Title: Default vs As-Needed Intraoperative Transesophageal Echocardiography (TEE) in Low-Risk Isolated Coronary Artery Bypass Graft (CABG) Surgery: A Randomized Controlled Trial

Short Title: Intraoperative Echocardiography in Low-Risk CABG Surgery

CLINICALTRIALS.GOV ID: NCT06154265

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1 List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ALARA	As Low As Reasonably Achievable
CABG	Coronary artery bypass graft
CI	Cardiac Index
CO	Cardiac Output
CRF	Case Report Form
DSMP	Data Safety and Monitoring Plan
EC	Ethics Committee
EF	Ejection Fraction
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
LFT	Liver Function Test
LV	Left ventricle
MRN	Medical Record Number
NIH	National Institutes of Health
NHLBI	National Heart, Lung, and Blood Institute
PAC	Pulmonary arterial catheter
PI	Principal Investigator
PPMC	Penn Presbyterian Medical Center
RV	Right ventricle
SAE	Serious Adverse Event
SV	Stroke volume
TEE	Transesophageal Echocardiography
TTE	Transthoracic Echocardiography
UADE	Unanticipated Adverse Device Effect

2 Statement of Compliance

I agree to conduct the trial as outlined in the protocol in accordance with the NIH's and NHLBI's guidelines and other applicable FDA regulations, ICH guidelines for Good Clinical Practices (GCPs), and conditions of approval imposed by the reviewing IRB/EC. The Sponsor's guidelines include, but are not limited to:

- Provide supervision of all testing of the device involving human subjects.
- If applicable, provide the NIH with information regarding past investigations or other research that was terminated, including an explanation of the circumstances that led to the termination.
- Allow the NIH and/or other regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner that ensures subject confidentiality.
- Notify the NIH as soon as possible if this study is to be inspected by a regulatory agency.
- Submit the proposed clinical investigation including the protocol and the consent form to an IRB/EC for approval, if required.
- Ensure informed consent is obtained prior to the use of any test articles.
- Submit any proposed change in, or significant deviation from, the protocol to an IRB/EC for approval, and ensure the changes are reflected in the informed consent form, as appropriate, and also approved by the IRB/EC.
- Document protocol deviations and violations with explanations as appropriate.
- Submit Adverse Events (AEs) to the Sponsor and IRB/EC as outlined in the protocol.
- Submit timely progress reports to the IRB/EC and Sponsor as appropriate.
- Maintain adequate and accurate records of all study procedures, observations, results, and other related information (such as safety, protocol compliance, and product accountability).

I agree that all information provided to me by the NIH including protocols, verbal and written information shall be kept confidential and restricted to the personnel involved in conduct of the trial. It is recognized that this information may be conveyed to the IRB/EC. I also understand that reports or information about the trial and its progress shall not be provided to anyone not involved in the trial other than the NIH or other legally constituted authority. The described study will be conducted in compliance with the protocol, clinical practice standards, associated federal regulations, and all University of Pennsylvania research requirements will be followed. Specifically: 45 CFR 46, 21 CFR Parts 50, 54, 56, and 812 and Good Clinical Practice: Consolidated Guidelines approved by the International Conference on Harmonization (ICH).

3 Protocol Synopsis

Title	Default vs As-Needed Intraoperative Transesophageal Echocardiography (TEE) in Low-Risk Isolated Coronary Artery Bypass Graft (CABG) Surgery: A Randomized Controlled Trial
Overview	The proposed study protocol will randomize low-risk isolated CABG surgery patients to receive either default or as-needed intraoperative TEE. Trial outcomes will include absolute recruitment rate, intervention fidelity, and incidence of gastroesophageal injury.
Primary Objectives	Primary objectives: 1. Recruitment feasibility assessment as measured by an absolute recruitment rate. Absolute recruitment rate is defined as the number of successfully enrolled participants divided by the total number of screened participants. 2. Assess intervention fidelity by calculating the rate of TEE performed among participants randomized to the as-needed TEE trial arm.
Secondary Objectives	Secondary Objectives: 1. Evidence of clinically-significant gastroesophageal dysfunction during hospitalization – either by patient-reported symptoms or by the presence of testing for swallowing difficulty, dysfunction, or upper endoscopy diagnostic procedures. 2. Evidence of end-organ dysfunction based on clinical notes (e.g. “transaminitis,” “acute kidney/renal injury”), and/or laboratory-based evidence of (e.g. liver function tests [LFTs], serum creatinine [Cr], lactate, etc.). 3. Incidence of in-hospital, post-surgical, cardiovascular re-intervention (e.g. return to the operating room for any reason, unplanned or emergency cardiac catheterization post-surgery, or placement on venoarterial extracorporeal membrane oxygenation [VAECMO]). 4. Incidence of all-cause in-hospital mortality
Population	Isolated CABG surgery patients meeting trial eligibility criteria (see inclusion/exclusion), scheduled to undergo surgery at hospitals within the University of Pennsylvania Health System.
Key Eligibility Criteria	In addition to meeting strict inclusion and exclusion criteria, subjects must be willing and capable of providing informed consent and physically capable of performing study related activities.
Site	Hospitals within the University of Pennsylvania Health System

Study Duration	24 months
Participant Duration	Active participations: Informed consent duration: approximately 30 – 60 minutes Study duration: 5 days (120 hours) starting with the time of patient enters the cardiac operating room for CABG surgery. Passive participation: Full study duration for the purposes of data acquisition, data cleaning, report generation, manuscript preparation and publication where applicable. Total time: ~24 months

