PROPOSAL FOR HUMAN RESEARCH

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APPROVED
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60 MDG IRB
TRAVIS AFB CA

CLINICAL INVESTIGATION FACILITY
60th Medical Group (AMC)
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FWA00003321, DoD 50004, IRB00002726

For assistance, call the IRB Coordinator at (phone # redacted 6Feb20

1. Title of Investigation

Assessment of Coronary Artery Calcium in Active Duty Enlisted Military Members with 10 or More Years of Service

2. Investigator and Investigation Staff

Name	Rank	Study Role	Date of Investigator Training	Staff/ Resident/ Fellow	Dept/ Office Symbol	Phone	DoD Assurance Number	E-mail
	Capt	PI	30 Jun 15	Resident	SGQX		50004	
name/contact inf o redacted 6Feb20	Lt Col	AI	16 Feb 17	Staff	SGQX	phone number redacted 6Feb20	50004	email addresses redacted 6Feb20
	CTR	SC	16 Mar 16	Staff	SGSE			
	CTR	SC	27 Apr 15	Staff	SGSE			
	CTR	CRN	19 Jun 17	Staff	SGSE			
	CTR	RA	28 Jan 16	Staff	SGSE			
	CTR	RA	05 Aug 17	Staff	SGSE			

Medical Monitor (MM): Dr. Brad Williams

3. Facility and/or Contractor

All subject enrollment, data collection and data analysis will be conducted at David Grant US Air Force Medical Center, Travis Air Force Base, California.

4. Purpose of Investigation

While the military is making strides towards improving the health and habits of service members, there are many aspects of the military culture that negatively affect the cardiovascular health of military members. Smoking/tobacco use, poor eating habits with MREs and ready access to fast food establishments on base, inconsistent exercise, the socioeconomic status of enlisted members and the stress of deployment are all factors that contribute to increased risk of cardiovascular disease during military service. Currently the calculation of a patient's Framingham risk score is the most commonly used method of calculating a patient's cardiovascular risk, and this calculation is based on age, smoking history, blood pressure, and lab values and compares it to a general population's risk. By the use of a cardiac CT scan, a Coronary Artery Calcium (CAC) score can be calculated and used to estimate the degree of atherosclerosis already present in each patient's coronary arteries, and thus establishing their risk of future cardiovascular events. CAC scoring is a more patient-specific way of identifying cardiovascular risk. The purpose of this study is to assess the prevalence of atherosclerosis in enlisted military members with at least 10 years of service and one or more cardiovascular risk factor and to determine if their risk of a cardiovascular event is higher than predicted by the Framingham score. If CAC scoring is demonstrated to be more accurate, particularly if it is more likely to detect risk, it may be used in the future to better risk stratify this population of the military. The CAC results in patients could also be a motivating factor to create changes in the military culture to attempt to mitigate these risks and create a healthier fighting force.

5. Category of Study and Risk Assessment

5.1. Category of Study

☐ **Medical Readiness** ☐ **Prevention** ☐ **Utilization Mgmt.** ☐ **Managed Care** ☒ **Diagnosis/Treatment/Other**
This study is placed in Diagnosis/Treatment/Other category as this will help better assess the risk each individual has of having a cardiovascular event in the future based on their Coronary Artery Calcium score.

5.2. Proposed Risk:

☐ Minimal Risk
☒ Greater Than Minimal Risk

This study is greater than minimal risk as a cardiac CT scan will be used, thus exposing the study subject to more radiation than on a typical day for that subject.

6. Proposed Research

6.1. Background and Review of Literature:

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in the United States (1). LDL lipoproteins are positively associated with the development of coronary artery disease. The most recognized guidelines for the screening and treatment of dyslipidemia for the prevention of cardiac events are The National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III), published by the National Heart Lung and Blood Institute. These guidelines focus primarily on LDL-C concentrations (2). The recommended treatment of dyslipidemia for primary and secondary prevention of cardiac events consists of dietary and lifestyle changes, lipid-specific pharmacotherapy with primarily HMG-CoA reductase inhibitors (statins) and non-lipid agents such as aspirin. Specific goals for the initiating and targeting of therapy are based on cardiac risk factors and the calculation of a Framingham Risk Score (FRS) if indicated. Yet, approximately three-quarters of all "first-time" myocardial infarctions occur in individuals who would not have been eligible for pharmacotherapy with a statin or aspirin based on the adopted risk stratification algorithm (3).

The FRS was developed by Wilson et al in 1998 and has become standard of care for estimating risk of a cardiovascular event over the next 10 years. The estimation takes gender, age, smoking status, systolic blood pressure, total cholesterol and HDL into account when predicting risk (4). Scores are converted into percentage of risk over the next 10 years using a table created by Wilson et al. Individuals with scores of 0-10% are considered low risk. A score of 11-15% indicates low-moderate risk, while a score of 16-20% indicates mod-high risk. Those with scores of >20% are considered high risk, while those with known coronary artery disease or acute coronary syndrome are considered very high risk (2). While the FRS at times is a basis for treatment decisions, this system of calculating risk is not individualized, and does not take into account other contributing factors such as family history, weight, etc.

This concerning discordance between FRS scores and "first-time" myocardial infarctions has led to the search for additional risk stratification tools for CAD to include novel biomarkers such as high sensitivity C-reactive protein (hs-CRP), Brain Natriuretic Protein (BNP) and lipoprotein subclasses, as well as imaging studies such as coronary artery calcium (CAC) screening with computed tomography (Cardiac CT), carotid intimal medial thickness testing (CIMT) with ultrasound and endothelial function assessment with brachial artery ultrasound. Many of these screening tools, when added to a FRS improve diagnostic accuracy. For instance, the Reynolds risk score adds hs-CRP and family history (5). Coronary calcium is unique to these other markers in that it is pathognomonic of coronary atherosclerosis (6). Multiple studies have shown calcium scoring to be superior to FRS in diagnostic accuracy. A high calcium score increases the risk of cardiac events greater than 10 fold. Conversely, a calcium score of zero has a negative predictive value (NPV) of 99%. This translates into an area under the receiver-operator curve (AUC) that increases from 0.67 with FRS to 0.75 for CAC in asymptomatic individuals (7). The incremental accuracy is even more impressive in uncomplicated type 2 diabetics. The AUC is 0.92 with CAC compared with 0.74 using the United Kingdom Prospective Diabetes Study Risk Score and 0.60 using the FRS (8). Despite the higher risk classification of type 2 diabetics, the FRS became less accurate in this study population, while the accuracy of CAC was improved. This suggests a disproportionate discordance between traditional risk assessment

tools and actual events in the uncomplicated type 2 diabetic patient compared with unselected asymptomatic patients.

CAC scores are reported as a numerical value and a percentage for age that is then regarded in terms of risk categories. A score of zero with no cardiovascular risk factors indicates no evidence of CAD and thus a very low risk of cardiovascular event in the next ten years. If the individual has cardiovascular risk factors with a CAC score of 0, they are considered moderately low risk. A score of 1-100 and a percentage for age percentile less than 75% indicates mild to moderate evidence of CAD and therefore indicates moderately high risk. A score of 101-399 or a percentage for age greater than 75% indicates moderate to high evidence of CAD and therefore is considered high risk with possible current partial blockage of coronary arteries. A score of >400 or any CAC score >100 with a >90% percentage for age indicates extensive evidence of CAD and thus high risk of cardiovascular event in the next ten years and could indicate further testing is needed to address potential majority blockage (9, 10).

