Title: Screening For Asymptomatic Obstructive Coronary Artery Disease Among High-Risk Diabetic Patients Using CT Angiography: A Randomized Control Trial

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Screening For Asymptomatic Obstructive Coronary Artery Disease Among High-Risk Diabetic Patients Using Ct Angiography: A Randomized Control Trial protocol 128-127

faCTor 64
**PROTOCOL SUMMARY**

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<td>A prospective, parallel, randomized study</td>
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<tr>
<td><strong>Brief Description:</strong></td>
<td>Patients with a known history of diabetes mellitus and no prior documented evidence of cardiovascular disease will be evaluated for inclusion in the study. Once qualified, patients will be enrolled and be randomized to either the Control Arm or to the Asymptomatic Screening Arm. Patients in the Control Arm will be followed by their primary care physicians with the recommendation that they follow standard guidelines for management of diabetic patients. Patients in the Asymptomatic Screening Arm will undergo CT screening for either coronary calcium scoring or multi-slice CT angiography as well as be placed on one of two medical regimens. Patients will be followed by telephone at six-month intervals for 1 year and annually thereafter until the study is complete (the last patient has completed 2 year follow up) for both primary and secondary outcomes.</td>
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<tr>
<td><strong>Purpose:</strong></td>
<td>The purpose of this study is to test the hypothesis that screening asymptomatic high-risk patients with diabetes for the presence of obstructive coronary artery disease through the use of 64-slice CT scanning will result in a significant reduction in death or myocardial infarction over two-years of follow-up.</td>
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<td><strong>Enrollment:</strong></td>
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<td>Patients with a known history of diabetes mellitus and no prior documented evidence of cardiovascular disease.</td>
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<td><strong>Primary Outcome:</strong></td>
<td>The combination of all cause death, non-fatal MI, and hospitalization for unstable angina.</td>
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| **Secondary Outcomes:** | 1. cardiovascular death  
2. hospitalization for congestive heart failure  
3. worsening renal failure (defined as progression of serum creatinine by ≥0.5 mg/dL  
4. stroke or carotid revascularization procedure  
5. limb amputation or peripheral vascular revascularization procedure  
6. cost  
7. functional status |
| **Sponsor:** | Cardiology Department, Cardiovascular Research Intermountain Medical Center, 5121 S. Cottonwood St., PO Box 577000, Murray UT 84157-7000 |
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1.0 INTRODUCTION

1.1 Background and Rationale

Coronary heart disease and its accompanying acute myocardial infarction is the single largest killer of American males and females. Although some patients experience premonitory symptoms prior to the actual myocardial infarction, which may induce them to seek medical care, for many patients, their first coronary symptom is the acute myocardial infarction itself. Of those patients who experience myocardial infarction, nearly half, or 400,000, die in an emergency department or before reaching a hospital, before ever having the opportunity to receive any particular medical care. This means that about 34% of all cardiovascular deaths occur in patients with no prior symptoms and before they ever get any direct medical care. This is estimated to be over 300,000 patients per year in the United States alone. These statistics emphasize a need for appropriate screening of asymptomatic patients for the presence of obstructive coronary artery disease.

Recent analyses performed at LDS Hospital evaluated patients presenting to the cardiac catheterization laboratory with acute myocardial infarction as their first symptom of coronary heart disease. Fifty-seven percent had single vessel disease, 25% two-vessel disease, 18% three-vessel disease, and 2% left main disease. Therefore, 43% of patients presenting with acute MI as their first symptom had co-existing multivessel disease. Half of them were found to have disease in which early revascularization would have been lifesaving (ie, left main, three-vessel disease, or two-vessel disease with proximal LAD). These statistics justify a specific screening approach to asymptomatic patients looking for significant obstructive coronary artery disease with the intent of providing not only aggressive medical therapy but also lifesaving revascularization therapy.

Among the major risk factors associated with cardiovascular disease, diabetes mellitus may be the most important. Diabetes mellitus and its precursor, the metabolic syndrome, is becoming epidemic in proportions in the United States. Diabetics are also more likely to develop severely obstructive, but yet asymptomatic, coronary artery disease. Because of this combination of aggressive atherogenicity and asymptomatic presentation, the most common cause of death in diabetics is coronary artery disease. In the large registry of diabetic patients followed by Intermountain Healthcare primary care physicians, the incidence of death or MI over two years of follow-up was 12.1%. Most of these patients were not previously known to have coronary artery disease. These statistics justify the selection of diabetic patients as an ideal initial high-risk patient population to test the hypothesis that screening asymptomatic patients for obstructive coronary artery disease may be lifesaving.

In the past, screening of asymptomatic subjects for obstructive coronary artery disease has been hampered by the use of non-invasive tests with fairly low sensitivity and specificity. The recent development of high resolution multi-slice CT scanning provides the opportunity to evaluate the actual coronary anatomy in a non-invasive fashion. The purpose of this protocol is to test the hypothesis that screening of asymptomatic high-risk patients with diabetes for the presence of obstructive coronary artery disease through the use of 64-slice CT scanning can result in a significant reduction in death or myocardial infarction over two-years of follow-up in this patient population.
2.0 STUDY OBJECTIVES

Determine whether the screening of asymptomatic high-risk patients with diabetes for the presence of obstructive coronary artery disease through the use of 64-slice CT scanning can result in a significant reduction in death or myocardial infarction in a specific population.

3.0 STUDY DESIGN

3.1 Selection of Subjects

A total of 1,100 patients with a known history of diabetes mellitus and no prior documented evidence of cardiovascular disease, who meet eligibility criteria, agree to participate in the study, and can grant informed consent will be enrolled.

<table>
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<td>coronary calcium score or multi-slice CT</td>
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1. Blood will be drawn to measure serum creatinine
2. Patients randomized to the asymptomatic arm will undergo either a multi-slice CT angiography or a coronary calcium score based on baseline creatinine levels
3. Asymptomatic arm patients will be randomized to receiving standard appropriate diabetic care or aggressive risk factor reduction care
4. Subjects will be asked to sign a consent for long term storage and future testing of donated plasma and DNA samples
5. If randomized to CT scan and enrolled in echo sub-study
6. Within 30 days of CT scan procedure

3.2 Subject Selection Criteria

Patients with a known history of diabetes mellitus and no prior documented evidence of cardiovascular disease will be evaluated for potential inclusion into this study.

3.2.1 Inclusion Criteria

1. The patient must sign a written informed consent, prior to any study procedures, using a form that is approved by the local Institutional Review Board.
2. Age: Males ≥ 50 years; Females ≥ 55 years with:
   a) History of diabetes mellitus (prior documentation of fasting glucose ≥ 126 mg/dl or hemoglobin A1C > 6.5%), either type 1 or type 2, documented for at least 3 years and on medication for at least 1 year.

OR

3. Age: Males ≥ 40 years; Females ≥ 45 years with:
   a) History of diabetes mellitus (prior documentation of fasting glucose ≥ 126 mg/dl or
hemoglobin A1C > 6.5%), either type 1 or type 2, documented for at least 5 years and on medication for at least 1 year.

3.2.2 Exclusion Criteria
1. Known coronary artery disease (stenosis ≥70%, history of myocardial infarction, or angina)
2. Symptomatic cerebral vascular disease (history of TIA, CVA, or cerebrovascular [carotid or cerebral arteries] revascularization)
3. Symptomatic peripheral vascular disease (history of claudication, amputation, or peripheral [including renal arteries] arterial revascularization)
4. Treatment with any other investigational drug within the previous 30 days
5. Any therapy or condition that would pose a risk to the patient or make it difficult to comply with study requirements.
6. Pregnant and/or lactating women, and women of child bearing potential not using acceptable means of contraception. Women of childbearing potential must be using adequate measures of contraception (as determined by the Investigator) to avoid pregnancy and should be highly unlikely to conceive during the study period. Women of childbearing potential must have a negative pregnancy test at screen.
7. Any life threatening condition/significant co-morbidity such that primary screening is inappropriate.