4 Background Information

There is no randomized evidence to support the use of intraoperative TEE in any type of cardiac surgery. This evidence gap is particularly problematic in isolated CABG surgery for three reasons. First, in contrast to the comparative effectiveness studies that have associated intraoperative TEE with improved outcomes after cardiac valve,[1, 2] proximal aortic,[2] observational research comparing clinical outcomes after isolated CABG surgeries with (vs without) intraoperative TEE have been equivocal.[3-5] Second, observational research cannot confirm a causal link between intraoperative TEE and improved outcomes. This is especially problematic in isolated CABG surgery given how TEE is used during surgery. For instance, unlike the direct mechanism by which intraoperative TEE could improve outcomes in valve surgery (e.g. facilitating real-time surgical planning,[6, 7] confirmation of pre-surgical valve pathology,[8, 9] or immediate identification and resolution of a technical error in valve surgery and avoiding a return to the operating room),[10] the mechanism by which intraoperative TEE could improve outcomes in isolated CABG surgery is indirect (e.g. hemodynamic monitoring by differentiating between cardiac failure[11-13] and hypovolemia).[14, 15] Third, while life-threatening complications directly attributable to intraoperative TEE are rare (incidence of esophageal perforation from TEE is 0.01%),[16] gastroesophageal injury from TEE after cardiac surgeries range 0.1% – 4%.[17-20] Thus, the true risk vs benefit of intraoperative TEE during isolated CABG surgery is unknown.

The unclear clinical efficacy, unknown real-world effectiveness, and undefined risk-benefit ratio of intraoperative TEE during isolated CABG surgery is an evidence gap that may only be resolved prospectively through randomization. Consistent with this assessment, preliminary qualitative research consisting of semi-structured interviews with cardiac surgeons (including Dr. Wilson Szeto, Chief of Cardiac Surgery at Penn Presbyterian Medical Center [PPMC]), suggests that cardiac surgeons believe that intraoperative TEE may expose their routine, lower-risk isolated CABG surgery patients to unnecessary complications related to TEE without a commensurate improvement in outcomes. Thus, this proposed feasibility RCT (pre-approved by Dr. Szeto to take place at PPMC), will capitalize on this existing clinical equipoise to test the practical feasibility of conducting an RCT by randomizing routine, lower-risk, isolated CABG surgery patients to either default or as-needed intraoperative TEE during surgery.

5 Product Description

This study proposes randomization of default vs as-needed use of transesophageal echocardiography (TEE) –a legally marketed, imaging device that is used intraoperatively during cardiac surgeries in the University of Pennsylvania Health System (UPHS).. The Office of Clinical Research (OCR) has determined that the ultrasound system (probes and machines) proposed for this trial meets the requirements for Exemption from a Food and Drug Administration (FDA), Investigational Device Exemption (IDE) because it is a, “Legally marketed device used in accordance with its labeling.” Please refer to the approved FDA IDE approval letter from OCR submitted with this protocol.

5.1 Detailed Product Description of Equipment

Figure 1: Transesophageal Echocardiography Probe

Figure 1: This image is a photograph of a Philips transesophageal echocardiography (TEE), ultrasound probe. During cardiac surgeries, this probe is passed through the

patients oropharynx and advanced into the esophagus and/or stomach to acquire real-time, ultrasound-based, cardiac images during surgery. https://www.usa.philips.com/healthcare/resources/feature-detail/ultrasound-tee-imaging

6 Study Objectives and Purpose

The overall objective of this RCT is feasibility testing. To accomplish this, we will randomize eligible isolated CABG surgery patients to receive either default (i.e., obligatory) vs as-needed (i.e. backup) intraoperative TEE. Enrolled subjects will be randomized after induction of anesthesia. Trial outcomes will include subject recruitment, overall rate of TEE performed in the as-needed trial arm, and clinical outcomes.

6.1 Primary Objective(s)

- Recruitment feasibility assessment as measured by an absolute recruitment. Absolute recruitment will be defined as the number of successfully enrolled participants divided by the total number of screened participants.
- Calculate the rate of TEE performed among participants randomized to as-needed TEE trial arm.

6.2 Secondary Objective(s)

- Describe the incidence of gastroesophageal symptoms, injury, or complications: defined as the rate of patient-reported gastroesophageal symptoms (e.g. painful or difficulty swallowing, hoarseness, or eating), swallowing dysfunction (defined by the need for a postoperative swallowing evaluation after surgery), or diagnosis of a new gastroesophageal problem (defined by the need for an upper endoscopy after surgery).