A consensus report issued by the American College of Cardiology and the American Diabetes Association emphasizes the concept of a global cardio metabolic risk. Factors that increase the risk of cardiovascular disease include dyslipoproteinemia, hypertension, diabetes and the prediabetic states such as insulin resistance or hyperglycemia, and central obesity. Smoking and sedentary lifestyle exacerbate the risk. The epidemic rise in the prevalence of one or more of these risk factors has created a heterogeneous population at risk that is perhaps not well represented by the traditional Framingham study population, which commenced in 1948.

The American College of Cardiology (ACC) and the American Heart Association (AHA) recognize the incremental benefit of CAC screening and endorse its use in intermediate risk individuals with a FRS between 10-20%. The SHAPE (Screening for Heart Attack Prevention and Education) Task Force report goes further, publishing guidelines calling for the use of CAC scanning or CIMT as part of a nation-wide screening program to detect CAD in males 45 years and older, and females 55 years and older (10).

Active duty military members are thought to be inherently healthier than their civilian counterparts due to the selection bias of health screening upon entry into the military. Webber et al. recently published a report in JAMA which showed a dramatic decline in the prevalence of atherosclerosis at the time of autopsy in US service members who died in the current conflicts in Iraq and Afghanistan, when compared to studies from the Vietnam and Korean War eras (11). It was suggested that there may be selection bias in an all-volunteer force, creating a "healthy warrior" phenomenon and that US service members today are healthier than in previous eras. Interestingly, in their study they found that "older age; lower educational level; higher BMI at military entrance; and prior diagnoses of dyslipidemia, hypertension, and obesity were associated with a higher prevalence of atherosclerosis." These risk factors are consistent with known risk factors for atherosclerosis. The study seems to demonstrate that service members dying in combat are not representative of the general U.S. population. However, in contrast to the conclusions drawn from this study, it also seems to demonstrate that these service members are not representative of the military population as a whole, either.

While the United States, as well as the developed world is in the midst of an obesity epidemic, which brings with it the accompanying metabolic risk factors mentioned above, the military is by no means immune to this trend. According to the 2008 Department of Defense Survey of Health Related Behaviors Among Active Duty Military Personnel, the prevalence of "overweight" service members among active duty personnel, as defined by a body mass index (BMI) above 25 kg/m² was 60% overall. The trends for obesity, defined as a BMI of greater than 30 kg/m², have likewise increased from 5% in 1995 to 12% in 2005, and 13% in 2008 (12). While it is true that the percentage of eighteen year-olds meeting the military's height and weight standards has decreased, it is also true that eighteen year-old applicants tend to have a higher BMI than their counterparts in the general population, which seems to argue against a "healthy warrior" selection bias (13, 14). Despite the efforts of the military to enforce and encourage physical fitness, the prevalence of a medical diagnosis and visit for obesity increased 2.5 fold from 1998 to 2008 (15). In addition, 15% of males and 20% of females reported difficulty meeting their service standard for weight and/or BMI (12).

Smoking continues to be a problem for US service members. Despite a significant decline in the rates of smoking from 51% in 1980 to 30% in 1998, it climbed to 34% in 2002 and has remained constant since that time. Likewise, the rates of heavy smoking declined sharply from 1980, but remained constant for the decade spanning 1998 to 2008. When compared to the civilian population, the overall rates are similar at 30% for military members vs. 29% for civilians. When broken down by age, the rates are higher for military members between the ages of 18-35, but lower between the ages of 36-64 when compared to civilians. When broken down by junior and senior officer and enlisted corps, the differences are striking; with rates of 40% among E1-3 vs. 10% among O1-3, and 21% among E7-9 vs. 5% among O4-10. 15% of all active duty military members initiated smoking after joining the military. And 30% of all current smokers began smoking after joining the military (12). Overall, the relatively high rate of smoking across the enlisted ranks suggests a culture of smoking throughout a military career that cannot be explained by adolescent recreational use.

Dietary behaviors among US service members also appear to be less healthy than their civilian counterparts. In gathering data to promote the Healthy People 2010 objectives, the 2008 DOD health behaviors survey revealed that only 12.6% of all personnel reported consuming greater than 3 servings of fruit per day, compared to a civilian estimate of 28%. Only 14.2% of service members reported consuming greater than 3 servings of vegetables per day compared to a civilian estimate of 49% (12). In many cases US service members have limited access to food options especially earlier in their careers when they are required to live in dorms and receive food allowances at the base dining facilities. Meals Ready to Eat (MRE's) are provided to service members during training exercises and deployments. MRE's contain on average of 1200-1300 calories apiece, with a goal of service members consuming a total of 3800 calories per day. They are high in fat (36%) and carbohydrates (51%) and low in protein (13%) and fiber (16). In an editorial accompanying the study by Webber et al, the author concluded "it is highly likely that the main finding of this study is valid: the prevalence of atherosclerosis in young men today is much lower than the prevalence in the Korean or Vietnam War eras. If these findings are

generalizable to the US population as a whole, then the cardiovascular health of the US population may have improved appreciably over the past 6 decades (17)."

It is tempting to conclude from this study that population health initiatives in the US, and more specifically the military, have led to a dramatic decline in rates of atherosclerosis in our younger population. It is also tempting to conclude that the current military lifestyle represents a model for healthy living and one that perhaps should be adopted by the US population as a whole. However, this conclusion is assuming that the warriors who died are both representative of the younger US population as a whole and the broader US military population, respectively. An alternative explanation for the findings by Webber et al. may be that the US service members accounting for the majority of deaths from combat and unintentional injuries are indeed healthier, but are not representative of the military community at large. Service members must undergo a thorough health and fitness screening process prior to each deployment. Members that do not pass are not deployable. Furthermore, within each service, there are additional screening measures for entry into occupations that are more likely to expose a service member to the risks of combat. The "healthy warrior" phenomenon, therefore likely exists only after multiple layers of screening, and is not likely present within the greater US military population.

Based on the prevalence of obesity and accompanying cardiovascular disease risk factors mentioned above, the military population is unlikely to be much healthier than the age-matched US population. In fact, it may be that the rates of atherosclerosis in US service members are higher than in their civilian counterparts. It is quite possible that the environment and lifestyle of the military may both select for and exacerbate cardiovascular risk. The Prospective Army Coronary Calcium Project, as reported by Taylor et al, showed that traditional cardiac risk prediction tools significantly underestimate subclinical atherosclerosis in a low risk unselected screening cohort of 650 active duty Army personnel between the ages of 39-45 years of age (18). The prevalence of coronary calcium was 20.6% for males and 4.3% for females. In a 3 year follow up of 2000 subjects from this study, coronary calcium was associated with an 11.8 fold increase in cardiovascular events in males. There were no events in women in this study, likely due to low numbers. The study also deemed calcium scoring cost effective at $37,633 per quality-adjusted life year saved.

