceived Risk for CHD & T2D	X	X		X	
Worry, Self-efficacy	X	X		X	
Patient Activation	X	X	X	X	X
Stages of Change	X	X	X	X	
Psychosocial Risk Factors: Depression (BDI), stress level (PSS) social isolation (social support item) Hostility (cook-medley)	 X X			X	

6. Adverse Events

An adverse event (AE) is the development of an unfavorable or unintended sign, symptom, disease or the deterioration of a pre-existing condition that occurs while a patient is enrolled in a clinical trial, whether the event is considered related or unrelated to the study interventions. An adverse event is any adverse change from the subject's baseline condition, including any clinical or lab test abnormality that occurs during the course of research after intervention has started.

6.1. Adverse Event Reporting

If at any time during the study protocol a subject develops an adverse event), he/she should first contact their primary care physician. In addition, the site PI and site coordinator as well as the coordinating center PI will be available to answer questions. The site coordinator will assess AEs at the 6 and 12-month visits and will record all reported events in the adverse event log including the subject's ID, date, and event description, duration and intensity. CRC will inform the principal investigator, who will consult with co-investigators on the action that should be taken. The action and date of implementation will also be recorded in the adverse event log. The investigators will participate in classifying events as "serious" or "non-serious" (see section 6.2), as well as "non-attributable," "possibly attributable" or "attributable" to the intervention (unlike a pharmaceutical trial where known side effects exist, the classification of "expected" vs. "unexpected" is inappropriate for this behavioral intervention).

Information for the adverse event must be recorded on the appropriate page of the case report form (CRF). Only data on AEs grade 3 and higher will be recorded in the database. AE assessment will be done according to CTCAE v.4 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Note: As a behavioral intervention study there are no expected AEs. However, as a precaution since the Beck Depression Inventory (BDI) is administered at Baseline and 6 Month Visits the following procedures will be followed.

As a part of the baseline and follow-up surveys, subjects will complete a depression assessment (Beck Depression Inventory). Answers to the following question need to be closely monitored:

CRC will review the survey immediately after subject has completed it at baseline and 6 month visits. If the subject indicated suidical ideations on the related item he/she will be referred to a therapist for evaluation.

Referrals for psychological care will be completed by the CRC at Travis site according to the David Grant Medical Center policies and procedures outlined in their site protocol.

6.2. Serious Adverse Events (SAE) Reporting

Study site personnel will immediately alert the site PI as well as the coordinating center PI of any serious adverse event (defined below) experienced by a subject that is related to the study or results in death. In addition, serious

adverse events related to study must be reported to regulatory authorities according to the definitions and timelines specified in the local laws and regulations.

A Serious Adverse Event is any untoward medical occurrence that:

- Results in death
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe;
- Requires inpatient hospitalization or causes prolongation of existing hospitalization;
- Results in significant or persistent disability or incapacity (defined as a short or long term, temporary, chronic or permanent disruption of the patient's ability to carry out normal life functions)
- Is a congenital anomaly or birth defect
- Results in the development of drug dependency or drug abuse or
- Is an important medical event (defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical or surgical) to prevent one of the other serious outcomes listed in the above definition). Examples of such events include, but are not limited to intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization).

Non-Serious Adverse Events – all other events that do not meet the SAE criteria.

7. Data Reporting/Regulatory Considerations

7.1. Data Entry

The research coordinators, data manager and PI are responsible for ensuring that data abstraction (information required by the protocol) is completed in a timely manner for every subject enrolled on study. De-identified

subjects' data will be entered by the site CRC into a secure electronic database (REDCap) by CGSU data managers. REDCap is a secure and HIPAA compliant web-based application .The data are backed up daily and stored on a secure server managed by Duke University School of Medicine IT Department. The PI, study coordinators and the CGSU data management staff are the only key personnel who will have access to the password-protected database. Subjects' surveys will also be administered through REDCap. Subjects will be assigned access to the system upon study registration and will be provided with the necessary directions by the study coordinators. The CGSU data management staff and PI will systematically review the information entered into the database. Errors or omissions will be documented and maintained with the study files. When the database has been declared complete and accurate, the database will be locked.