6.3 Selection of Subjects

Subjects will be enrolled based on the inclusion/exclusion criteria listed in sections 6.3.1 and 6.3.2. The Principal Investigator or a qualified designee will be responsible for confirming that all subjects screened are eligible for the study based on the following inclusion and exclusion criteria:

6.3.1 Inclusion Criteria

1. Scheduled to undergo isolated CABG surgery at a hospital within the UPenn Health System
2. Age ≥18 years
3. Ejection fraction ≥50%
4. Transthoracic echocardiography performed within one year of the CABG surgery
5. Left heart catheterization performed within one year of the CABG surgery
6. English language fluency or facilitated by a language interpreter
7. Able to provide informed consent either in English or via a language interpreter
8. Willing to comply with all study procedures

6.3.2 Exclusion Criteria

1. Documented valve (aortic, mitral, tricuspid, or pulmonic) disease (stenosis or regurgitation) moderate or greater.
2. Any CABG surgery with either “possible” or “definite” aortic intervention listed as a planned part of the procedure.
3. Any CABG surgery with either “possible” or “definite” valve repair/replacement listed as a planned part of the procedure.
4. Having undergone any previous cardiac surgeries (i.e. scheduled with a “REDO” modifier).
5. Proximal/critical left main coronary disease (e.g. ≥90% stenosis).
6. Preexisting anomalous coronary arteries
7. Preexisting end-stage renal disease on hemodialysis
8. Preexisting chronic kidney disease (CKD) stage 3, 4, or 5
9. Stroke with residual focal neurological deficits within 90 days of surgery
10. Any of the following presurgical, mechanical circulatory support devices:
    a. Intraaortic balloon pump
    b. Percutaneous right ventricular assist device (RVAD)
    c. Impella
    d. Extracorporeal membrane oxygenation (ECMO)
11. Absolute contraindication to echocardiography defined as one or more of the following documented conditions:
    a. Esophagectomy
    b. Esophagogastrectomy
    c. Esophageal trauma
12. Any of these three relative contraindications to TEE:
    a. Esophageal varices
    b. Gastric bypass surgery
    c. Descending thoracic aortic aneurysm
    d. Oropharyngeal anatomical abnormalities
13. Severe pulmonary hypertension defined as:
    a. Pulmonary arterial pressure ≥60 mmHg
    b. Pulmonary vascular resistance (PVR) ≥3 Woods Units
14. Hemodynamic instability after induction and following placement of an endotracheal tube will be defined as one or more of the following events or scenarios:
    a. Placement of an intraaortic balloon pump (IABP)
    b. Initiation of venoarterial extracorporeal membrane oxygenation (VAECMO)
    c. Placement of a right or left percutaneous mechanical circulatory support device.
    d. Initiation of epinephrine infusion at a dose ≥0.08 mcg/kg/min (i.e. exceeding 4 – 6 mcg/min) for a duration ≥5 minutes

e. Initiation of norepinephrine at a dose ≥0.10 mcg/kg/min (i.e. exceeding 6 mcg/min) for a duration ≥5 minutes
f. Initiation of phenylephrine infusion at a dose ≥1.5 mcg/kg/min (i.e. exceeding 100 mcg/min) for a duration ≥ minutes
g. Initiation of vasopressin infusion at a dose ≥0.04 units/min for a duration ≥ 5 minutes

7 Withdrawal of Subjects

Study participation is voluntary. Subjects may refuse to consent or withdraw from the study at any time without penalty or loss of benefits.

8 Overview of RCT

This study will be a prospective, parallel design, randomized controlled trial.

8.1 Detailed Study Protocol

- Overview of protocol phases (listed in sequence)

8.2 Screening

- The cardiac surgery outpatient office will serve as the primary location for pre-screening potentially eligible participants but inpatients who meet inclusion criteria will also be eligible. Screening of the clinic schedule or the inpatient cardiac surgical census will identify potential patient subjects that meet study entry criteria. Eligible patients will be approached after it is determined that CABG is indicated for standard of care. Patients will not be approached for enrollment on the day of surgery to allow adequate time for the patient to consider the risks and benefits to participation.
- Patient subjects will be invited to participate in trial at after completing their pre-operative surgical office visit at a UPenn cardiac surgery clinic or following admission to the hospital. Time allotted for patient subject enrollment in the study will be approximately 30-45 minutes in order to adequately allow for a comprehensive discussion on the risks/benefits to patient participation, and to answer any questions that might arise during the consenting process. If English is not the subject's first language an interpreter will be used to facilitate the informed consent process in the subject's native language. The subject will be provided the cellphone number of the PI or their designee and informed that they can call the PI or designee with any questions.

8.3.1 Informed Consent Process

- Study participation is voluntary. Potential subjects, and/or their legal representatives, are given the most current IRB/EC-approved consent

form to read. If English is not the subject's first language, a short document in their native language will be provided. They will be provided ample time for review and an opportunity to ask questions about the study. If they agree to participate, they will sign the consent form and be given a copy of the signed document for their records. The original signed copy of the consent form(s) will be retained by the Principal Investigator. Each of these actions/steps will be documented. Only after Informed Consent has been obtained, may the study procedures begin. Informed Consent may also be documented through a 21 CFR Part 11 compliant eConsent tool.

8.3.2 Inability to Provide Consent

- For this study, eligible subjects must be willing and physically able to undergo all study procedures. If they are unable to provide consent, they may not participate.
- Enrollment shall proceed via a signed written Informed Consent by each subject. No study activities will be allowed without prior written consent of the subject. Subjects meeting the eligibility criteria shall be consented and enrolled by the Principal Investigator or CRC delegate. Informed Consent may also be documented through RedCap, a compliant web platform for managing data. Study participation is voluntary. Subjects may refuse to consent or withdraw from the study at any time without penalty or loss of benefits. All steps will be completed in one-day, and subject will be dismissed from the study.

8.3.3 Financial Compensation for Trial Participation

- Patients will not be financially compensated for participation in this trial.

8.3.4 Records of Informed Consent

- Copies of the informed consent document will be provided to all patients participating in the trial.
- It will be reiterated that subjects may elect to de-enroll from the trial at any time.