Given that the true rates of atherosclerosis within the greater military population are unknown and that the cluster of cardio metabolic risk factors are present at a relatively young age and in greater numbers than the general population, we aim to study the prevalence of subclinical atherosclerosis in US enlisted service members with one or more cardio metabolic risk factor using coronary artery calcium scoring with cardiac computed tomography. While the military has not adopted the SHAPE Task Force guidelines, or any other screening protocol involving imaging based modalities, the value of using risk factors to select individuals who may stand to benefit from the greater predictive power of coronary artery calcium scoring may prove to be useful in this population. This approach could be key to understanding the prevalence of subclinical atherosclerosis, measuring the effect of population health initiatives on rates of atherosclerosis over time and ultimately improving our ability to meet the stated objective of DoD health promotion, which is to return the veteran back to society in relatively good health.

6.2. Hypotheses or Research Questions or Objectives:

Hypothesis: Enlisted military members with 10 or more years of service and at least one cardiovascular risk factor will demonstrate a higher risk of future cardiac events as assessed by coronary artery calcium scoring than the risk calculated by the Framingham Risk Score.
The primary aims of this study are as follows:

1) Determine prevalence of atherosclerosis in active duty enlisted military members with 10 or more years of military service and at least one cardiovascular risk factor using coronary artery calcium scoring.

2) Assess the rate of reclassification of subjects from one risk category using Framingham Risk Scores (FRS) to another risk category using the results of the Coronary Artery Calcium (CAC) score.

3) Compare FRS to the CAC percentage for age risk score for enlisted subjects with at least 10 years of military service and at least one additional cardiovascular risk factor to determine how well the results correlate with one another.

The secondary aims of this study are as follows:

1) Compare CAC scores between each group in the following categories to see if there is associations between these categories and formation of calcified plaques:
    a. Those meeting the criteria for metabolic syndrome vs. those not meeting criteria (See attachment 1 – Diagnostic Criteria for Metabolic Syndrome)
    b. Those who lived in the dorms for >5 years compared to those living in the dorms for <5
    c. Those with PT test failures vs. those without
    d. Number of years of military service in the following groups: 10-14 years, 15-19 years 20-24 years and 25+ years
    e. Those with 1 risk factor vs. 2 risk factors, vs. 3 risk factors, vs. 4 risk factors, vs. 5 risk factors (as listed in the inclusion criteria section).

2) Compare FRS to CAC cardiovascular risk for each of the following categories:
    a. Those meeting the criteria for metabolic syndrome vs. those not meeting criteria
    b. Those who lived in the dorms for >5 years compared to those living in the dorms for <5
    c. Those with PT test failures vs. those without
    d. Number of years of military service in the following groups: 10-14 years, 15-19 years 20-24 years and 25+ years
    e. Those with 1 risk factor vs. 2 risk factors, vs. 3 risk factors, vs. 4 risk factors, vs. 5 risk factors (as listed in the inclusion criteria section)

6.3. Relevance/Significance:

- One of the mottos of the military medical corps is to preserve the fighting force. This concept is essential to the military branches accomplishing their missions. Through public health information and research studies, the military is pushing to change the military culture to support a healthier active force, thus leading to a healthier retiring population. Recognizing the need for further change in the military culture could lead to new policies and support for military members that could reduce the risk of atherosclerosis and heart disease in the future. Of those that died in combat in the Iraq/Afghanistan conflicts, 8.5% demonstrated evidence of atherosclerosis on autopsy (9). Due to higher smoking rates, obesity, MRE consumption, access to fast food on base and stress of deployments, enlisted military members with more than 10 years of military service will likely demonstrate a higher prevalence of atherosclerosis. Understanding the prevalence in this group could lead to changes in health initiatives and could lead to further studies in the future that use CAC scoring to measure the effect of new population health initiatives over time.

- For the subjects enrolled in this study, learning about their personalized cardiovascular risk could motivate life style changes that may decrease their likelihood of having a significant cardiac event in the future. This could greatly improve their quality of life, potentially prolong their lives and decrease costs of healthcare over time.

6.4. Research Design and Methods:

- **Design:**
  - This study is designed to be an observational study to determine the prevalence of atherosclerosis in enlisted military members with 10 or more years of service. The study is also designed to determine if coronary artery calcium scoring predicts higher or lower cardiovascular risk scores for enlisted military members with 10 or more years of service than the Framingham risk score predicts. (See flow diagram below).

- **Methodology:**

  - **Recruitment:** (See Recruitment section 6.7 below for more information).

  - **Enrollment/Consent:** (*For flow of the subject through the study, this section is briefly mentioned here, for more in-depth details please see the consent description in section 6.7 below.)*

    - Subjects interested in the study will meet with a study coordinator or other team member who has been trained on the study/consent process to undergo the consent process. The study team member enrolling the subject will have the subject sign a HIPAA authorization prior to initiating the interview. (See attachment 2 – HIPAA Authorization). The study

team member will then have the subject fill out the front portion of the initial interview/questionnaire and the study team member will fill out the back portion (See attachment 3 – Initial Interview/Questionnaire). At this time if the subject meets inclusion/exclusion criteria (See attachment 4 – Inclusion/Exclusion Criteria Checklist), the study team member will consent the subject for participation in the study. (See attachment 5 – Informed Consent Document).

- **Data Collection:** At the same appointment after consent is obtained, the study team member will provide the subject with a study packet to include a copy of their HIPAA Authorization, their Informed Consent Document, and a patient handout about what to expect for the cardiac CT for CAC scoring. (See attachment 6 – Patient Handout on Cardiac CT). The study team member will then take the subject's blood pressure and waist measurement. Blood pressure will be taken on the right arm with feet/legs uncrossed and the subject in a seated position for at least 5 minutes. The waist measurement will be completed as defined by Air Force physical fitness testing standards, one inch above the iliac crest and parallel to the ground. The study team member will then check the subject's AHLTA record to determine if hemoglobin A1C and/or lipid panel have been drawn in the past 3 months. If these labs have been drawn they will record them on the back portion of the initial interview. If the labs have not been drawn in the past 3 months, the study team member will order the required labs in CHCS and instruct the subject to proceed to the lab when fasting.

- **Verification of Interview:** After the initial encounter, a study team member will confirm with AHLTA record if the subject has a diagnosis of hypertension, diabetes or pre-diabetes and ensure this information matches the information provided on the initial interview. A study team member will also verify that the subject has no documented history of Coronary Artery Disease (CAD), Coronary Artery Bypass Grafting (CABG), Myocardial Infarction (MI), or Percutaneous Intervention/Stent Placement (PCI) or significant radiation exposure in the past 12 months (see exclusion criteria).

- **Initial Labs:** If HgbA1C and a lipid panel have not been drawn in the past 3 months, the subject will be sent to the lab for initial blood work. The HgbA1C lab will help establish if the subject is diabetic/pre-diabetic, and if the subject is a known diabetic will help determine how well their diabetes is controlled. The lipid panel will help establish if the subject has dyslipidemia/hyperlipidemia. A recent (within 3 months) HDL and Total Cholesterol value are needed directly for calculating the Framingham risk score. Labs will be ordered by the study coordinator or AI using an order set in CHCS marked as "for research purposes".

    - **HgbA1C:** Will be drawn as per normal lab protocol. Results will be recorded in CHCS.

- **Lipid Panel:** Will be drawn as per normal lab protocol including HDL measurement, Triglyceride measurement and total cholesterol measurement. The LDL will be calculated using the Friedewald equation (standard equation used by labs to determine LDL without having to directly measure LDL – this is how LDL is resulted when a "lipid panel" is ordered). The Non-HDL will be calculated by subtracting HDL from the total cholesterol measurement. Results will be reported in CHCS.