7.2. Data Storage and Confidentiality

Subject confidentiality will be ensured at all times. Each subject will be assigned a unique study ID. Only key research personnel will have access to the list of study IDs and patient names for the purposes of scheduling follow-up surveys and obtaining laboratory test results. Subject identifiers will not be made available to any other institutions, hospitals, insurers, or agencies. The results of studies emerging from this work may be published but individual subjects will not be identifiable in these publications.

It is the PI's responsibility to ensure the subjects' privacy. However, in compliance with federal guidelines, the investigator will permit a representative from the coordinating center, Duke Clinical Genomics Study Unit (CGSU)-Center for Applied Genomics and Precision Medicine (CAGPM) , to review that portion of the subject's medical record that is directly related to the study. This will include all relevant study documentation including medical histories to verify eligibility and laboratory test results to verify transcription accuracy. As part of the required content of informed consent, the subject will be informed that his/her medical record, may be reviewed.

7.3. Records Retention

The Investigator must retain source documents, and case histories designed to record all observations and other data pertinent to the investigation (e.g. case report form) for the maximum period required by applicable regulations and guidelines, or Institution procedures.

If a change in the PI occurs, the records shall be transferred to a mutually agreed upon designee (e.g., another Investigator, IRB).

8. Statistical Considerations

8.1. Sample Size/Power Calculation

The objective of the power analysis was to determine the minimum sample size needed to reject the null hypothesis that the three-way genetic information by health coaching by time interaction was equal to zero in the context of a longitudinal general linear mixed model. The model was assumed to have two levels of genetic information (present or absent), two levels of health coaching (present or absent), and five levels of time (0, 1.5, 3, 6 and 12 months after randomization). In producing the required sample-size estimates, we further assumed that each of the four group means over time would take on standardized mean values. The type I error rate was set to be no greater than .025 as there will be two primary analyses. Controlling each one at no greater than .025 controls the overall experiment type I error rate to be no greater than .05. Calculations indicated that with a sample size of 99 subjects per group, or 396 total, the power to reject the null hypothesis concerning the three-way interaction was .80. Assuming an attrition rate of at most 15% and the current pilot diabetes study attrition of 11%, over the 12 month time period we calculated a possible required sample size of (396/.86)=460 to attain the target sample of 400. Sample size calculations are not provided for detecting the direct effects or interactive effects of the two interventions pooled over time, primarily because we expect the genetic information by health coaching interaction to change over time, as reflected in the three-way interaction.

Due to delayed/slow recruitment the sample size is revised as following (modification approved in contract amendment):

A reduced sample size, but collecting data out to 12 months as planned:

a. Coming from the stance that we want to preserve as much of the original thinking behind the power analysis as possible, we eliminated the calculation and testing of the three way

interaction which was originally planned. This three way interaction said that the interaction of Health Coaching and genetic testing peaks at 6 months. The idea was that there was a synergy between genetic testing and health coaching which would push health behavior means for the subjects receiving both components to far greater than the individual effects of either one. Elimination of the three way interaction takes away our ability to say when this occurs (time).

Pattern	Type I error rate	Power	Within Person Correlation	Sample Size per Group	Total Sample Size
1	.025	.80	.350	25	100
1	.025	.85	.350	27	108
2	.025	.80	.350	44	176
2	.025	.85	.350	49	196
3	.025	.80	.350	56	224
3	.025	.85	.350	63	252

b. Means for the four groups pooled across time showing JUST the coaching by genetics testing interaction for each pattern.

c. Examining the health coaching by time and the genetic testing by time interactions. Assuming the same means over time for pattern 2, the means for the two interactions would be as shown in the two tables immediately below.

Health coaching by time interaction for pattern 2

	NO HC	HC
0	0.05	0.05
1.2	0.15	0.5
3	0.275	0.95
6	0.125	1.5
12	0.05	0.85

Genetic testing by time interaction for pattern 2

	No Genetics	Genetics
0	0.05	0.05
1.2	0.225	0.425
3	0.425	0.8

6	0.525	1.1
12	0.225	0.675

d. Results of power calculations when the three way interaction for the groups, as well as the three way interaction for time by health coaching by genetic testing are eliminated. These are the power for detecting the interaction which is the smallest (the genetic testing one).