8.3 Randomization and Trial Protocol

8.4.1 Randomization

- Randomization will occur on the day of surgery after placement of an arterial line for invasive hemodynamic monitoring (routine for all patients undergoing isolated CABG surgery) and following induction of anesthesia and successful placement of the endotracheal tube. This will ensure that any patient who is hemodynamically unstable (defined by the exclusion criteria listed above) following induction of anesthesia is excluded from the trial (and will receive an obligatory intraoperative TEE).

8.4.2 Trial Protocol for Default (i.e., Obligatory) TEE: Control Arm

- After induction, patients randomized to the default TEE trial arm will have the TEE probe passed into the esophagus after the endotracheal tube has been secured.
- The protocol for those enrolled in the default TEE trial arm will have one pre-surgical TEE exam (defined as ≥10 video acquisitions) and one post-surgical TEE exam (defined as ≥10 video acquisitions).
- While use (or lack of use) of TEE during isolated CABG surgery are both considered standard-of-care by national guideline recommendations, at the University of Pennsylvania, the typical practice is to place the TEE as a default monitor (i.e., immediately following induction of anesthesia and placement of the endotracheal tube). Therefore, for this pilot trial, this trial arm – the default/obligatory TEE – will be considered the control.

8.4.3 Trial Protocol for As-Needed (i.e. Backup) TEE: Intervention Arm

- After induction of anesthesia, patients randomized to the as-needed TEE trial arm will not have the TEE probe placed after the endotracheal tube has been secured. However, both the TEE machine and TEE probe will both be present in the operating room to minimize any delay in probe placement if TEE is requested by the cardiac surgeon or deemed medically necessary by the cardiac anesthesiologist.
- As described above, because the typical practice at University of Pennsylvania is the obligatory placement of the TEE. Therefore, for this pilot trial, this trial arm – the as-needed/backup TEE – will be considered the intervention arm.

8.4 Data Collection

8.5.1 Electronic Medical Record (EMR) Data Collection

- The PI (MacKay) or other IRB-approved research personnel will collect post-surgical, clinical information from the electronic medical record, pre-surgically, and up to 5 days post-surgery. All data will be collected and securely stored on RedCap or on a single, password-protected, UPenn-regulated, laptop owned by the PI (MacKay). No paper records will be kept.

8.5.2 Survey Data Collection

- The PI (MacKay) or other IRB-approved research personnel will conduct two interviews with the patient: (1) the first interview will occur following extubation (i.e. removal of the breathing tube after CABG surgery) within a 6 – 24 hour post-surgical window; (2) the second interview will occur at any point between 1 – 5 days post-surgery. These interviews will take approximately 15 – 30 minutes.

- No identifying information from the patient will be collected. Survey data will be labeled only by subject number.
- Patient Interview Questions
    - 1. Did you, or do you currently have symptoms of throat soreness?
    - 2. Does your throat feel dry or scratchy?
    - 3. Have you had difficulty swallowing liquids, pills, or food?
    - 4. Has swallowing been painful?
    - 5. Have you felt nauseous or vomited?
    - 6. Have you had symptoms of acid reflux?
    - 7. Did you ever have the taste of blood in your mouth?
    - 8. Have you had any GI symptoms I haven't asked you about?

8.5 Expected Duration of Subject Participation

- Duration of physical patient participation will be:
    - Approximately 30 – 45 minutes to complete the informed consent process
    - Approximately 15 – 30 minutes to conduct interview 1
    - Approximately 15 – 30 minutes to conduct interview 2
    - Passive participation will continue until the global study is completed.

8.6 Adverse Events Reporting

- The Principal Investigator or delegate must report any Adverse Events (AE) from the time the subject signs the Informed Consent Form until the conclusion of the study-related activities. This study is not for diagnostic purposes, so if incidental health findings are discovered as part of a scan, these must be recorded on the AE log and the subject must be referred to their physician by the study PI (MacKay).
- A Detailed Data Safety and Monitoring Plan (DSMP) has been included as an addendum to this protocol. The DSMP will comprehensively review AE, SAE, definitions, reporting procedures, and protocols.

8.7 Study Termination

- This study may be suspended or terminated at any time by the will of the NIH, NHLBI, UPenn IRB, or the FDA.

9 Sites

This is a single site study being conducted at Penn Presbyterian Medical Center (PPMC), a site within the University of Pennsylvania Health System.

10 Data Management and Statistical Analysis Plan

The study data will be captured on Case Report Forms (CRF), as appropriate. The study data, including adverse events, will be summarized for final reports to NHLBI and the NIH. Only staff delegated by the PI (MacKay) will have access to the data.

10.1 Primary Endpoint Analysis

The goal of this RCT is to assess the real-world feasibility of undertaking a trial that will randomize isolated CABG surgery patients to default (i.e. obligatory) as-needed (i.e. backup) intraoperative TEE. Therefore, primary RCT endpoints are process-related. These include

1. Absolute subject recruitment
2. Number of TEEs performed in the as-needed TEE trial arm

10.2 Secondary Endpoint Analysis

Although this study is not powered to detect a difference in clinical outcomes between the default and as-needed intraoperative TEE groups, to plan for a future RCT that would be powered to detect a difference in clinical outcomes. We will collect clinical data on gastroesophageal dysfunction (symptoms or injury), incidence of end-organ dysfunction, and incidence of death as defined by the following:

1. Evidence of clinically-significant gastroesophageal dysfunction during hospitalization – either by patient-reported symptoms or by the presence of testing for swallowing difficulty, dysfunction, or upper endoscopy diagnostic procedures.
2. Evidence of end-organ dysfunction based on clinical notes (e.g. “transaminitis,” “acute kidney/renal injury”), and/or laboratory-based evidence of (e.g. liver function tests [LFTs], serum creatinine [Cr], lactate, etc.).
3. Incidence of in-hospital, post-surgical, cardiovascular re-intervention (e.g. return to the operating room for any reason, unplanned or emergency cardiac catheterization post-surgery, or placement on venoarterial extracorporeal membrane oxygenation [VAECMO]).
4. Incidence of all-cause in-hospital mortality

10.3 Sample Size and Power Determination

- To account for screen failures (i.e., exclusions after enrollment), we are planning to obtain informed consent for up to 75 patients to ensure we active our enrollment goal of 22 patients randomized to each trial arm.

11 Risk and Benefit Analysis

The standard-of-care intraoperative TEE device has passed quality assurance testing according to international regulatory guidelines. But specific to low-risk, isolated CABG surgery, the risk vs benefit profile for intraoperative TEE as an invasive hemodynamic monitoring device is currently unknown. Consequently, given that neither arm of the trial will be deprived of intraoperative TEE, the benefits of a greater understanding of who, when, and why intraoperative TEE should be used in isolated CABG surgery outweigh the risks in participating in a trial randomizing patients to two standard-of-care trial arms. The concrete risks associated with RCT participation and the steps put in place to mitigate these risks will be reviewed.

11.1 Risks Associated with Trial Participation

- The following risks are inherent to participation in this RCT:
  (1) Risk of gastroesophageal harm from the TEE probe itself: Patients in the default TEE treatment arm will be exposed to, (patients in the as-needed TEE treatment arm may be exposed to) the gastroesophageal clinical risks associated TEE. Patients in the as-needed TEE treatment arm may be exposed to the gastroesophageal clinical risks associated with the use of The current cardiac surgery literature indicates that the risk of clinically significant gastroesophageal injury ranges 0.1% – 4%.[17-20] On balance, patients randomized to the default TEE trial arm will have a greater risk of gastroesophageal injury than patients randomized to the as-needed TEE trial arm.
  (2) Risk of harm from the absence of continuous TEE monitoring during isolated CABG surgery: Patients randomized to the as-needed intraoperative TEE arm may be exposed to potential negative consequences associated with delayed diagnoses of hemodynamic instability. For instance, if EKG changes are detected intraoperatively and a TEE is deemed necessary (by the cardiac surgeon or cardiac anesthesiologist) to investigate for potential regional wall motion abnormalities caused by graft ischemia, confirmation of the diagnosis by TEE may take minutes in the as-needed TEE treatment arm (vs. seconds in the default TEE treatment arm). On balance, patients randomized to the as-needed trial arm will have greater risk of delayed diagnosis than patients randomized to the default TEE trial arm.
  (3) Loss of time: Participating in the trial will require patients to spend additional time above and beyond the typical perioperative timeframe for undergoing an isolated CABG surgery to review trial-related information, consider the risks associated with participation in the trial (i.e. informed consent process), and answer trial-related questionnaires after surgery.
  (4) Loss of privacy and confidentiality: Although the risk of occurrence is unlikely, there is a risk of inadvertent disclosure of protected health information (PHI),

which could lead to breaches of patient privacy, identity left, and loss of public trust (among other serious consequences).

11.2 Risk Minimization Actions

Risk to trial subjects will be minimized by: (a) training of all staff directly-involved in research activities in the ethical conduct of research; (b) strict protection of confidentiality through detailed standard operating procedures and on-site monitoring; (c) careful handling of sensitive data, including procedures and processes in place to ensure data are securely stored and transferred.

While the potential risks to subjects are low overall, any harm will be reported to the principal investigator (PI) immediately, and any serious event will be reported to both the data safety and monitoring board and the University of Pennsylvania IRB within 48 hours of its occurrence.

- The following are the protections against the trial risks (itemized above in section 11.1 above):
  (1) Risk of harm from the TEE probe itself: Patients will be (if randomized to the default trial arm) and may be (if randomized to the as-needed trial arm) exposed to the gastroesophageal clinical risks associated with use of the TEE probe itself. However, the current standard of care for isolated CABG surgery at PPMC involves the obligatory placement of an intraoperative TEE to be used continuously throughout surgery unless clinically contraindicated. Consequently, patients enrolled in this trial will not be exposed to undue risk from placement of the TEE probe beyond that of the standard of care. Moreover, patients randomized to the as-needed TEE trial arm may be protected against suffering the gastroesophageal complications related to the TEE procedure itself if they undergo surgery without the use of TEE.
  (2) Risk of harm from the absence of continuous TEE monitoring during isolated CABG surgery: Patients randomized to the as-needed intraoperative TEE arm may be exposed to consequences associated with delayed diagnoses of hemodynamic instability (e.g. EKG changes indicating impending myocardial ischemia and need for TEE assessment). To protect against this risk of delayed diagnosis of myocardial ischemia (or other unforeseen intraoperative complications), in consultation with cardiac surgeon collaborators, we have outlined strict inclusion and exclusion criteria to limit trial participation to the lowest-risk, normal ejection fraction, isolated CABG surgical patient population. Additionally, we will randomize patients after induction of anesthesia to ensure that only hemodynamically stable patients are enrolled in this trial.
  (3) Loss of time: Participating in the trial will require patients to spend additional time above and beyond the typical perioperative timeframe for undergoing an isolated CABG surgery to review trial-related information, review the risks associated with participation in the trial (i.e. informed consent process), and

answer trial-related questionnaires. We are protecting subjects against the risk of loss of time by developing and administering trial questionnaires as efficiently as possible in the postoperative time period. We do not anticipate the time required to complete these questionnaires will exceed 30 minutes during the postoperative time period, will not delay a trial participant's discharge from the hospital, and any phone call follow-up will be scheduled at a time of the trial participant's convenience.