- **CT scan:** A cardiac CT for Calcium Scoring will be ordered in CHCS with "CAC Study Participant" noted in the comment section. Radiology will then walk the subject in the same day if space is available, or the radiology front desk will schedule the subject for a future date/time. Prior to CT scanning, all subjects will fill out the standard questionnaire that radiology provides that includes a question for females about the possibility of being pregnant. All females who answer yes to this question will be dropped from the study. Subjects will be scanned on a Siemens 128 slice multi-detector CT. A cardiac CT trained technologist from the department of Radiology will scan the subject. A cardiothoracic radiologist will interpret the studies. Cardiac CT for Coronary Artery Calcium scoring is not considered standard of care unless a patient has a Framingham risk score between 5-20% to greater characterize risk. Some subjects in this study may have a Framingham risk <5%. (Please see section 6.5 and 6.8 below for more information on incidental findings and radiation exposure.)

- **CT Scan Methodology:** Coronary artery calcium (CAC) examinations will be performed by certified radiology technologists using a 128 multi-detector computed tomography (MDCT) scanner (SOMATOM Definition Flash second generation, 2×64, Siemens AG, Erlangen, Germany). Images will be obtained using 40- to 50-slice (3mm thickness) protocol with prospective image acquisition triggered to 60% to 80% of the electrocardiographic RR interval with suspended respiration. Off-line reconstructions of the images will be performed on syngo Acquisition Workplace Calcium Scoring (software version 2011A).

- **Interpretation of CT Scan:** After CT scan, the cardiothoracic radiologist will read the images to determine the coronary artery calcium scoring using the following method:

  - A focus of coronary calcium will be defined as the presence of four or more contiguous pixels with >130 Hounsfield units. Total and per-vessel (right coronary artery, left main coronary artery, left anterior descending branch and left circumflex branch) CAC burden will be assessed by the cardiac radiologist using the Agatston scoring method.

- **Follow-Up:** Scan results with CAC scores will be read within 10 days after the CT scan. The research coordinator or other study team member will be alerted

when results are placed in CHCS. When results are available, the research coordinator will review the results. Follow-up plan will depend on CAC score:

- **For CAC score of zero (0):** Subject will be informed of their score via a results letter that explains the meaning of the score, explains their Framingham Risk Score and provides results of the initial lab work that was drawn (See attachment 7 – Results Letter). These letters will be produced on an individual case basis and mailed to study subjects. If subjects in this category are noted to have abnormal HgbA1C and/or lipid panel their primary care manager (PCM) will be notified of abnormal results via encrypted e-mail.

- **For CAC scores of 1-400:** The study coordinator or other research team member will place a consult/referral into CHCS to the Metabolic Clinic with the words "CAC results follow-up" in the description section. At this time a telephone-consult will be placed in the subject's AHLTA record (See attachment 8 – Telephone Consult Template) and their PCM will be notified via an encrypted e-mail of the subject's CAC results and their referral to the metabolic clinic (See attachment 9 – PCM Notification E-Mail Template). If subjects in this category are noted to have abnormal HgbA1C and/or lipid panel their primary care manager (PCM) will be notified of abnormal results via encrypted e-mail. The Metabolic Clinic will see these referrals and have the HL&VC receptionist call the subject to directly schedule a follow-up appointment. The follow-up appointment will be within 60 days of the CAC scan. If subjects fail to attend their follow-up appointment, they will be contacted by a member of the study team to remind them of the importance of following up. The research coordinator will ensure subjects attend follow-up as scheduled, and will document whether they have followed up in the subject's study chart. At the follow-up appointment, the following will be discussed:
  - Coronary Artery Calcium Score Results
  - Framingham Risk Score
  - What the two scores mean
  - Lab Results
  - Lifestyle changes that can be made to decrease risk, i.e. smoking cessation, increasing exercise, dietary changes, etc.

- **For CAC >400:** The study coordinator or other research team member will place a referral into CHCS to the cardiology clinic for further evaluation. At this time a telephone-consult will be placed in the subject's AHLTA record (See attachment 8 – Telephone Consult Template) and their PCM will be notified via an encrypted e-mail of their CAC results and their referral to cardiology (See attachment 9 – PCM Notification E-Mail Template). If subjects in this category are noted to have abnormal

HgbA1C and/or lipid panel their primary care manager (PCM) will be notified of abnormal results via encrypted e-mail. The HL&VC will contact the subject to schedule a follow-up appointment for the subject to be seen within 30 days, but no later than 60 days of the CAC scan. At the cardiology follow-up appointment, the following will be discussed:

- Coronary Artery Calcium Score Results
- Framingham Risk Score
- What the two scores mean
- Lab Results
- Lifestyle changes that can be made to decrease risk, i.e. smoking cessation, increasing exercise, dietary changes, etc.
- Medications that could reduce risk of cardiac events in the future
- Interventions, imaging or further testing that may be necessary to further evaluate/treat the subject

- **Measurements:**
  - Framingham Risk Score – (See attachment 10 – Framingham Risk Calculation Tables), includes age, systolic blood pressure, HDL level, Total Cholesterol level and smoking status
  - HgbA1C (if not previously tested within 3 months prior to study enrollment)
  - Lipid Panel (if not previously tested within 3 months prior to study enrollment)
  - Coronary Artery Calcium Score
  - Waist Circumference
  - Blood Pressure

- **Demographic Info to be Collected:**

  - Branch of Military Service
  - Rank
  - Number of Years of Military Service
  - Number of Deployments >2 months
  - Number of Years living on base in Dormitories
  - Number of PT test failures
  - Number of Cardiac Risk Factors (Tobacco use, Diabetes, pre-diabetes, hypertension, waist circumference, hyperlipidemia)

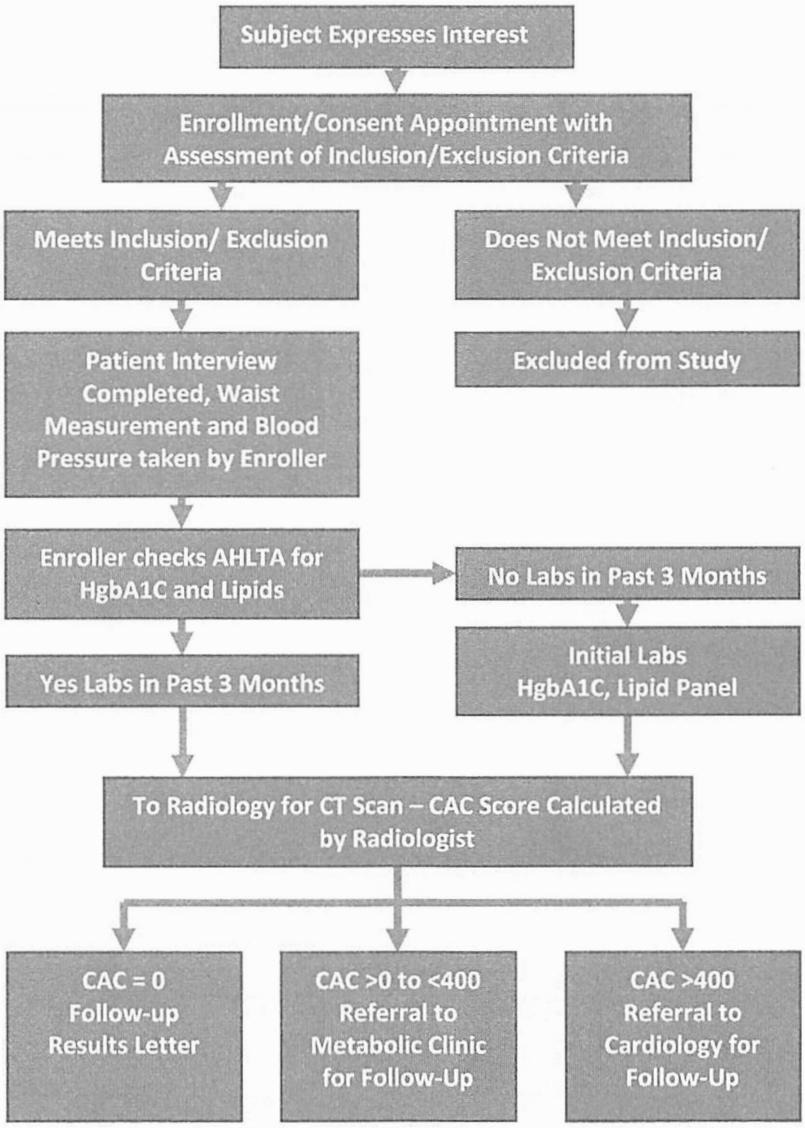
6.5. Intervention/Treatment:

- Subject will undergo one cardiac CT scan. Appointment for scan will take 10-20 minutes, the majority of which will be subject check in and positioning. Average radiation exposure for a CAC CT is 0.89 millisieverts (mSv). For context, the average population radiation exposure from background is approximately 3.11 mSv at sea level (4.5 mSv at high altitude), meaning

that the dose from this study is less than half of a person's baseline annual dose from sources such as cosmic radiation. Furthermore, a mammogram is approximately 0.73 mSv.

- **Incidental Findings:** As per usual radiology operating procedure, all cardiac CT scans will be reviewed in their entirety for any abnormalities. The report will be placed in CHCS/AHLTA and can be reviewed by the subject's primary care physician. The radiologist reading the films will also make follow-up recommendations for any concerning abnormal findings. The abnormalities will be brought to the attention of the provider who orders the cardiac CT. That provider will then inform the PI or AI of any abnormal findings. The PI/AI will then inform the subject of these findings as well as the follow-up recommendations of the radiologist. An encrypted e-mail will be sent to the subject's primary care physician if incidental findings are discovered.

Study Flow Chart (displayed on following page):



6.6. Data Collection/Analysis:

Sample Size/Power Analysis

- Based on an 8.5% expected prevalence of atherosclerosis in the active duty military population, the sample size requirement for a 95% confidence interval for a proportion of +/- 0.05 is 120 subjects. As the prevalence among active duty with >10 years of military service and at least one cardiovascular risk factor is likely higher, for this study the estimated prevalence is 10%. The sample size requirement for a 95% confidence interval for a proportion +/- 0.05 with a prevalence of 10% is 138 subjects. For this study, anticipated failure of completion/drop out is estimated to be approximately 10%, so 150 male volunteers will be recruited to achieve this confidence interval for prevalence of active duty atherosclerosis in enlisted members

with 10 or more years of military service. Females do not tend to demonstrate coronary artery calcium in the same manner/degree as males. Therefore an additional pilot sample of 30 female volunteers will be used to assess the prevalence detected in the female active duty population.

Data Analysis

- Primary Aims:
  - Determine prevalence of atherosclerosis in active duty enlisted military members with 10 or more years of military service using coronary artery calcium scoring.
    - A 95% confidence interval will be calculated for the observed prevalence in the active duty population.
  - Assess the rate of reclassification of subjects from one risk category using Framingham Risk Scores (FRS) to another risk category using the results of the Coronary Artery Calcium (CAC) score.
    - For the purposes of this study, the SHAPE guidelines will be used to classify the CAC scores and percentage by age into the following categories:
      - Low Risk: CAC of 0 and no cardiovascular risk factors
      - Low-Moderate Risk: CAC of 0 with cardiovascular risk factors
      - Moderate-High Risk: CAC 1-100 ***and*** percentile for age <75%
      - High Risk: CAC 100-399 ***or*** percentile for age >75%
      - Very High Risk: CAC >100 ***and*** percentile for age >90% ***or*** CAC >400
    - For the purposes of this study, the FRS percentages will be classified into the following categories:
      - Low Risk: FRS 0-10%
      - Moderate Risk: FRS 11-15%
      - Moderate-High Risk: FRS 16-20%
      - High Risk: FRS >20%
      - Very High Risk: Acute Coronary Syndrome or known Coronary Artery Disease or significant multiple risk factors

This study will assess the rate at which CAC scoring reclassifies the FRS of a subject to a different risk category. To do so a descriptive table will be used to demonstrate the changes seen. The net reclassification improvement (NRI) will be calculated to describe further the amount of reclassification that is accomplished by using the CAC scoring method (19). Please see reference 19 for more information.

  - Compare the Framingham Risk Score (FRS) to the Coronary Artery Calcium (CAC) score for enlisted subjects with at least 10 years of military service to determine how well the results correlate with one another.

- Linear Regression model will be used to determine if the FRS score correlates with the CAC score.

- Secondary Aims:
  - A t-test will be used to compare CAC scores between each group in the following categories to see if there are associations between these categories and formation of calcified plaques:
    - Those meeting the criteria for metabolic syndrome vs. those not meeting criteria (See attachment 1 – Diagnostic Criteria for Metabolic Syndrome).
    - Those who lived in the dorms for >5 years compared to those living in the dorms for <5.
    - Those with PT test failures vs. those without.

  - Analysis of Variance (ANOVA) and/or Logistic regression will be used to compare CAC scores between each group in the following categories to see if there are associations between these categories and formation of calcified plaques:
    - Number of years of military service in the following groups: 10-14 years, 15-19 years 20-24 years and 25+ years
    - Those with 1 risk factor vs. 2 risk factors, vs. 3 risk factors, vs. 4 risk factors, vs. 5 risk factors (as listed in the inclusion criteria section).

  - The correlation between CAC and FRS scores will be described using multiple linear regression for the following categories:
    - Those meeting the criteria for metabolic syndrome vs. those not meeting criteria.
    - Those who lived in the dorms for >5 years compared to those living in the dorms for <5.
    - Those with PT test failures vs. those without.
    - Number of years of military service in the following groups: 10-14 years, 15-19 years 20-24 years and 25+ years.
    - Those with 1 risk factor vs. 2 risk factors, vs. 3 risk factors, vs. 4 risk factors, vs. 5 risk factors (as listed in the inclusion criteria section).

Source of Research Material per Participant:

Source of Research Material per Participant	Standard Care	Research Driven
Blood Sample – Hgb A1C	0	1 **
Blood Sample – Lipid Panel	0	1 **
Cardiac CT Scan	0	1
Outpatient Record Review	0	1
Subject Interview	0	1
Demographics	0	1

** In some subjects, the labs could be standard of care, but since the labs will not be standard of care for all subjects, they are listed here as research driven.

6.7. Subject Population

Age Range: ☒ ≥ 18 y/o ☐ Children (< 18)

Sex: ☒ Male ☒ Female

Vulnerable Population: ☒ No ☐ Yes (explain)

- Children, pregnant women, fetuses, neonates, mentally disabled, and prisoners will not be used in this research study as the population this study is looking at military members with at least 10 years of service. Any females identifying that they may be pregnant will be excluded from the study.