4.0 STUDY PROCEDURES (Appendix A)

4.1 Screening
For the most part, patients will be recruited from among Intermountain Healthcare’s >30,000 patient registry of diabetic patients, though other patients may also be included. After enrollment, qualifying and consented patients are randomized to one of two arms: Control Arm or Asymptomatic Screening Arm. Data gathered in this manner is used to evaluate the patient in relation to the exclusion criteria listed. It may be necessary to exclude subjects based on this assessment.

A patient evaluation log will be maintained throughout the study; the log will record all patients considered for enrollment in the trial and indicate whether they were enrolled or not enrolled. In the case of non-enrollment, an explanation will be provided as to the reason for their exclusion.

4.2 Management of Patients Randomized to the Control Arm
Subjects randomized to the control arm will continue to be followed by their primary care physicians with the recommendation that they follow standard guidelines for management of diabetic patients.

4.3 Management of Patients Randomized to the Asymptomatic Screening Arm
Subjects randomized to the Asymptomatic Screening arm will undergo initial CT screening in the following fashion:

- Subjects with serum creatinine of < 2.0 mg/dl (men) or <1.8 mg/dL (women) will be screened using multi-slice CT angiography with contrast.
- Those with serum creatinine ≥ 2.0 mg/dl (men) or ≥1.8 mg/dL (women) will be screened without contrast to obtain a coronary calcium score. Subjects with abnormal serum creatinine results will be notified by a study investigator. Further cardiac screening will be determined based on these results.

4.3.1 Subjects Receiving Multi-Slice CT Angiography (serum creatinine of < 2.0 mg/dl (men) or <1.8 mg/dL (women))
Subjects will be placed, based on the severity of atherosclerotic plaquing detected, into one of four groups:
1. Severely stenotic (defined as ≥70% stenosis in at least one major coronary vessel)
2. Moderately stenotic (50%-70% stenosis)
3. Mildly stenotic (10%-49% stenosis)
4. Normal (<10% stenosis and minimal or no plaquing).

Subjects with severe stenosis in a proximal or large vessel will proceed to coronary angiography and revascularization as needed. Subjects with moderate stenosis in a proximal or large vessel will be referred for adenosine stress cardiac MRI. If ischemia is detected, they will also be referred for coronary angiography. Subjects with either mild stenosis or moderate-severe stenosis in a mid-distal or small vessel coronary arteries will receive no further imaging studies.

4.3.2 Subjects Undergoing CT Evaluation for Coronary Calcium Scoring (serum creatinine ≥ 2.0 mg/dl (men) or ≥1.8 mg/dL (women) )
Subjects will be placed, based on their coronary calcium score, into one of three groups:
1. Score = 0-10
2. Score = 11-100 and <75th percentile
3. Score >100 or >75th percentile

Subjects with coronary calcium scores >100 or >75th percentile will be referred for adenosine stress cardiac MRI. If ischemia is detected, they will be referred for coronary angiography. Subjects with coronary calcium scores = 0-10 or 11-100 and <75th percentile will receive no further imaging studies.

4.4 Medical Management (Only for those patients randomized to the Asymptomatic Screening Arm)
In addition to the imaging studies and potential coronary revascularization procedures performed as described above, all subjects will be placed on one of two medical regimens:
- Standard Appropriate DM Care
- Aggressive Risk Factor Reduction Care

4.4.1 Standard Appropriate DM Care
Subjects assigned to this form of medical care will be managed by their primary physicians. This type of care will consist of targeting the goals proposed by Intermountain Healthcare for all patients with diabetes. These include the following three targets: HgA1C <7.0%, LDL cholesterol <100 mg/dL and Systolic BP<130 mm Hg. Subjects assigned to Standard Care will include all control subjects, as well as all screened subjects with either a normal CT angiogram or a coronary calcium score = 0-10.

4.4.2 Aggressive Risk Factor Reduction Care
Subjects assigned to this form of medical care, in addition to standard medical care provided by their primary physicians, will also be managed by their primary physicians, but will receive more aggressive risk factor reduction management according to a set of guidelines that will be given to the primary physicians. This aggressive management strategy, designed to address the increased medical risk among the asymptomatic diabetics with detected vascular disease, will consist of more aggressive glucose and lipid targets than is in the Standard Care protocols and specific medication algorithms designed to accomplish these more aggressive targets. The targets and proposed medication algorithms are described below:
1. **Emphasize diet, exercise.** Provide individual counseling if needed.

2. **Target LDL chol <70 mg/dL.** Vytorin 10/40 mg if baseline LDL ≥100, simvastatin 40 mg (initially) if LDL<100. Reduce dose and add Co-enzyme Q 50mg BID for myalgias. If short of goal, substitute rosuvastatin (Crestor) for simvastatin (without or with ezetimibe).

3. **Target HDL chol >50 mg/dL.** Achieve LDL goal first. 1) Add fenofibrate 145 mg qd. 2) Add niacin (Niaspan), titrated 0.5-2g hs (pretreated with ASA 325 mg 1 h before), if diabetes controlled. 3) Exercise, weight loss.

4. **Target TG <150 mg/dL.** Achieve LDL goal first. 1) Add fenofibrate 2) Add fish oil (omega 3 source), 4 g/d. 3) Treat as for HDL above. 4) Low cholesterol diet (<50 g/d). 5) Weight loss, exercise.

5. **Target HbA1C <6.0%.** Titrate insulin sensitizing therapy (metformin, pioglitazone) unless contraindicated. Add insulin providing therapy (e.g., sulfonylureas, insulin – including insulin pump or TID dosing) as needed.

6. **Target systolic BP <130 mm Hg.** ACEI (alt., ARB) in everyone (unless contraindicated) as first agent, titrate as allowed by creatinine (<2.5). Add long acting dihydropyridine calcium channel blocker, thiazide diuretic (often with K supplement or K-sparing agent to keep K ≥4). Use JNC GL for diabetics for further suggestions.

### 4.4.3 Results

Subjects with normal results will be contacted via a phone call, by the clinical coordinator. After results have been given, results will be mailed to the subject and their designated primary physician.

Subjects assigned to aggressive risk factor reduction management, will be contacted via a phone call by the investigator or qualified designee. After results have been given, result will be mailed to the subject and their designated primary physician.

Subjects with abnormal results may be scheduled for an additional study visit if indicated, so that the investigator or qualified designee can communicate results and suggested follow-up. If appropriate, additional imaging or procedures may be scheduled at that time. After results have been given, either in person or by phone, results will be provided to the subject and their designated primary physician.

### 4.5 Follow-Up

After enrollment into the protocol, all subjects will be followed until the study is complete (the last patient has completed 2 year follow up). Follow-up will occur by telephone at six-month intervals for 1 year. After the 1 year (12 month) visit, follow-up will occur annually until the study is complete. Outcomes will be ascertained by directly questioning the patient and by review of medical records. All primary outcomes will be adjudicated by an independent events committee. An assessment of absolute events will be completed at the end of the study via computer query of all patients enrolled to identify endpoints, even those enrollees that did not sign an addendum. This will include a computer query to review the social security death index and electronic medical records for those patients for whatever reason were not contacted or able to be contacted to assess for primary endpoint data.