(4) Loss of privacy and confidentiality: Although the risk of occurrence is unlikely, there is a risk of inadvertent disclosure of protected health information (PHI), which could lead to breaches of patient privacy, identity left, and loss of public trust (among other serious consequences). A number of procedures will be implemented to protect trial participants against loss of privacy and confidentiality. First, subjects will identify three methods to contact them for follow-up and the name of one additional contact in the event the patient cannot be reached. No other methods will be used. Second, trial participants will be protected against loss of confidentiality as much as possible by conducting all study procedures, including postoperative questionnaires, in private locations. Third, to protect the subjects' records, study instruments will not contain patient names but instead will contain a unique identifying (ID) number in order to match subjects over the repeated measures. This ID number will be the only identification on all research instruments filled out by the patient. Fourth, no subject will be identified or named in any report or publication. Fifth, data will be analyzed in the aggregate and individual participant data will remain anonymous. Additional protections can be found in the Data Management Plan below.

11.3 Anticipated Benefits

- Anticipated direct benefits of this RCT for patients, surgeons, and anesthesiologists
    - The direct benefits to an individual patient participating in the trial: (a) if randomized to the as-needed TEE trial arm, subjects may avoid gastroesophageal complications directly-attributable to TEE probe placement and manipulation; (b) if randomized to the default TEE trial arm, subjects will have the benefit of immediate (i.e. within seconds) intraoperative TEE imaging during surgery.
    - The direct benefits to the cardiac surgeon include: (a) avoidance of gastroesophageal complications directly-attributable to TEE that could impact post-surgical recovery among patients randomized to the as-needed intraoperative TEE arm; (b) potential increased efficiency of pre-surgical preparation (i.e. no additional time required before incision to perform TEE exam and review findings with cardiac anesthesiologist) among patients randomized to the as-needed TEE arm.

    - The direct potential benefits to the cardiac anesthesiologist include: (a) additional time to focus on intensive procedural tasks (e.g. placement of radial arterial catheter and internal jugular central venous access) instead of completing intraoperative TEE exam among patients randomized to the as-needed TEE arm; (b) increased transparency about the risks vs benefits of intraoperative TEE use in isolated CABG surgery during the informed consent process (i.e. many anesthesiologists believe the risks of TEE outweigh the benefits in low-risk isolated CABG surgery).
- Anticipated indirect benefits of this RCT is the knowledge to be gained
    - In isolated CABG surgery, the clinical effectiveness of intraoperative TEE is uncertain and the risk vs benefit profile is unknown. In particular, among the lowest risk, routine isolated CABG surgery patient population, it is not clear if the theoretical benefits of intraoperative TEE monitoring outweigh the actual risks of the invasive nature of the TEE procedure itself. This uncertainty is a significant evidence gap with high clinical equipoise and is an opportunity to study the clinical efficacy and effectiveness of intraoperative TEE during isolated CABG surgery prospectively by randomization. This proposed RCT will provide critical information on the feasibility of a future multicenter, randomized controlled trial to study the true clinical efficacy, real-world effectiveness, and risk vs benefit profile for TEE in isolated CABG surgery.

12 Deviations

All non-compliance to protocol procedures shall be reported as a protocol deviation. The Principal Investigator is not allowed to deviate from the protocol unless prior approval from the NIH and the IRB is granted. Only protocol deviations made to protect the rights, safety and well-being of subjects are allowed without prior approval from the Sponsor and the IRB/EC.

Examples of protocol deviations include, but are not limited to:

- Failure to obtain written consent for an enrolled subject
- Enrollment of an ineligible subject
- Interview(s) one or two conducted outside the allotted timeframe specified above

All protocol deviations shall be recorded on the Protocol Deviation Form. Deviations that affect the rights, safety, and well-being of the subject must be reported within 24 hours to the IRB by the Principal Investigator.

13 Safety Reporting

Please refer to the Data Safety and Monitoring Plan (DSMP) document.

13.1 Routine Reporting

Subjects should be evaluated for AEs from the time Informed Consent Form is signed until conclusion of study-related activities. Documentation of the outcome of all safety events, assignment of relatedness, and seriousness is the responsibility of the Principal Investigator.

All AEs occurring during the trial are to be recorded on the Adverse Event CRF as soon as possible following awareness of the event.

The PI is responsible for reporting AE to the appropriate IRB as dictated by the guidelines defined by the IRB.

13.2 Expedited Reporting

All SAEs must be reported to the IRB within 24 hours of the Investigator becoming aware of the event.

Additionally, any medical device deficiencies that might have led to a SAE if:

- suitable action had not been taken;
- intervention had not been made; or
- circumstances had been less fortunate

SAEs must also be reported to the NIH within 24 hours of the Investigator becoming aware of the event.

Furthermore, any new findings or updates in relation to previously reported SAE or device deficiencies which may have potentially led to SAE must be reported to the NIH within 24 hours of the PI becoming aware of the new findings or updates.