Number of Subjects:

- Total Number of Subjects (nation-wide/study-wide): __180___
- Number of Subjects Planned for DGMC: __180___
- Number of Subjects Planned for (Specify Institution): __0___

Inclusion/Exclusion Criteria:

- **Inclusion Criteria:**
  - Active Duty Military Members with at least 10 years of service
  - Enlisted Rank
  - Males 35 years and older OR Females 45 years and older (please note the age difference is due to the fact that female plaque formation with calcification has been shown to lag that of males by about 10 years)
  - One or More of the Following Risk Factors:
    - **Smoker** – at least 5 pack years in the past 5 years (pack year = number of packs per day * number of years of smoking)
    - **Diabetic** (Fasting glucose of >125 mg/dL on two or more blood draws, or Random Blood Glucose of >200 mg/dL on a single blood draw, or HgbA1C >6.5%, or previous diagnosis of diabetes listed in the subject's medical record) or **Pre-diabetic** (Fasting glucose >100 on two or more blood draws or HgbA1C 5.7-6.4)
    - **Hypertension** (SBP > 140 or DBP >90 or on blood pressure medications or diagnosis of hypertension in medical record)
    - **Waist Circumference** > 40 inches for males or >35 inches for females
    - **Hyperlipidemia** (LDL>130, HDL<40 for males, HDL <50 for females, Triglycerides >200, on lipid lowering medications and/or diagnosis of hyperlipidemia in medical record)

- **Exclusion Criteria:**

- Males <35 years old
- Women <45 years old (please note the age difference is due to the fact that female plaque formation with calcification has been shown to lag that of males by about 10 years)
- Officer Rank – officers are excluded as we are looking at the enlisted culture in the military.
- History of any of the following:
  - Coronary Artery Disease (CAD)
  - Coronary Artery Bypass Grafting (CABG)
  - Myocardial Infarction (MI)
  - Percutaneous Intervention/Stent Placement (PCI)
  - Angina – cardiac chest pain
  - Radiotherapy (external beam, brachytherapy, radiopharmaceutical)
- Under the care of any of the following types of providers in the past 12 months (As these subjects are at greater risk of having had significant radiation exposure to the chest over the past 12 months):
  - Radiation/Medical Oncologist
  - Interventional Radiologist
  - Cardiologist
  - Cardiothoracic Surgeon
  - Vascular Surgeon
- Females who think they may be pregnant
- Pregnant females

Recruitment:

- **Fliers** – Will be posted throughout the Heart, Lung & Vascular (HL&VC), Family Medicine, Family Health, Internal Medicine and Flight Medicine clinics, DGMC cafeteria, elevators and other public areas of DGMC. Advertisement posters/fliers will also be posted in other public buildings on Travis AFB in order to ensure recruitment of a population representative of the active duty population at Travis AFB. Research coordinators may also sit near advertisement posters in the HL&VC waiting room and cafeteria to answer any potential participant's questions. (See attachments 11 & 12 – Recruitment Fliers – landscape and portrait).

- **Pamphlets** – Will be placed in the waiting rooms of primary care clinics, and to be given out by primary care providers and PHA administrators who identify members with more than 10 years military service. (See attachment 13 – Recruitment Trifold Pamphlet).

- **First Sergeant Distribution** – First Sergeants will be notified of the study via a flier e-mailed to them or via presentation by a study team member at the First Sergeant's meeting. They will be asked to pass the flier on by e-mailing it out to their enlisted personnel as an FYI, and/or by posting it in their work spaces and break rooms for their squadron.

- **E-mail/Newspaper** – The research team may elect to advertise the study via e-mail sent out by wing and hospital public affairs offices. The research team may also elect to advertise via Air Force newspaper publications or other military newspapers at surrounding bases. (See attachment 14 – Recruitment Research Announcement).

  --- If these methods fail to produce the number of subjects needed within 3 months, the following recruitment methods may be used:

- **Presentation at Transition Assistance Program (TAP) Course** – A member of the research team will give a brief presentation at each TAP course, which is mandatory for all military personnel who anticipate separation or retirement within 1 year. Presenter will follow attached script and answer any questions that may arise. (See attachment 15 – Recruitment Script for TAP Course).

- **Information table outside TAP Course** – A member of the research team will man a table located outside the TAP course classroom during lunch break and/or at the end of the day to distribute informative pamphlets and answer questions about the study. These pamphlets are the same as mentioned above.

- **Retirement Physicals** – The research team may elect to advertise in clinics where retirement physicals are conducted via pamphlets and educating physicians about the ongoing study. These potential subjects will be identified by contacting clinic nurse managers in Family Medicine, Family Health, Flight Medicine and Internal Medicine.

- **Presentation at Smoking Cessation Classes** - A member of the research team will give a brief presentation about the CAC study at each smoking cessation class similarly to the TAP course presentations. Fliers/pamphlets may be handed out at these classes.

- **EMR chart review** – Upcoming appointments at DGMC will be reviewed for inclusion/exclusion criteria. If patient fits study criteria they will be contacted via telephone or in person, before or after scheduled clinic appointment.

- **Briefing Presentations**: Members of the research teams may advertise the study at a number of briefing opportunities across Travis AFB where potential qualifying candidates may attend. This includes, but is not limited to: briefings for PTLs at the gym, classes provided in Nutritional Medicine, or the AFRC Newcomer's Information Fair.

- **Hospital Marquee:** The research team may elect to advertise the study via the hospital marquee to reach a wider pool of potential candidates.

- **Online Announcements:** The research team may advertise the study on any Travis AFB approved sites including, but not limited to: the SharePoint home page and DGMC News + Notes

Consent:

- Subjects that have expressed interest in the study will be scheduled for an informed consent review/initial visit at the Clinical Investigation Facility (CIF). The subject will be brought to a private exam room or office where they will be individually consented by the research coordinator, the PI or other research team member that has been trained on the protocol. The study team member will explain the nature and scope of the study, discuss potential risks and benefits of participation, answer questions for the subject and ensure the subject fully understands informed consent. The study will be explained to the subject in lay terms. At least one hour of study staff time will be set aside for each participant to receive information, ask questions and consider participation in the study. The subject may elect to discuss the study with others if they so choose, prior to agreeing to participate. If the subject agrees to participate, the IRB approved informed consent document and the Health Insurance Portability and Accountability Act (HIPAA) Authorization Form will be signed and personally dated by the subject and investigator or study staff that have been delegated responsibility and have been trained on the protocol. A copy of the signed consent form will be made and provided to the subject. The original signed consent form will be turned into the protocol office and a copy will be placed in the subject's study folder and stored with other protected health information in a locked filing cabinet in an office that is locked when the office owner is not in the room. A copy of the ICD will be placed into their electronic medical record as well. Subjects will be assured that they may withdraw from the study at any time and for any reason and their medical treatment will not be compromised. Research procedures will not start until the IRB approved informed consent document has been signed and dated by the subject and research team member who has been delegated responsibility for consenting subjects and has been trained on the protocol.