### 4.6 Lost to Follow-up

The clinical coordinator will first attempt to contact the subject via a phone call. If unsuccessful, the personal contact (obtained from the subject’s contact information form) will be called for updated information. After documentation of 3 unsuccessful attempts (on 3 different days over a 1 month period) by the clinical coordinator, a certified letter will be sent to the last known address of the subject. A subject will be considered lost to follow-up if there is no response from the certified letter.
5.0 DATA MANAGEMENT AND STATISTICAL ANALYSIS

5.1 Sample Size and Power Calculations
Based on the measured 2 year event rate for death/MI of 12.1% among all diabetics enrolled at Intermountain Healthcare, it is estimated that, among those meeting the inclusion/exclusion criteria, the control group should have a 2-year event rate of at least 16%. Therefore, using the Log-rank test of survival, it is estimated that with 482 subjects per arm there will be >80% power with an alpha of 0.05 to detect a 40% reduction in events in the screening arm compared to control. Thus, to account for patients that withdraw or are lost to follow-up, we plan to enroll a total of 550 subjects in each arm for a total of 1,100 subjects.

5.2 Data Collection and Monitoring
All required data for this trial will be collected on standardized Case Report Forms (CRFs). Research coordinators will perform primary data collection drawn from source-document (hospital chart) reviews.

5.3 Evaluation Endpoints

5.3.1 Primary Outcome: The combination of all cause death, non-fatal MI and hospitalization for unstable angina.

5.3.2 Secondary Outcomes
1. Cardiovascular death
2. Hospitalization for congestive heart failure
3. Worsening renal failure (defined as progression of serum creatinine by \( \geq 0.5 \) mg/dL)
4. Stroke or carotid revascularization procedure
5. Limb amputation or peripheral vascular revascularization procedure
6. Cost (cost of initial screening procedures and the costs of any cardiovascular or diabetic hospitalizations)
7. Functional status (physical and mental results of the SF-12)

5.4 Statistical Analysis

5.4.1 Statistical Methods
Assessment in differences between arms for the occurrence of the primary outcome and secondary outcomes (cardiovascular death, hospitalization for congestive heart failure, worsening renal failure, stroke or carotid revascularization procedure, and limb amputation or peripheral vascular revascularization procedure) will be evaluated using the time from procedure day to first event using the Kaplan-Meier Survival Estimate and log-rank test. The student’s t-test and analysis of variance (ANOVA) will be used to determine differences in cost and functional status between the different groups (control vs. asymptomatic [standard medical therapy and aggressive medical therapy]).

Baseline characteristics and demographics will be evaluated to determine differences in arms using the chi-square and student’s t-test for categorical and continuous variables, respectively. Exploratory analyses of the endpoints will be performed on patient subgroups. Analyses will be performed on an intention-to-treat basis.
Appendix A: Outline of Study

**Inclusion Criteria (see section 3.2.1)**
1. Able to consent
2. Age: M=40 yrs, F=46 yrs
3. Diabetes (glue<125 mg/dL) >3 years or >5 years, en medica 1 yr

**Major exclusion Criteria (see section 3.2.2)**
1. Known CAD, structural heart dis, nI stress/CTA within 4 yrs, nI Stress test within 1 year
2. Treatment in another study
3. Any life-threatening condition

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**Control**

- Creatinine ≥0 mg/dL

**Asymptomatic Screening**

- Creatinine >2.0 mg/dL (if >1.5 use renal protection protocol)

- **Coronary Ca- Score**
  - 0-10 and ≤75th percentile
  - 11-100 and >75th percentile
  - >100 or >75th percentile

- **Severe stenosis in a proximal segment or large vessel**

- **Moderate stenosis in a proximal segment or large vessel**

- **Mild stenosis or moderate or severe stenosis in a mid-distal or small vessel**

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**Adenosine stress cardiac MRI**

- Nuclear study if Creatinine ≥2.0

- **Angiography and revascularization as needed**

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**Primary Outcome (Death/MI/USA)**

1. CV death
2. C/H/F
3. Worsening renal failure
4. CAV or carotid revascularization
5. Cost
6. Functional status
7. Satisfaction

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*all patients will receive Visipaque. If creatinine 1.5-2.0 mg/dL, patients will receive fluid pre-loading*.

**severely stenotic ≥70% stenosis in at least one major vessel; moderately stenotic = 50-70% stenosis; mildly stenotic = 10-49% stenosis; normal = <10% stenosis and minimal or no plaquing. Any vessel that would prompt invasive angiography will be reviewed and agreed upon by a second reader.

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*The Intermountain Medical Center Radiology Department Sodium Bicarbonate Protocol will be used:*

Normal sodium bicarbonate is made up by pharmacy by adding 177 ml of 8.4% sodium bicarbonate in 1000 ml D5W to equal 150 mEq/1000 ml D5W. Infuse at 3 ml/kg/hr (not to exceed 330 ml/hr) for 1 hour. Decrease infusion rate to 1 ml/kg/hr. Infuse at this rate during the procedure and for an additional 4 hr after procedure, not to exceed one liter.
Appendix B: Adverse Events

Definition
An adverse event is defined as any undesirable experience associated with trial activities including any clinically significant abnormal sign, (abnormal physical exam or laboratory finding) symptom, illness, or other medical event temporally associated with a subject’s participation in the research, whether or not considered related to the subject’s participation in the research.

Adverse events information will be collected throughout the study and will be reported using the appropriate case report form. Adverse events will be recorded on the case report forms by the investigator or study’s clinical coordinator. Event, date of onset, severity, duration, and relationship to the procedure or study medication will be recorded on the appropriate case report form. Adverse events will be followed until they are adequately resolved or explained.

Serious Adverse Events and Death
The Investigator must decide whether each event meets the definition of a "serious" adverse event. The regulatory definition of a serious adverse event is: any adverse event temporally associated with the subject’s participation in research that meets any of the following criteria:

- results in death
- is life-threatening or places the subject at immediate risk of death from the event as it occurred
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- results in a congenital anomaly or birth defect; or
- any other adverse event based upon the investigator’s medical judgment, that may jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Any serious adverse event occurring within 30 days of the study procedure must be reported to the IRB and within one working day after the investigator or study team first learns of the event.

Anticipated Adverse Events Adverse events associated with diabetes are considered expected in this trial as all participants are known to have had diabetes for at least 3 years.

Unanticipated Adverse Events Death, onset of cancer and those events that are not associated with diabetes will be considered unexpected.
Appendix C: Study Responsibilities

Investigator Responsibility/Performance
The investigator shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of medical and clinical research practice and the regulations in 21 CFR 812 Subpart E, Responsibilities of Investigators. The investigator will provide copies of the current study protocol to all sub-investigators or other staff responsible for study conduct.

Institutional Review Board (IRB)
The investigators must submit the investigation plan and protocol to the IRB and obtain IRB written approval before initiation of the study. The investigator is also responsible for fulfilling any conditions of approval imposed by the IRB, such as regular reporting, study timing, etc. Upon completion or termination of the trial, the principal investigator should submit a final written report to the IRB as required by the IDE regulations in 21 CFR 812.150.

Patient Recruitment and the Consenting Process
Recruitment of subject for this trial will be accomplished per institutional standards (reflected in the Cardiology Research Group SOP for recruitment, screening and enrollment) will be investigators and their designees are responsible for obtaining informed consent from potential patients per Cardiology Research Group SOP/IHC guidelines prior to conducting any study procedures. The individuals conducting the consenting process will explain the contents of the approved ICF to the patient including:

- The investigational nature of the study,
- The scope and aim of the research
- HIPAA information as it specifically relates to this trial
- Known or foreseeable benefits and risks as well as discomforts that patients may experience
  - compensation for trial related injury
- The duration of the study
- The nature of any trial related expenses
- Voluntary nature of participation
- Nature of appropriate alternatives to trial enrollment
- Contact information for participants in the event they need addition information.