14 Labeling

As intraoperative TEE is defined as a standard-of-care (i.e. non-investigational) device, no labeling is required.

15 Direct Access to Source Data/Documents

Source data will be stored on the hard drive of a single, highly secured, password-protected computer accessible only to the PI.

15.1 Source Data

Source data for this study will include:

- Protected Health Information (PHI) including: (1) name; (2) medical record number (MRN); (3) date of surgery

Electronic medical record (EMR) clinical data including: (1) medical and surgical history; (2) presurgical data and imaging (e.g. laboratory values, cardiac catheterization, transthoracic or transesophageal echocardiography, etc.); (3) intraoperative hemodynamic data (e.g. intraoperative blood pressure, pulmonary

arterial pressure, mixed venous oxygen saturation, type and dose of intotropes, etc.); (4) postsurgical data and imaging (e.g. postsurgical care notes, laboratory values, imaging, etc.)

15.2 Data Monitoring

Monitoring will be performed over the course of the study to assess continued compliance with the protocol and applicable regulations.

15.3 Data Confidentiality

Study records, including each subject's signed informed consent, and other study-related documents (including all source data and documents listed above) pertaining to the conduct of the study shall be kept in a secure area. Confidentiality shall be maintained. Documents related to the study, including the Trial Master File, are to be kept for a minimum of two years after study completion.

Specific measures that will be taken to ensure protected health information remains confidential include: (1) All images and data will be stored on the hard drive of one computer with password protection; (2) Any data shared with collaborators will be stripped of all identifying information (e.g. de-identified).

Because all RCT data collected in this research will be de-identified after the study is complete, the information may be shared with other researchers within Penn, or other research institutions, and the NIH. It would not be possible for future researchers to identify any individual from the de-identified data.

15.4 Privacy

Patients will be consented one-on-one, in a private office room if consented in the cardiac surgical outpatient clinic or their private bay in the preoperative holding area. Either a door will be shut or a curtain will be drawn for the consenting process to maintain patient subject privacy.

16 Publication Policy

In accordance with the NIH Public Access Policy and Federal law, an electronic version of the final, peer reviewed, publication(s) resulting from this trial will be submitted to PMC to be made publicly available no later than 12 months after the official date of publication.

17 Ethical Considerations

This study is conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol and all study materials are to be reviewed by an Institutional Review Board (IRB)/Ethics Committee (EC), prior to enrollment of any subject. Any additional requirements imposed by the IRB/EC shall be followed. Any amendments to the protocol must be reviewed and approved by

the NIH, and subsequently, by the designated IRB/EC, according to the approval committee's requirements.

Only authorized personnel associated with the conduct and/or review of the study and the resultant data shall have access to information that links subject identifiers to the corresponding assigned study code. Disclosure of subject information to personnel other than those permitted by the NIH, NHLBI, its designees or representatives, or appropriate regulatory agencies is prohibited.

18 References

1. MacKay EJ, Neuman MD, Fleisher LA, et al.: Transesophageal echocardiography, mortality, and length of hospitalization after cardiac valve surgery. Journal of the American Society of Echocardiography. 33:756-762. e751, 2020.
2. MacKay EJ, Zhang B, Augoustides JG, et al.: Association of intraoperative transesophageal echocardiography and clinical outcomes after open cardiac valve or proximal aortic surgery. JAMA Network Open. 5:e2147820-e2147820, 2022.
3. Metkus TS, Thibault D, Grant MC, et al.: Transesophageal echocardiography in patients undergoing coronary artery bypass graft surgery. Journal of the American College of Cardiology. 78:112-122, 2021.
4. MacKay EJ, Werner RM, Groeneveld PW, et al.: Transesophageal echocardiography, acute kidney injury, and length of hospitalization among adults undergoing coronary artery bypass graft surgery. Journal of cardiothoracic and vascular anesthesia. 34:687-695, 2020.
5. MacKay EJ, Zhang B, Heng S, et al.: Association between transesophageal echocardiography and clinical outcomes after coronary artery bypass graft surgery. Journal of the American Society of Echocardiography. 34:571-581, 2021.
6. Nicoara A, Skubas N, Ad N, et al.: Guidelines for the use of transesophageal echocardiography to assist with surgical decision-making in the operating room: a surgery-based approach: from the American Society of Echocardiography in collaboration with the Society of Cardiovascular Anesthesiologists and the Society of Thoracic Surgeons. Journal of the American Society of Echocardiography. 33:692-734, 2020.
7. Shapira Y, Weisenberg DE, Vaturi M, et al.: The impact of intraoperative transesophageal echocardiography in infective endocarditis. IMAJ-RAMAT GAN-. 9:299, 2007.
8. Otto CM, Nishimura RA, Bonow RO, et al.: 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Journal of the American College of Cardiology. 77:450-500, 2021.
9. Shanewise JS, Cheung AT, Aronson S, et al.: ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography. Journal of the American Society of Echocardiography. 12:884-900, 1999.
10. Zoghbi WA, Chambers JB, Dumesnil JG, et al.: Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound: a report From the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac

Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography. Journal of the American Society of Echocardiography. 22:975-1014, 2009.