6.8. Risks/Benefits:

- **Risks:**
  - **Exposure to Radiation:** For a working population composed of both sexes, the lifetime risk of fatality from cancer is 4% per sievert (Sv) for the type of radiation used in a CAC CT. As mentioned previously, average radiation exposure for a CAC CT is 0.89 milisieverts (mSv). For context, the average population radiation exposure from background is approximately 3.11 mSv at sea level (4.5 mSv at high altitude), meaning that the dose from this study is less than half of a person's baseline annual dose from sources such as cosmic radiation. Furthermore, a mammogram is approximately 0.73 mSv.

  - **Emotional Response to/Stress Due to Results:** Some subjects may have results that indicate a high risk of a cardiovascular event in the future. This news could be emotionally stressful to the individual, however knowing their cardiovascular risk could lead to improved quality of life long term.

- **Incidental Findings:** There is a possibility that while reviewing the cardiac CT scan that the radiologist may discover an abnormality not related to the study. If this occurs, the radiologist will follow standard radiology operating procedures and will report all incidental findings in their written report to be placed in the subject's electronic medical record. The radiologist will also place recommendations for follow-up. All abnormal findings will be brought to the attention of the ordering provider, and will be reported to the PI/AI. The PI/AI will then inform the subject of the abnormalities found and will provide recommendations for follow-up. The PI/AI will then send an encrypted e-mail to the subject's primary care provider with the information about the abnormality.

- **Impact on Future Insurance:** Subjects who separate from the military in a way that does not permit the continuation of TriCare benefits may have increased insurance premiums and/or difficulty obtaining civilian insurance upon separation/retirement if this study determines they have coronary artery disease, even if they are asymptomatic. However, learning about a subject's atherosclerosis may lead to treatment and life style changes that may reduce the risk of heart attack and other cardiovascular events, thus decreasing the insurance costs long-term.

- **Possibility of Medical Board:** There is the possibility that the cardiac CT scan could discover a medical problem/condition that would require a medical evaluation board to assess the ability of the enlisted member to continue duty in the military. Based on the inclusion criteria, the likelihood of a subject in this study ending up medically boarded from service is very slight.

- **Impact on TriCare/Veterans Affairs (VA):** This study could potentially identify individuals as having coronary artery disease who were not formerly recognized as having this diagnosis. This could lead to subjects starting new medications that would need to be covered by their insurance following separation/retirement. This could also lead to establishment of the fact that the subject's coronary artery disease developed while on active duty and could have significant impact on the VA system and disability claims at time of retirement. However, learning about a subject's atherosclerosis may lead to treatment/life style changes that may decrease the cost/impact on the TriCare/VA system in the future.

- **Risks of blood draw:** infection, bleeding, discomfort, bruising

- **Risks of collecting protected health information:** potential loss of privacy and/or confidentiality

- **Benefits:**
  - **Benefits to the Subject:**
    - Earlier detection of coronary artery disease.
    - More accurate/personalized assessment of cardiovascular risk.

- One-on-one counseling to discuss results and risk factor modification in order to motivate the subject and potentially improve outcomes for subjects with CAC >0.
- For subjects with CAC score of zero, a letter informing them of their result and encouraging them to continue making healthy lifestyle choices may reinforce the subject's positive behaviors.

- **Benefits Outweigh the Risks:** This study will provide subjects with their Coronary Artery Calcium score. This score helps establish a risk score that indicates a more personalized/individualized likelihood of a cardiovascular event in the future. By informing the subject of their risk score and having a results letter sent or counseling session reviewing their results, they are able to better understand what interventions/lifestyle modifications can be completed to potentially decrease their risk of a cardiovascular event in the future. This study can also provide the military with information about the prevalence of atherosclerosis in enlisted members with 10 or more years of service, which could assist public health and the military in making policies/influencing the military culture to promote healthy changes that decrease the risk of atherosclerosis.

6.9. Safeguards for Protecting Subjects:

- This study involves greater than minimal risk to subjects as it involves the exposure to radiation during a CT scan. Primary monitoring of the study will be performed by the study team, who will review accrual and any adverse events on a real-time basis. The study team will ensure that all eligibility criteria and consent requirements are met prior to a subject's participation in the study and that all study procedures and adverse event reporting occur according to the IRB approved protocol. Potential adverse events and risk factors for this study are specifically listed in section 6.8 within this protocol and will be discussed with subjects prior to enrollment. Any event will be graded by severity and outcome. Study staff will make certain that all adverse events are recorded and reported according to AFI 40-402 and SGSE Operating Instruction 40-402-01. Cumulative adverse events will be reviewed monthly. The study team with the advisement of the medical monitor and IRB will make decisions regarding cessation of accrual, and whether or not to close the study on the basis of frequency or severity of Unanticipated Problems Involving Risk to Subject or Others (UPIRSOs), and/or Serious Adverse Events (SAEs). Any deviation, cessation in accrual or early study close will be communicated to the IRB immediately.

- All subjects will be treated in compliance with AFI 40-402 and applicable FDA and DHHS guidelines.

- All study staff members will be informed by direct personal communication about any UPIRSOs or SAEs. If any protocol changes are needed, the PI will submit a modification request to the IRB. Protocol changes will not be implemented prior to IRB approval unless necessary to eliminate apparent immediate hazards to the research subjects. In

such a case, the IRB will be promptly informed of the change following implementation (within 5 working days).

- Standard measures for protection of subject privacy and confidentiality that are currently being practiced will continue. All electronic data will be housed on a Common Access Card enabled computer accessible only to study personnel within a secured office. All electronic transmissions of data will be encrypted over a secured network. All hard copy records will be stored in a locked file cabinet in a secure room for the duration of the study. Upon the close of the study all records will be transferred to the CIF for storage for three years then moved to base storage IAW DODI 3216.02.

- All subjects enrolled in the study will be provided with a phone number to contact during business hours if they are experiencing any concerning symptoms. All enrollees are DoD beneficiaries and can therefore seek treatment at DGMC any time they or the research team are concerned about a change in their health. The emergency room at DGMC is available 24 hours per day, seven days a week.

- **Privacy:** All subject interviews will be conducted in a private office, behind a closed door. Any phone calls to subjects for appointment reminders or any other reason will be conducted in an office behind closed doors.

- **Protecting Collected Information:** During data collection, subject identifiers will be present on the data to ensure accuracy. Protected Health Information will be restricted to the PI, AI, research coordinators and the statisticians who all have been HIPAA trained. All paper documentation will be stored in locked files and all electronic materials will be stored in password-protected electronic databases. Once all data have been collected, subject identifiers will be removed by the PI/AI. PHI will be shared with the subject's primary care provider if abnormal lab results, abnormal CAC score, or incidental findings on chest CT are discovered. Other than the primary care provider if necessary, PHI will not be shared with anyone outside the study team.

- **Risk Modification:**
  - **Exposure to Radiation:** The radiation exposure risk is equivalent to 24 chest x-rays, and is approximately ½ of the background radiation the subject would be exposed to in a year. While the radiation dose cannot be decreased, the CT protocol is designed to run the scan with as few slices/as little radiation exposure as is necessary to obtain the required images. All females who may be pregnant or are pregnant at the time of expressing interest in participation will be excluded from this study.

  - **Emotional Response to/Stress Due to Results:** Some subjects may have results that indicate a high risk of a cardiovascular event in the future. This news could be emotionally stressful to the individual. Subjects will be provided with the study coordinator's phone number which they can call during business hours if they are feeling overwhelmed by the results of their test. The DGMC ER is also available 24

hours a day. The study coordinator will offer information about mental health services available at Travis Air Force Base if requested.