If the family of the patient is available, they should also be included in the consenting process. The patient will be asked to read (or the ICF can be read to them) the IRB approved (approval is clearly noted by the presence of the IRB stamp) consent agreement that contains the required elements of informed consent per 21 CFR 50. The patient must sign and date the ICF before the patient can be considered enrolled in this trial. A copy of the signed consent agreement will be given to the patient, per IHC research SOP, a copy of the signed and dated ICF will be placed in the patient’s medical chart, and the investigator will retain one copy as part of the study records.

Record Retention
The investigators are responsible for maintaining accurate, complete, and current records relating to the conduct of the investigation including: all correspondence with the IRB, Core Laboratory, DSMB or FDA including required reports:
1. Records of all subject case history, including study-required case report forms (CRFs), evidence of informed consent, all relevant observations of adverse effects, the condition of all subject upon entering and during the course of the investigation, relevant medical history, the results of all diagnostic testing, and the date of each study treatment.
2. Records concerning adverse events whether anticipated or not.
3. The protocol and documentation of any (date and reason) of each deviation from the protocol

The investigator will maintain the records for an indefinite period (not less than 2 years) after the date the investigation is completed or terminated. Records can be sent to archival storage if the facility has a valid contract with Intermountain Healthcare. Records may be used to support a pre-market approval application or further product development, provided written agreements are formed between the investigator and the manufacturer. If the investigator transfers custody of the records to another person, the FDA must be notified within 10 working days after the transfer occurs.

Confidentiality of Personal Health Information
The Cardiology Research Group regulatory and clinical coordinators will maintain all patients’ information supplied by the clinical investigators in accordance with Health Insurance Portability and Accountability Act of 1996 (HIPAA) and Intermountain Healthcare’s guidelines for compliance. The patient files will be secured at LDS Hospital using a numeric code to identify each subject (Intermountain Healthcare campus + sequential enrollment number, e.g. 128-000.)
Appendix D: Safety Oversight/Other Administrative Oversight

Events Evaluation Committee
The purpose of this clinical investigation is to determine if expected diabetic complications are prevented or occur with less intensity if early and aggressive preventative intervention is implemented in this population. Therefore, by definition, all adverse events associated with the progression of diabetes in all randomized patients will be evaluated and analyzed for endpoint events.

An independent Events Evaluation Committee will be assembled for this investigator initiated trial and will assume responsibility for regular review of the trial in regard to safety, outcome, interim analysis plan, and approval of the stopping rules. The events Evaluation Committee consists of the members who are not affiliated with the conduct of the faCTor 64.

The following data will be made available to the EEC by the investigators:
- demography
- all angiographic studies/over-read disagrees
- laboratory data as applicable
- adverse events, events qualifying as serious and all deaths occurring during trial participation regardless of association with trial activities
- withdrawal and reasons (if known) of patient’s withdrawal from the study.

Data Safety Monitoring Board (DSMB)
This body will be comprised of individuals familiar with the CT angiography procedure or the recommended parameters care available for diabetic patient and who have no affiliation with the conduct of the faCTor 64 trial.

The EEC will deliver all analyses to the DSMB. The DSMB will then review submitted safety data in order to make a recommendation for continuation or stopping the trial.

The first review will occur 6 months (± 10 days) from the date of the first randomization. The meeting proceedings will be confidential; however, the DSMB will issue a recommendation for continuation or discontinuation of the faCTor 64 trial immediately after the meeting.

The site will be self monitored (per Cardiology Research Group SOP to ensure that the study is conducted in full compliance with all applicable regulations and within the trial protocol parameters. The committee will regularly review the clinical trial complication rates (including all adverse events) and will evaluate the progress of the trial whenever unexpected complications occur.

Factor 64 CT Angiography Readers
A panel of readers will be responsible for the reading of each CT scan and the principal investigator will assume responsibility for informing the patient’s primary provider of the results and the recommendations for the appropriate care based on the treatment group. A CT angiography procedure protocol is provided; however the reader’s analysis of the CT scans will be the basis of treatment recommendations.

The purpose of this trial is to observe the “real life” treatment decisions associated with the care of the diabetic patient. To monitor quality and reliability, intra-observer and inter-observer variability will be determined for a subset of patients in this trial. Each reader will have 10 of their original scans randomly selected to be re-analyzed in an effort to determine intra-reader variability. Each of the readers will also re-analyze two of the other reader’s original scans for the analysis of inter-reader variability. Comparisons
between the re-analyzed scans will utilize the mixed model effects to determine the reliability of the evaluations.

**Factor 64 CT Angiography Over-readers**

All cardiac CT scans for the Factor 64 trial will be read and interpreted by the designated readers as described above. The readers will complete a report with the risk stratification and medical management recommendations. These recommendations will be followed clinically for the patients enrolled in the study. De-identified CT scans will then be sent in batches to Johns Hopkins University to be read as a quality assurance measure. Should discrepancies occur that would indicate a change in medical management, the safety monitoring board will discuss/compare the internal reader’s interpretation and the interpretation from Johns Hopkins University. Johns Hopkins University collaborates with the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH). Subsets of the CT scans received by Johns Hopkins will be sent to the NHLBI for analysis based on the severity of CAD.

If there is a discrepancy between the eventual Johns Hopkins study over-read and the original clinical interpretation AND if that would result in different management, that discrepancy will be reviewed by two CCT readers. They must agree that the evaluation from Johns Hopkins is correct for further action to ensue:

- If a significant stenosis was not identified by the original reader and if this would have resulted in stress testing, cath, or more aggressive medical management, then the patient and referring physician will be contacted and therapy will be changed to follow the study algorithm.
- If a significant stenosis was originally reported that would result in stress testing or cath, then that procedure will not be performed (unless it has already been completed). No changes will be made in medical management unless it is determined that this therapy is resulting in harm to the patient.
- Any discrepancies between the Johns Hopkins and IHC interpretations will be documented.

**Executive Operations Committee**

The Intermountain Heart Institute (IHI) Executive Committee will be responsible for the day-to-day administrative management of the trial. This committee will meet periodically to monitor subject enrollment, clinical site progress, and protocol compliance. This committee will be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications. A list of current members of the Executive Committee is available upon request from the office of the Director of Cardiovascular Research, Intermountain Heart Institute.

**Publications Committee**

This committee will be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications.
Appendix E:

World Medical Association Declaration of Helsinki

Recommendations Guiding Physicians in Biochemical Research Involving Human Subjects:

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, 35th World Medical Assembly, Venice, Italy, October 1983, 41st World Medical Assembly, Hong Kong, September 1989, and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996.

INTRODUCTION
It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the doctor with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a subject, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES
1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the
Investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with the medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give consent, the minor’s consent must be obtained in addition to the consent of the minor’s legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every subject -- including those of a control group, if any -- should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the subject to participate in a study must never interfere with the physician-subject relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1, 2).

1. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the subject.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS
(Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers -- either healthy persons or patients for whom the experimental design is not related to the subject's illness.