Pattern	Type I error rate	Power	Within Person Correlation	Sample Size per Group	Total Sample Size
2	.025	.80	.350	43	172
2	.025	.85	.350	49	196

While we will have lost the power to examine a 3-way interaction (health coaching by genetic risk testing by time), with the participants, we will still be able to:

1) Examine 2 way interaction effects of health coaching by time and genetic risk testing by time (estimated minimum sample needed 172-196);
   AND/OR
2) Examine the 2 way interaction of health coaching and genetic risk testing (comparative effectiveness without time point considered in interaction; estimated sample needed 176-196).

Assuming an attrition rate of at most 15% the required minimum sample size is 212.

8.2. Analysis Plan

Demographic characteristics of the sample (income level, age, gender, race/ethnicity, educational level) will be provided using descriptive statistics to describe the overall sample and by group to ensure that randomization was effective. Distribution of variables will be determined prior to further statistical analysis. SAS software (80) will be used for all analyses.

To address the primary aims, mixed models will be used. The first aim is to determine the direct and interactive effects of genetic risk information incorporated with standard CHD/T2D risk counseling and a health coaching intervention for CHD/T2D on behavior change (diet, physical activity) in AF primary care patients over 12 months. The goals of the statistical analysis will be to quantify: (1) the extent to which genetic risk counseling influences the trajectory of change in physical activity and diet measures from baseline to 3, 6, and 12 months; and (2) the extent to which the genetic risk information augments the trajectory of the effects of health coaching on diet and physical activity measures over the same time period. We will fit two general linear mixed models to these data (81), with

physical activity and diet measures at each of the five points in time. For either model, there will be three independent variables: genetic risk information (G) with values of 1 or 0, health coaching (HC), also with values of 1 or 0, and time since randomization, with values of 0, 3, 6, and 12 months. Within the context of the linear mixed model, we should observe a statistically significant three way interaction of time by genetic information by health coaching. The particular type of longitudinal model selected for analysis will depend upon preliminary analyses of the data. For example, a subject specific (also called hierarchical) model with random intercept and slope assumes that within subject variances increase or decrease over time. A model hypothesizing only a random intercept does not assume that within subject variances show this pattern. Another consideration will be the extent of missing data; some longitudinal models are better than others at handling missing data.

The second part of the primary analysis will determine the direct and interactive effects of genetic risk information incorporated with standard CHD/T2D risk counseling and a health coaching intervention for CHD/T2D on metabolic outcomes (fasting blood glucose, SBP, BMI, waist circumference, LDL, triglycerides, total cholesterol) over 12 months. The statistical analysis will be the same as above except that the dependent variables will be fasting blood glucose, SBP, BMI, waist circumference, LDL, triglycerides, and total cholesterol.

To address Aim 2, we will examine the mediating effects of level of CHD/T2D genetic risk (number of risk alleles) and consequent reclassification of FRS in the case of CHD risk (decreased, neutral, or increased) on behavior change (diet, physical activity) at 6 months. The goal of this analysis is to quantify the extent to which subgroups of patients exhibit different levels of change in diet and physical activity behavior at 6 months post randomization depending on reclassification of FRS and T2D risk level. We also want to know if the differences depend on whether or not the genetic results were delivered in the context of health coaching. For these analyses, we will use results from only the two groups of patients randomized to receive genetic testing (n=200). Because we will have only two points in time, we will use the simpler linear regression model, with the dependent variable being either diet or physical activity collected at 6 months post randomization. There will be six independent variables: the outcome measured at baseline (a covariate), the results of the genetic testing (entered as two dummy coded variables), a dummy coded variable to indicate the presence or absence of health coaching, and two dummy coded variables representing the interaction of health coaching and the results of genetic testing. We are particularly interested in comparing the diet and physical activity changes of patients whose genetic test results move their Framingham risk or T2D levels either up or down (based on number of higher-risk alleles) to those whose genetic