- **Impact on Future Insurance:** Subjects who later separate from the military may not continue to receive TriCare benefits and may have increased civilian insurance premiums and/or difficulty obtaining civilian insurance if this study determines they have coronary artery disease, even if they are asymptomatic. There is no way to decrease this risk, but subjects can opt to not participate in this study if they are concerned about impact on future insurance.

- **Risks of blood draw:** Infection, bleeding, discomfort, bruising. These risks are decreased by using sterile needles, cleaning the skin prior to blood draw and pressure applied after withdrawing the needle.

- **PCM Notification:** Primary care physicians will be notified of all CAC scores >0 via an encrypted e-mail that includes follow-up recommendations (See attached PCM Notification E-Mail Template). A telephone consult note will also be entered in AHLTA with CAC score results. Any abnormal HgbA1C or lipid panel labs will be brought to the attention of the PCM via encrypted e-mail.

- **Data Monitoring:** Data will be monitored monthly by the PI and study staff to identify any adverse events, and to ensure all subjects who underwent cardiac CT scan and CAC scoring attended all recommended follow-up, to include a results letter, follow-up in metabolic clinic, OR follow up in cardiology.

- **Stop Rules:** No stop rules are anticipated. As this is an observational study looking partly at prevalence of atherosclerosis in enlisted military members with 10 or more years of service, the study team does not anticipate stopping the study early. However if interim statistical analysis shows a prevalence of atherosclerosis = 0, then the principle investigator may stop the study.

7. Conflict of Interest

No conflicts of interest have been identified by any of the research team members.

8. Collaborative Efforts

No collaboration with other facilities will be pursued at this time.

9. Investigation Schedule

	Mar-Apr 2013	May 2013-Nov 2013	Nov 2013-Nov 2016	Nov 2013-Nov 2016	Nov 2013-Nov 2016	Nov 2013-Dec 2016	Dec 2016	Dec 2016-Mar 2017
IRB Approval	X	X						
Surgeon General Approval		X	X					

Recruitment			X	X				
Enrollment			X	X	X			
Baseline Data			X	X	X			
Testing			X	X	X			
Data Collection			X	X	X	X		
Statistical Analysis					X	X	X	
Publications/Reports						X	X	X

Estimated Date of Investigation Beginning: 01 August 2013
Estimated Date of Completion: 30 December 2016

10. Use of Investigational Drug(s) ☒ No ☐ Yes
No investigational drugs will be used in this investigation.

11. Use of Investigational Device(s) ☒ No ☐ Yes
No investigational devices will be used in this investigation.

12. Support Required

Lab Support:
Request CLIA certificates from all non-DGMC laboratories for your files.

Test Name	Standard Care?	Which lab will perform each test?	Support letter attached?
HgbA1C	Yes and No	DGMC	Yes
Lipid Panel	Yes and No	DGMC	Yes

** Note: Some of these labs will be standard of care if the subject is diabetic and/or has hyperlipidemia and has not had labs drawn in the past 3 months. Those without these diagnoses will have these labs drawn for research purposes only.
See attachment 16 – Letter of Support – DGMC Lab

Radioactive Materials or Radiology Support:
If radioisotopes or radiation-producing equipment will be used, describe here.

Procedure	Standard Care?*	Which facility will perform proc.?	Support letter attached?
Cardiac CT	No	DGMC	Yes

See attachment 17 – Letter of Support – Radiology
* Any Radiation exposure that is not standard care requires Radiation Safety Committee review.
See attachment 18 – Radiation Safety Committee Approval

Nursing/Technician Support:
N/A

CIF Support:
Describe what you will be asking the CIF staff to do in support of your research or specialized lab equipment you will need to carry out your proposal (bio-statistician consultation, research support staff/coordinator, lab technician support, etc.).

Task	Personnel needed	Time and Frequency	Support letter attached?
Biostatistics Consultation	name redacted	~4 hours, once at end of data collection	Yes
Study Coordinator Study Coordinator	6Feb20	0.1 FTEs or less	Yes
		0.1 FTEs or less	Yes

See attachment 19 – Letter of Support – CIF

Other Support:
Heart Lung and Vascular Center – follow-up appointments for subjects will be required with the metabolic clinic or the cardiology clinic. (See attachment 20 – Letter of Support – HL&VC).

13. Budget, Equipment, and Supplies
N/A

14. Manpower

Rank	AFSC/Job Title	# hours duty time	# hours off-duty time
Lt Col	Staff	50	50
Capt	Resident	180	100
Study Coordinator	Contractor	185	0
Study Coordinator	Contractor	185	0
Clinical Research Nurse	Contractor	10	0
Research Assistant	Contractor	10	0
Research Assistant	Contractor	10	0
Clinical Pharmacist	Contractor	40	0

15. Authorized Institutional Official (AIO)
(name/contact info redacted 6Feb20),

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17. Attachments

1. Diagnostic Criteria for Metabolic Syndrome
2. HIPAA Authorization
3. Initial Interview/Questionnaire
4. Inclusion/Exclusion Criteria Checklist
5. Informed Consent Document
6. Subject Handout on Cardiac CT
7. Results Letter
8. Telephone Consult Template for AHTLA Notes
9. PCM Notification E-Mail Template
10. Framingham Risk Calculation Tables
11. Recruitment Flier – Landscape
12. Recruitment Flier – Portrait
13. Recruitment Trifold Pamphlet
14. Recruitment Research Announcement
15. Recruitment Script for TAP Course
16. Letter of Support – Lab
17. Letter of Support – Radiology
18. Radiation Safety Committee Approval
19. Letter of Support – CIF
20. Letter of Support – Heart Lung & Vascular Center
21. Adverse Event Log
22. Certificate of Compliance
23. Curriculum Vitae for Each Study Team Member and Medical Monitor
24. Human Protections Training Certificates for Each Study Team Member
25. IIAs for non-staff
26. HIPAA Waiver
27. Screening/Phone Script

ENROLLING NOW!

You Could Have Heart Disease Without Knowing It

The CAC Research Study is Looking at Your 10 Year Risk of Heart Attack or Stroke Using a CT Scan

You May Be Eligible If You:

- **Are Active Duty ENLISTED Military with ≥10 Years of Service**
- **Are a Male ≥35 Years Old OR a Female ≥ 45 Years Old**
- **Have at Least One Risk Factor for Heart Disease**

For More Information Call:

name/contact info redacted

6Feb20

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- **Are a Male ≥35 Years Old OR a Female ≥ 45 Years Old**
- **Have at Least One Risk Factor for Heart Disease**

For More Information Call:
(Name/contact info redacted 6 Feb 20)

18. Commander's Acknowledgment of Review and Approval

Principal Investigator: I am aware that I am not authorized to accept any funds or other form of compensation for conducting research. All subjects will be treated in compliance with applicable Air Force, DoD and federal regulations, as well as applicable FDA and DHHS guidelines. I have read, understand, and signed the attached Certificate of Compliance. I understand I must complete a review of this protocol at least every 12 months to prevent expiration of the study's approval. I will notify the protocol office **prior** to relocations, separation actions, or closure.

☐ Initial Submission
(ALL signatures required)

☒ Amendment Submission
(PI signature ONLY)

23 Aug 2017
Date

signature/name
redacted 6 Feb 20