3. The Investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In the research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.
Screening For Asymptomatic Obstructive Coronary Artery Disease Among High-Risk Diabetic Patients Using CT Angiography: A Randomized Control Study (The FaCTor Study)

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# Coronary CT Angiography

## 10 Steps to Success

### Checklist

<table>
<thead>
<tr>
<th>Step</th>
<th>Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patient Preparation &amp; Positioning</td>
</tr>
<tr>
<td>2</td>
<td>Breath-Hold Training (HR Steady?)</td>
</tr>
<tr>
<td>3</td>
<td>Calcium Scoring Scan (CACS)</td>
</tr>
<tr>
<td>4</td>
<td>Determine the Start and End Positions</td>
</tr>
<tr>
<td>5</td>
<td>Planning the Coronary CTA Scan</td>
</tr>
</tbody>
</table>
| 6    | Use **SureCardio** to Select the Scan parameters with Automated Breath-Hold Training  
*mA must be set manually!* |
| 7    | Calculate the Contrast Bolus |
| 8    | Acquire the S&V Image for **SureStart** |
| 9    | Final Check – GO Coronary CTA |
| 1    | Cardiac Reconstruction |
**Exclusion Criteria (General):**

1. Known CAD (stenosis > 70%, MI, angina)
2. Symptomatic cerebral vascular disease
3. Symptomatic peripheral vascular disease
4. Treatment with other investigational drug within last 30 days
5. Pregnant/breastfeeding women. Women of childbearing age must have negative pregnancy test at screening and adequate measures of contraception.
6. Life-threatening conditions/comorbidities that make primary screening inappropriate (e.g. heart failure, significant AS)
7. Therapy or conditions that pose risk or make it difficult to comply with study requirements

**Exclusion Criteria Additional (CTA):**

1. Allergy to iodine
2. Allergy to beta-blockers
3. h/o contrast induced nephropathy
4. Elevated serum creatinine > 2.0 (Scr 1.5-1.9, renal protection protocol)
5. Atrial fibrillation, advanced AV block (second or third degree), other irregular heart rhythm
6. History of moderate bronchospastic lung disease/asthma/severe COPD

**Pre-Coronary CT Angiogram Plan:**

1. Clinical trial coordinator will contact enrollees with pre-study instructions and beta blocker protocol (see attached CCTA instruction sheet)
2. Pre-study checklist:
   A. No caffeine morning of procedure
   B. No solid food 4 hours prior to procedure
   C. Continue to take all medications except erectile dysfunction drugs (Viagra, Cialis, Levitra) and metformin (or metformin combinations) (see attached CCT instruction sheet)
   D. Drink plenty of fluids day of exam
   E. Check for serum creatinine within last 4 weeks (all patients are diabetics)
   F. Prescribe oral beta-blockers per protocol
3. Can contact Intermountain Cardiac Imaging – Advanced Diagnostic Center (Chris McGann, Brent Wilson, Melissa Sarhan) at (801) 408-8112 at any time with questions
**Beta Blockade Protocol**

**FOR PATIENTS WEIGHING <70 KG**

<table>
<thead>
<tr>
<th>Heart Rate &lt;50 bpm</th>
<th>No additional beta blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate 50-60 bpm</td>
<td>Metoprolol 50 mg by mouth 60 to 90 minutes before the exam</td>
</tr>
<tr>
<td>Heart Rate &gt;60 bpm</td>
<td>Metoprolol 50 mg by mouth the evening prior to the exam <strong>AND</strong> 50 mg by mouth 60 to 90 minutes before the exam</td>
</tr>
</tbody>
</table>

**FOR PATIENTS WEIGHING >70 KG**

<table>
<thead>
<tr>
<th>Heart Rate &lt;50 bpm</th>
<th>No additional beta blocker</th>
</tr>
</thead>
<tbody>
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<td>Heart Rate 50-60 bpm</td>
<td>Metoprolol 50 mg by mouth 60 to 90 minutes before the exam</td>
</tr>
<tr>
<td>Heart Rate &gt;60 bpm</td>
<td>Metoprolol 100 mg by mouth the evening prior to the exam <strong>AND</strong> 100 mg by mouth 60 to 90 minutes before the exam</td>
</tr>
</tbody>
</table>

**Metformin Protocol**

Metformin (Glucophage, Glucophage XR, Glumetza, Fortamet, Riomet, ACTOPLUS Met, Avandamet, Glucovance, Janumet, Metaglip) should be stopped the day of and for two days following the coronary CTA. During this time, the patient should be advised to monitor their blood sugar carefully and to contact their primary care physician should blood sugars rise dramatically (>300 mg/dL).

Patients should be informed that this precaution is being taken because the use of iodinated contrast materials can causes changes in kidney function and has been associated with lactic acidosis in patients taking metformin.
Itinerary - Day of Scan:

1. Radiology nurse meets all patients in Radiology waiting room
2. Toshiba block times
   - 8-10 am
3. Patients scheduled to arrive at:
   - 7:00 am
   - 7:15 am
   - 7:30 am
4. ER 33 Prep room and radiology sleep room
   - continuous ECG monitoring
5. Gown patients
6. IV line in right antecubital vein, 18-gauge
7. IV beta-blockade if HR > 65
8. Discuss scan/coach breathing/warnings about flushing during contrast

Breath Hold Training

The patient should practice breath holding before starting the examination. The breath-hold instruction given should be the same as the breathing instruction recorded in the scanner. This should be a single “breath in and hold” command.

The patient should be instructed to hold their breath at about 75% of maximum lung capacity and to take the same size breath each time they are told.

This important step has two purposes:

- To ensure that the patient can hold their breath for the required scan time
- To monitor the patient’s heart rate during breath holding. Make sure that a steady heart rate is displayed with a clean ECG signal.

Note: The patient’s heart rate should not fluctuate more that 10% during breath-hold training

Nitroglycerin

0.4 mg sublingual NTG will be given to the patient IMMEDIATELY AFTER the calcium scoring scan has been completed.
**Calcium Scoring Scan (CACS)**

- Select and perform the non-contrast faCTor64 CACS protocol

Confirm that the scan plan covers the entire heart for this scan.

- Remember, the smaller the display FOV, the higher the in-plane resolution. The display FOV should be between 200 and 220 mm.

**Note:** The calcium scoring (CACS) protocol uses prospective cardiac gating. Adjust the percent R-R trigger, according to the patient’s heart rate as shown in the chart below.

<table>
<thead>
<tr>
<th>Heart Rate (bpm)</th>
<th>% Cardiac Phase (Trigger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>79</td>
</tr>
<tr>
<td>60</td>
<td>75</td>
</tr>
<tr>
<td>70</td>
<td>71</td>
</tr>
<tr>
<td>80</td>
<td>67</td>
</tr>
<tr>
<td>90</td>
<td>63</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of Scans</th>
<th>kV</th>
<th>mA</th>
<th>Rot. Time</th>
<th>Slice Thickness</th>
<th>SureIQ</th>
<th>FOV</th>
<th>Recon. Thick.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scanogram</td>
<td>2</td>
<td>120</td>
<td>50</td>
<td>**</td>
<td>**</td>
<td>Sharp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S&amp;S Gated</td>
<td>12</td>
<td>120</td>
<td>300</td>
<td>0.23</td>
<td>3 mm (12)</td>
<td>Cardiac CaScore</td>
<td>M</td>
<td>3 mm / 3 mm</td>
</tr>
</tbody>
</table>
**Determining the Start and End Positions for the CTA**

From the calcium scoring examination, select the start and end positions for the CT angiogram.

- It is advisable to plan 1 cm above the superior image selected and 1 cm below the inferior image selected in case the patient’s breath holding is inconsistent
- Note that the proximal LAD is often located superior to the origin of the left main coronary artery

**Planning the Coronary CTA Scan**

This examination uses the same scanogram as the CACS scan. The magnification factor used for the CACS scan is automatically applied to this protocol.