results do not. In our regression analysis, this comparison will be facilitated by creating two dummy coded variables; dummy 1 will be 1 if the patient has 'low' risk based on number of risk alleles and zero otherwise. Dummy 2 will be 1 for patients with 'high' risk based on number of risk alleles and zero otherwise. When group membership is coded in this way, the regression coefficients (parameters) fit to the data represent differences in adjusted group means. "Adjusted" refers to group differences on outcome measures obtained at 6 months, while statistically eliminating any differences between groups on outcomes at baseline. Thus, the regression coefficient for dummy 1 will reflect the differences in average adjusted outcome at 6 months between patients whose genetics results shifted their risk down and patients whose results did not affect their risk. Similarly, the regression coefficient for dummy 2 will reflect differences in adjusted outcome means comparing patients whose risk shifted up to those whose risk was unaffected by their genetic test results. The interaction components of this model will allow us to assess whether or not these comparisons significantly differ depending upon whether or not the patient received health coaching.

Secondary analyses will examine the mediating effects of perceived CHD/T2D risk, self–efficacy, worry, patient activation and readiness for change on the effects of genetic risk information on diet and physical activity at 6 months post randomization. The analytic strategy will be to determine the extent to which genetic risk treatment effects on diet and physical activity occur subsequent to treatment effects on perceived CHD/T2D risk, self-efficacy, worry, patient activation and readiness for change. For example, one set of analyses will estimate the direct relationship between genetic risk counseling and changes in physical activity at 6 months (independent of evaluation of the effects of treatment on perceived risk). Additionally, the extent to which genetic risk counseling influences perceived risk at 6 weeks and 3 months post randomization, *which in turn affects behavior change at 6 months,* will be assessed. This analysis will be repeated using diet as the dependent variable. Then both will be repeated using self-efficacy, worry, patient activation and readiness for change as mediators. In each analysis, mediation will be estimated via a series of linear regressions. Mediation will be *tested statistically* by examining the empirically generated sampling distribution of the parameters involved in the mediational hypothesis: the effect of treatment on the mediators at 6 weeks and 3 months, the effect of the mediators at 3 months on the dependent variable at 6 months, and the product of these effects. We will use bootstrapped sampling distributions of the parameters involved in each meditational hypothesis. Recent work supports this method rather than the more traditional Sobel tests, especially with smaller samples.

9. Protection of Human Subjects

9.1. Ethical Considerations

This study will be conducted in compliance with the protocol, Good Clinical Practice guidelines established by the International Conference on Harmonization, and the ethical standards set forth in the Declaration of Helsinki 2004 (available at: http://www.wma.net/e/policy/b3.htm).

9.2. Institutional Review

Prior to patient accrual, this protocol and the protocol informed consent must be approved in writing by the the DUHS Institutional Review Board (IRB). A signed and dated statement that the protocol and informed consent have been approved by IRB will be kept in the study binder in the Principal Investigator's staff office. The term of study approval will not exceed one year. A progress report will be submitted annually to the IRB and re-approval obtained to continue the study. The IRB will also approve any significant changes to the protocol as well as a change of PI. Records of all study review and approval documents will be kept on file by the PI and/or his staff. Adverse events will be reported to the IRB per established policy. The IRB will receive notification of the completion of the study and final report within 3 months of study completion or termination. The PI will maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents. Initial approval letters from each site's IRB will be obtained and submitted to Duke IRB prior to the initiation of the study. During the study conduct sites IRB continuing review letters will be obtained and submitted to Duke IRB annually.

9.3. Monitoring Plan of Participating Sites

Random-sample data quality and protocol compliance audits will be conducted by a team of assigned CGSU staff. Three monitoring events are suggested as a guideline, depending on the quality and volume of data. The first compliance audit will be initiated after 3-5 subjects are enrolled at a site. The second audit will be conducted at study mid-term (after 50% of enrollment is reached) and the last one at the end prior to the data lock (after enrollment is complete and final data has been entered). Audits by the coordinating center may entail: (1) shipping source documents and research records for selected patients from participating sites to the coordinating center for audit, or (2) on-site auditing of selected patient records at participating sites. Audits carried out during the clinical

and reporting phase of this study will ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and all applicable laws, rules and regulations. This includes inspection of study-related records by the coordinating center auditor and/or its designee, IRB representatives, health authority representatives or the relevant regulatory authorities at any time.