- Select the faCTor64 coronary CT angiography protocol
- Enter the numerical start and end table positions in the eXam Plan

<table>
<thead>
<tr>
<th>No.</th>
<th>Start</th>
<th>Start Time</th>
<th>Wait</th>
<th>Start Pos.</th>
<th>End Pos.</th>
<th>Scan Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P</td>
<td>***</td>
<td>0.0</td>
<td></td>
<td></td>
<td>S&amp;V</td>
</tr>
<tr>
<td>2</td>
<td>P</td>
<td>***</td>
<td>5.0</td>
<td>***</td>
<td>***</td>
<td>SureStart</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
<td>Helical</td>
</tr>
</tbody>
</table>

- Place the S&V slice for SureStart at the same position as the start of the helical scan
Using **SureCardio** to Select the Scan Parameters in Breath-Hold Training

- Open the **SureCardio** menu by clicking the Scan Details tab
- Click the “Breath Ex.” Icon to start the automated breath hold practice
- **SureCardio** will monitor the patient’s heart during the breath hold training
- The patient’s recorded heart rate range will be automatically displayed. The optimal scan parameters will be selected to provide the best temporal resolution for the recorded heart rate range.

![SureCardio Scan Parameters](image)

**Scan Delay after Breathing Instruction.**

The patient’s heart rate is often unstable for the first 2 seconds after holding their breath. Be sure to provide a 2-second delay time between the breathing instruction and the start of scanning.

This can be achieved 2 ways:

1) In a site recorded voice instruction, the delay time can be added by stopping the recording 2 seconds after the instruction

2) You can add a two second delay time in the breath command software

**Note: You can set this up as a system default for all ECG gated scans**

![Breath Delay Settings](image)
Exposure Parameter Selection

Goal: <25 mSieverts

***ECG Dose Modulation ON with the following settings: 85% power reduction, 60-85% RR interval

The mA selection will depend on the Helical Pitch determined by SureCardio AFTER automated breathing exercise.

Note: Helical Pitch determines which table to use

MALE and FEMALE PATIENTS

Pitch 10.4 to 12.5

<table>
<thead>
<tr>
<th>Weight (kilograms)</th>
<th>Weight (pounds)</th>
<th>kV</th>
<th>mA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 kg</td>
<td>&lt;130 lbs</td>
<td>120</td>
<td>350</td>
</tr>
<tr>
<td>60 – 79 kg</td>
<td>130 – 179 lbs</td>
<td>120</td>
<td>400</td>
</tr>
<tr>
<td>80 – 99 kg</td>
<td>180 – 219 lbs</td>
<td>120</td>
<td>450</td>
</tr>
<tr>
<td>100-119 kg</td>
<td>220-263 lbs</td>
<td>120</td>
<td>500</td>
</tr>
<tr>
<td>≥ 120 kg</td>
<td>≥ 264 lbs</td>
<td>120</td>
<td>550</td>
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</tbody>
</table>

Pitch 12.6 and above

<table>
<thead>
<tr>
<th>Weight (kilograms)</th>
<th>Weight (pounds)</th>
<th>kV</th>
<th>mA for 0.35-s Rotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 kg</td>
<td>&lt;130 lbs</td>
<td>120</td>
<td>400</td>
</tr>
<tr>
<td>60 – 79 kg</td>
<td>130–179 lbs</td>
<td>120</td>
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</tr>
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<td>100-119 kg</td>
<td>220 - 263 lbs</td>
<td>120</td>
<td>550</td>
</tr>
<tr>
<td>≥ 120 kg</td>
<td>≥ 264 lbs</td>
<td>120</td>
<td>600</td>
</tr>
</tbody>
</table>
Contrast Bolus

Single-phase contrast with saline flush

Goal: complete washout of contrast from right side of heart

Contrast: Isovue 370 mg/L (Bracco Diagnostics)

Duration of contrast Injection = Scan Time + 10 seconds

Amount of Contrast to Inject = (Scan Time + 10 seconds) x Injection Rate

<table>
<thead>
<tr>
<th>Weight (kilograms)</th>
<th>Weight (pounds)</th>
<th>Injection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60 kg</td>
<td>&lt; 133 lbs</td>
<td>4 mL/sec</td>
</tr>
<tr>
<td>≥ 60 kg</td>
<td>≥ 134</td>
<td>5 mL/sec</td>
</tr>
</tbody>
</table>

Acquiring the SureStart S&V Image

- Confirm that the descending aorta can be clearly identified on the SureStart slice

- Place the SureStart ROI over the descending aorta as shown above
- Set the SureStart trigger at 180 HU

Note: Make sure that a suitable WW/WL has been set for real-time visualization
Final Check - GO Coronary CTA

- Reassure the patient that it is normal to experience a sensation of warmth following contrast administration.
- Inform the patient that the next breath-hold is the last one.
- Confirm that the patient’s heart rate is steady.
- It is a good idea to have someone monitor the first few seconds of contrast administration to avoid extravasation.

GO

1. Start contrast injection.
2. Start the SureStart exposure after 15 seconds.

Post Coronary CT Angiogram Instructions

On leaving the facility after the coronary CT, patients will be told to do the following:

- Remember to drink at least one liter of water over the next 12 hours (as long as they do not have the diagnosis of congestive heart failure)
- Remove the bandage from the IV site in the evening. If that site becomes tender, red, or swollen over the next week, they should contact their primary care physician
- If the patients take metformin (Glucophage, Glucophage XR, Glumetza, Fortamet, Riomet) or a metformin-containing combination medication ACTOPLUS Met, Avandamet, Glucovance, Janumet, Metaglip), they may resume their normal dosage in two days. While they are holding the medications, they should continue to monitor their blood glucose levels carefully and should contact their primary care physician should the levels rise >300 mg/dL (or beyond their comfort range)

Coronary CT angiogram results will be available to the primary care provider within 72 hours.

Cardiac Reconstruction

A. Coronary CTA

FOR ROUTINE EXAMINATIONS

Use phaseXact – automated phase selection software

phaseXact software automatically determines the best cardiac phase for motion-free imaging. Phase selection is performed in the raw data domain requiring no human interaction.

1. In the exam plan turn phaseXact on by clicking on the % icon for reconstruction phase input. A drop down menu will appear.

2. Select “Best Phase”

After the exam plan is completed phaseXact will find and reconstruct the best motion free cardiac phase.
Reconstruct the “Best Phase” + 50 msec and the “Best Phase” – 50 msec for diastole AND for systole using the FC43 kernel. The +/- 50 msec time periods will need to be manually entered (i.e. will not be selected with the automatic “window” option).

Then reconstruct the “Best Phase” for diastole AND for systole using the stent FC05 kernel (no need to reconstruct using the FC05 kernel for the +/- 50 msec phases as well).

Not counting the reconstructions for functional analysis, each study will have 8 reconstructions for the CTA analysis (6 using the “regular ccta” FC43 kernel and 2 using the “stent” FC05 kernel).

For example, if the “Best Phase” for diastole is 750 msec and the “Best Phase” for systole is 300 msec, the patient should have the following reconstructions:

700 msec (using FC43 kernel)
750 msec (using FC43 kernel)
800 msec (using FC43 kernel)
250 msec (using FC43 kernel)
300 msec (using FC43 kernel)
350 msec (using FC43 kernel)
750 msec (using FC05 kernel)
300 msec (using FC05 kernel)

FOR DIFFICULT CASES

ImageXact – Guided imaged based phase selection software

In the case a patient’s heart rates becomes very unstable during the scan, phaseXact may not be able to automatically determine the best motion free cardiac phase. In this case, ImageXact will help by guiding the operator through a simple and accurate manual phase selection process.

The concept of imageXact is to perform reconstruction at an absolute time point after the R wave (R + ms) using Toshiba's adaptive segmental reconstruction algorithm. Phase selection is performed using a single slice usually located at the mid-heart level and reconstructed through the entire cardiac cycle.
The software guides you through the steps to determine the exact cardiac phase for motion-free images.

1) Select a slice location at the mid-heart level. Click "Next".

Note: This slice should demonstrate the three main coronary arteries in cross-section (end-on). The image does not need to be motion free.

The selected slice is reconstructed for one cardiac cycle at 20-ms intervals. (The interval can be changed in the details menu.)

2) Review these images to find the phase(s) that best demonstrate the coronary arteries at this slice position. Click "Select Phase".

Note: Remember to view the entire cardiac cycle before making your selection.

The R-R phase of the displayed image is automatically entered in the reconstruction list.
Reconstruct at “best phase” +/- 50 msec for diastole and for systole using the FC43 kernel and at “best phase for diastole and for systole using the FC05 kernel (see above).

3) Click "Recon".

The entire volume is reconstructed at the selected phase(s).

REMEMBER: Overlapping reconstructions will improve Z-axis resolution. For 0.5-mm slices, reconstruct at 0.3-mm intervals.

B. Reconstruction for CFA (Cardiac Functional Analysis)

CFA is performed to evaluate left ventricular function. Quantitative measurements, including ejection fraction etc., can be obtained from the same data acquired for the CTA study.

To perform CFA, we recommend reconstruction of 10 phases from 0% to 90% at 10% intervals. Spatial resolution is not of primary importance for CFA, so the amount of data can be reduced by reconstructing volumes with a 1-mm slice thickness.

Method

In the Raw data screen:

1) Enter 10 phases for reconstruction from 0% to 90% at 10% intervals. (In Cardiac Phase, enter 0,90,10.)

2) Change the reconstruction slice thickness and reconstruction slice interval to 1 mm and 1 mm.

3) Adjust the start and end positions of the reconstruction range to cover the heart only (if necessary).

4) Start the reconstruction and close.
Effective slice thickness 1.0 mm  Recon. Interval 1.0 mm

Number of images 111 (Max. 134)

- ECG Gating
  - Recon. Mode: Half
  - Options: ECG, ECG Save, ECG Edit

Cardiac phase 0, 90, 10

R-R Range 0.8 - 2.0 Sec

Sure IQ Settings

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>FC</th>
<th>QDS</th>
<th>Boost3D</th>
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<tr>
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<tr>
<td>Stent</td>
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<td>QDS +</td>
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<tr>
<td>Smooth</td>
<td>2</td>
<td>QDS +</td>
<td>ON</td>
</tr>
<tr>
<td>Ca Score</td>
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<td>Off</td>
<td>Off</td>
</tr>
</tbody>
</table>

Deidentification of Patient Information

CTAs sent to Johns Hopkins University for over-read will be deidentified and will only contain patient randomization number.
SCREENING FOR ASYMPTOMATIC OBSTRUCTIVE CORONARY ARTERY DISEASE AMONG HIGH-RISK DIABETIC PATIENTS USING CT ANGIOGRAPHY: A RANDOMIZED CONTROL TRIAL

Statistical Analysis Plan
Version 3

Prepared by: Stacey Knight

CONFIDENTIAL
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1. PREFACE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Intermountain Heart Institute protocol Screening For Asymptomatic Obstructive Coronary Artery Disease Among High-Risk Diabetic Patients Using CT Angiography: A Randomized Control Trial.

This study is being completed to assess the safety and efficacy of screening using coronary CT angiography (CCTA) for the detection of coronary artery disease (CAD) in diabetic patients.

The following documents were reviewed in preparation of this SAP:

- Case report forms (CRFs) for Protocol protocol 128-026.
- ICH Guidance on Statistical Principles for Clinical Trials.

The reader of this SAP is encouraged to also read the clinical protocols for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study.
2. **PURPOSE OF SAP**

   The purpose of this SAP is to outline the planned analyses to be completed for this study. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Also, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP performed will be clearly identified in the respective study report.
3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective is to determine whether the screening of asymptomatic high-risk patients with diabetes for the presence of obstructive coronary artery disease through the use of 64-slice CT scanning can result in a significant reduction in death, myocardial infarction and unstable angina in a specific population.

3.2 StudyEndpoints (Target Variables)

3.2.1 Primary Target Variable

The primary target variable (endpoint) is major adverse cardiovascular events (MACE) which is the composite of all-cause death, MI, and hospitalization for unstable angina. Outcomes were ascertained by directly questioning the patient (or family if needed), reviewing medical records and querying Intermountain Healthcare electronic health records, and searching the national Social Security Death Index and the Utah State Death Certificate Database. Primary and secondary events were adjudicated by consensus of a 3-investigator team masked to study arm and CCTA results.

3.2.2 Secondary Target Variable(s)

Secondary target variables (endpoints) are the following

1. cardiovascular (CV) death
2. hospitalization for congestive heart failure
3. worsening renal failure (defined as progression of serum creatinine by ≥0.5 mg/dL) – *this is a safety endpoint*
4. stroke or carotid revascularization procedure
5. limb amputation or peripheral vascular revascularization procedure
6. cost
7. functional status

*Added Aug 2014:* Coronary artery death, combination of CV death, MI and unstable angina hospitalization, and combination of CAD death, MI and unstable angina hospitalization.
4. STUDY METHODS

4.1 Overall Study Design and Plan

A prospective, parallel, randomized study

4.2 Selection of Study Population

The study population is patients with a known history of diabetes mellitus and no prior documented evidence of cardiovascular disease.

Inclusion Criteria:

1. Age: Males ≥ 50 years; Females ≥55 years with: History of diabetes mellitus (prior documentation of fasting glucose ≥ 126 mg/dl or hemoglobin A1C > 6.5%), either type 1 or type 2, documented for at least 3 years and on medication for at least one year.
2. Age: Males ≥ 40 years; Females ≥45 years with: History of diabetes mellitus (prior documentation of fasting glucose ≥ 126 mg/dl or hemoglobin A1C > 6.5%), either type 1 or type 2, documented for at least 5 years and on medication for at least one year.
3. The patient or legally authorized representative must sign a written informed consent, prior to the procedure, using a form that is approved by the local Institutional Review Board.

Exclusion Criteria:

1. Known coronary artery disease (stenosis >70%, history of myocardial infarction, or angina)
2. Symptomatic cerebral vascular disease (history of TIA, CVA, or cerebrovascular [carotid or cerebral arteries] revascularization)
3. Symptomatic peripheral vascular disease (history of claudication, amputation, or peripheral [including renal arteries] arterial revascularization)
4. Treatment with any other investigational drug within the previous 30 days
5. Any therapy or condition that would pose a risk to the patient or make it difficult to comply with study requirements.
6. Pregnant and/or lactating women, and women of child bearing potential not using acceptable means of contraception. Women of childbearing potential must be using adequate measures of contraception (as determined by the Investigator) to avoid pregnancy and should be highly unlikely to conceive during the study period. Women of childbearing potential must have a negative pregnancy test at screen.
7. Any life threatening condition/significant co-morbidity such that primary screening is inappropriate.
4.3 Method of Treatment Assignment and Randomization

Randomization will be done using a 1:1 permuted block randomization scheme with blocking size from 2-8.