9.4. Protocol Amendments

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Prior to starting the study, the protocol will be approved by each institution's Institutional Review Board or Independent Ethics Committee (IEC). Amendments to the protocol may be made only with consent of the lead site and the principal investigator and are subject to IRB approval prior to instituting.

9.5. Informed Consent Process

The PI or designee will fully explain the purpose and potential risks and benefits of the study to the subject prior to enrollment and address any questions posed by the subject. In accordance with federal guidelines, all subjects will sign a statement of informed consent which has been approved by the IRB. The subject will receive a copy of the executed consent document. The signed consent will be retained at the investigative site for each subject. The informed consent document serves as authorization as defined under HIPPA and contains the appropriate statements regarding privacy and confidentiality of protected health information (PHI) as well as information on withdrawal from the study. The PI will report to the IRB any changes in the research protocol and all unanticipated problems involving risks to human subjects and others. No changes will be made in the research activity without IRB approval. The investigator or designee will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits, and any discomfort the study may entail. Each subject will be informed that participation in the study is voluntary and that he may withdraw from the study at any time and that withdrawal of consent will not affect his subsequent medical treatment or his relationship with the treating physician.

The informed consent will be given by means of a standard written statement, written in non-technical language. The subject will read and consider the statement before signing and dating it, and should be given a copy of the signed document. No patient will enter the study before his informed consent has been obtained.

9.6. Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

It is the responsibility of the research staff to ensure that protocol subjects received, understands, and signs the informed consent document before enrolling the patient onto this trial. Personnel must provide a HIPAA form and obtain acknowledgment before the subject participates in this study.

10. Risk/Benefit Assessment

10.1. Risks of Drawing Blood:

Risks associated with drawing blood from the subjects arm include minimal discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

10.2. Potential Risk of emotional reactions to the genetic tests results

Participants may have emotional reactions to learning that they do- or do not— carry a gene change for heart disease or diabetes. Participants who feel distressed will be directed to the site study doctor and he may refer them to a genetic counselor or other provider for further assistance as necessary

10.3. Potential Risk of Loss of Confidentiality

Participant information and data will be de-identified and stored on a secured server (REDCap) by the PI and study staff. Hard copies of data will be stored in a locked file drawer in a locked office. Participants may refuse to answer any questions that cause them to feel uncomfortable.

10.4. Alternative

The alternative for potential participants is not participating in the study.

10.4. Benefits:

If participant is enrolled and continues partipation through the SRA visit, he/she will learn about their specific risk for future CHD and T2D based on their Framingham Risk and Diabetes risk score.

10.5. Costs to the Subject – there will be no costs to the participant.

10.6. Compensation

According to Air Force policies and standard procedures, participants will receive a token of appreciation for their participation at completion of the baseline and 6 and 12 month follow up visits. This will be a water bottle, pen or similar items. Participants will not receive cash or equivalent compensation for their participation in this study.

References:

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2. McCarthy, M.I., *Genomics, type 2 diabetes, and obesity.* N Engl J Med, 2010. **363**(24): p. 2339-50.
3. Florez, J.C., et al., *TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program.* N Engl J Med, 2006. **355**(3): p. 241-50.
4. Sheridan, S.L., et al., The effect of giving global coronary risk information to adults: a systematic review. Archives of Internal Medicine, 2010. 170(3): p. 230-9.

5. Brautbar, A., et al., *Impact of adding a single allele in the 9p21 locus to traditional risk factors on reclassification of coronary heart disease risk and implications for lipid-modifying therapy in the Atherosclerosis Risk in Communities study.* Circ Cardiovasc Genet, 2009. **2**(3): p. 279-85.

List of Appendices.

Appendix P. Validation Summary