4.4 Treatment Masking (Blinding)

The blinding of subjects or clinicians in this study is not possible. So no blinding was done.
5. SEQUENCE OF PLANNED ANALYSES

5.1 Interim Analyses

Three interim analyses are planned for this study. Using the Lan-DeMets version of the O’Brien-Fleming group sequential boundaries for a 4-looks sequential design (3 interim analysis for every 250 patients + final analysis), the statistical power to test the primary study end point is approximately 80% based on a maximum sample size of 1100 patients randomized in a 1:1 allocation ratio and an overall experimental type I error equal to 0.05 using a 2-sided hypothesis test. Specific details of sample size for the adopted sequential design are given in Tables 1 and 2, and in Figure 1. All statistical tests will be 2-tailed with an overall study probability of a type I and type II error equal to 0.05 and 0.80, respectively.

Figure 1.

Table 1. Superiority coordinates and p-values from Figure 1.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Lower Confidence Interval</th>
<th>Upper Confidence Interval</th>
<th>H0 Reject Upper Alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 patients</td>
<td>-4.3326</td>
<td>4.3326</td>
<td>0.00000</td>
</tr>
<tr>
<td>500 patients</td>
<td>-2.9631</td>
<td>2.9631</td>
<td>0.0030</td>
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</table>
Table 2. Futility coordinates and p-values from Figure 1.

<table>
<thead>
<tr>
<th></th>
<th>Lower Confidence Interval</th>
<th>Upper Confidence Interval</th>
<th>H0 Accept Upper Alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>750 patients</td>
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<tr>
<td>Final Analysis</td>
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<td>0.0440</td>
</tr>
</tbody>
</table>

5.2 Final Analyses and Reporting

All final, planned, analyses identified in the protocol and in this SAP will be performed only after the last patient has completed a minimum of 6 months of follow-up. Key statistics and study results will be made available to investigators following database lock and prior to completion of the final report.

Any, post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in appendices to the report. Any results from these unplanned analyses will also be clearly identified in the text of the report.
6. **SAMPLE SIZE DETERMINATION**

Based on the measured 2 year event rate for death/MI of 12.1% among all diabetics enrolled at Intermountain Healthcare, it is estimated that, among those meeting the inclusion/exclusion criteria, the control group should have a 2-year event rate of at least 16%. Therefore, using the Log-rank test of survival, it is estimated that with 482 subjects per arm there will be >80% power with an alpha of 0.05 to detect a 40% reduction in events in the screening arm compared to control. Thus, to account for patients that withdraw or are lost to follow-up, we plan to enroll a total of 550 subjects in each arm for a total of 1,100 subjects.

7. **ANALYSIS POPULATIONS**

The following analysis populations are planned for the studies:

- **Intent-to-Treat Efficacy/ Safety (Full Analysis set):** This population includes all patients who are randomized and completed baseline questionnaire with treatment group assignment based on randomization regardless of treatment (or lack thereof) received.

- **Per-Treatment Efficacy:** This population includes all patients who are randomized and completed baseline questionnaire with treatment group assignment based on actual treatment received.
8. GENERAL ISSUES FOR STATISTICAL ANALYSIS

8.1 Analysis Software
All analysis will be performed using SAS® Software version 9.3 or later. Graphs will be generated using R software.

8.2 Methods for Withdrawals, Missing Data, and Outliers
The outcome data for patients that withdraw from the study will be censored at time of withdrawal. Any variable with greater than 10% missing will be examined to determine the reason for missing. If no bias is detected, these variables will continue to be examined. If the missingness is greater than 20%, the variable will not be used in analyses. Values outside acceptable range for any variable will be deemed to be errors and nulled, unless corrected value can be determined through chart review.

8.3 Data Transformations
Transformation of lipid and other lab values may be done using standard transformation methods such as natural log.

8.4 Planned Subgroups, Interactions, and Covariates
Exploratory subgroup analyses include subjects with diabetes type 2, subjects with high hemoglobin A1c, subjects on insulin, subjects with hyperlipidemia, subjects on statins, obese subjects, and subjects with hypertension. Other unplanned subgroup analyses will be clearly identified in the text of the report.

8.5 Derived and Computed Variables
The following derived and computed variables have been initially identified. It is expected that additional variables will be required. The SAP will not be amended for additional variables that are not related to the primary target or key secondary target variables. Any additional derived or computed variables will be identified and documented in the SAS programs that create analysis files.

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Description</th>
<th>Valid Values (Ranges)</th>
<th>Computation Methods, Notes, or Equation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>Body Mass Index (kg/m²)</td>
<td>12 to 80</td>
<td>$\frac{lbs}{inches^2} \times 703$ or $\frac{Kg}{m^2}$</td>
</tr>
</tbody>
</table>

Variable Name | Description                  | Valid Values (Ranges) | Computation Methods, Notes, or Equation(s) |
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Baseline Comorbidities</td>
<td>ICD-9 code (x=wildcard)</td>
<td></td>
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</tr>
<tr>
<td>-------------------------------------</td>
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<td></td>
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</tr>
<tr>
<td>Hypertension</td>
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<td>Hyperlipidemia</td>
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<tr>
<td>Asthma</td>
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<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>58x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
9. **STUDY SUBJECTS**

9.1 **Disposition of Subjects and Withdrawals**
All subjects who provide informed consent will be accounted for in this study. The frequency and percent of subjects in each population, study withdrawals, subgroups, and major protocol violations will also be presented.

9.2 **Protocol Violations and Deviations**
All protocol deviations will be tracked, reported to the IRB and included in final report.

9.3 **Inclusion and Exclusion Criteria**
The reason that screened patients that do not meet inclusion/exclusion criteria will be tracked and reported.

10. **DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS**
Subjects’ baseline characteristics will be described using frequencies and proportions for categorical variables and means and standard deviations, or medians and interquartile ranges, for continuous variables. Bivariate associations between randomization status and baseline characteristics will done using non-parametric tests (Wilcoxon rank sum or Kruskal–Wallis) and chi-square tests.

11. **EFFICACY ANALYSES**

11.1 **Primary Outcome Analysis**

The analysis of the primary outcome of MACE will include the following test of hypothesis:

\[ H_0: \text{the time to first MACE events are same for the two randomization groups (CCTA vs no CCTA)} \]

The alternative hypothesis is:

\[ H_1: \text{the time to first MACE events are different for the two randomization groups (CCTA vs no CCTA)} \]

The model used to complete the primary analysis is a Cox proportional hazards regression (with time to first event) was used to determine hazard ratios (HRs) comparing MACE events by intention-to-treat in CCTA versus non-CCTA randomized subjects. Kaplan-Meier curves are presented as well. In addition to the intention-to-treat analysis, a per-treatment analysis will be done using the
same statistical methods. Finally, all the independent variables in the composite MACE variable will be examined individually.

11.2 Secondary Outcome Analysis

The secondary outcomes as listed in Section 3.2.2 will be analyzed using Cox proportional hazards regression (with time to first event).

11.3 Other Efficacy Variable Analysis

Additional efficacy analyses will be done for the change in hemoglobin A1c, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglycerides, systolic blood pressure, and dystolic blood pressure from baseline to one-year. One-year follow-up will be based on lab results closest to the year mark and/or study related follow-up visit by the research coordinator. Pairwise changes from baseline to 1-year follow-up lipids, hemoglobin A1c, and blood pressure were tested using paired t-tests, and intergroup assessment (for CCTA vs no CCTA) will done using non-parametric tests.

All analyses will be done using both intention-to-treat and per-treated approaches.
12. **SAFETY ANALYSES**

The primary safety endpoint is the worsening renal failure (defined as progression of serum creatinine by ≥0.5 mg/dL at 30 days and persisting at one year). This will be tested using a Fisher’s exact tests based on intention-to-treat and per-treatment.