11. Hahn RT, Abraham T, Adams MS, et al.: Guidelines for performing a comprehensive transesophageal echocardiographic examination: recommendations from the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. Journal of the American Society of Echocardiography. 26:921-964, 2013.
12. Eltzschig HK, Rosenberger P, Löffler M, et al.: Impact of intraoperative transesophageal echocardiography on surgical decisions in 12,566 patients undergoing cardiac surgery. The Annals of thoracic surgery. 85:845-852, 2008.
13. Silva F, Arruda R, Nobre A, et al.: Impact of intraoperative transesophageal echocardiography in cardiac surgery: retrospective analysis of a series of 850 examinations. Revista portuguesa de cardiologia: orgao oficial da Sociedade Portuguesa de Cardiologia= Portuguese journal of cardiology: an official journal of the Portuguese Society of Cardiology. 29:1363-1382, 2010.
14. Cheung AT, Savino JS, Weiss SJ, et al.: Echocardiographic and hemodynamic indexes of left ventricular preload in patients with normal and abnormal ventricular function. Anesthesiology. 81:376-387, 1994.
15. Charron C, Caille V, Jardin F, et al.: Echocardiographic measurement of fluid responsiveness. Current opinion in critical care. 12:249-254, 2006.
16. Hilberath JN, Oakes DA, Shernan SK, et al.: Safety of transesophageal echocardiography. Journal of the American Society of Echocardiography. 23:1115-1127, 2010.
17. Kallmeyer IJ, Collard CD, Fox JA, et al.: The safety of intraoperative transesophageal echocardiography: a case series of 7200 cardiac surgical patients. Anesthesia & Analgesia. 92:1126-1130, 2001.
18. Hogue Jr CW, Lappas GD, Creswell LL, et al.: Swallowing dysfunction after cardiac operations: associated adverse outcomes and risk factors including intraoperative transesophageal echocardiography. The Journal of Thoracic and Cardiovascular Surgery. 110:517-522, 1995.
19. Hulyalkar AR, Ayd JD: Low risk of gastroesophageal injury associated with transesophageal echocardiography during cardiac surgery. Journal of cardiothoracic and vascular anesthesia. 7:175-177, 1993.
20. Lennon MJ, Gibbs NM, Weightman WM, et al.: Transesophageal echocardiography-related gastrointestinal complications in cardiac surgical patients. Journal of cardiothoracic and vascular anesthesia. 19:141-145, 2005.

19 Appendix

19.1 Data Safety and Monitoring Plan

19.1.1 Adverse Event (AE) and Serious Adverse Event (SAE) Collection and Reporting

19.1.1.1 Safety Monitoring Definitions and list of AEs and SAEs to be tracked

(1) Adverse Event (AE) – Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease process, temporally associated with the subject's participation in the research, whether or not considered directly-related to the subject's participation in the research. The itemized list of adverse events we will track is provided in this section (subsection 5).

a. Clinically-significant but non-life threatening gastroesophageal complications possibly related to transesophageal echocardiography (TEE).
b. Cardiovascular complications after isolated CABG surgery.
c. Breach of confidentiality.

(2) Serious Adverse Event (SAE) – Any AE that results in death or a life-threatening AE.

(3) List of AEs and SAEs (severity of which will be assessed on a case-by-case basis)

a. Death
b. New myocardial infarction (MI) post-surgery
c. Unplanned post-surgery percutaneous coronary intervention (PCI)
d. Unplanned CABG surgery revision
e. Unplanned open valve repair or replacement
f. Stroke
g. Transient ischemic attack (TIA)
h. Return to operating room for bleeding
i. Cardiac tamponade
j. Pericardial effusion
k. Prolonged intubation (defined as >48 hours of mechanical ventilatory support)
l. Pneumonia
m. Surgical site infection
n. Unplanned ICD or pacemaker insertion post-surgery
o. Post-surgery angina
p. New-onset atrial fibrillation
q. Pulmonary embolism (PE)

r. Deep vein thrombosis (DVT)
s. Gastrointestinal or esophageal complication requiring diagnostic testing
t. Failed swallow evaluation

(4) Study-Related AE or SAE – An AE or SAE is considered study-related if the principal investigator (PI) determines that the AE or SAE is definitely, probably, or possibly related (where possibly related is defined as a reasonable probability that the AE or SAE may have been caused by randomization to default or as-needed intraoperative TEE). Any AE or SAE deemed to be remotely related or not related to randomization is not considered to be study-related.

(5) Unanticipated Problem or Unexpected AE or SAE – Problems or events in which trial participation places patients or others at a greater risk of harm (including physical, psychological, economic, or social) than was previously known or recognized. The term “unanticipated problem” is used in this context because some situations may not have produced an adverse event but may still be considered an unanticipated problem (e.g. an incidence of unsecured patient data which may not result in a breach of confidentiality). An event is unexpected if it is not described in the study protocol or informed consent document.

(6) Each AE that is tracked will be assessed for:

a. Grade:
    i. Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    ii. Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
    iii. Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care or ADLs.
    iv. Grade 4 Life-threatening consequences; urgent intervention indicated
    v. Grade 5 Death related to AE.
b. Relatedness to trial participation:
    i. Definitely
    ii. Probably
    iii. Possibly
    iv. Remotely
    v. Unrelated
c. Expectedness after cardiac surgery
    i. Expected
    ii. unexpected
d. Severity
    i. Mild
    ii. Moderate
    iii. severe

19.1.1.2 Process by which AEs and SAEs will be Reported

(1) Research staff becomes aware of the AE/SAE (either reported by the patient directly or by scheduled reviews of the electronic medical record [EMR])
(2) Research staff notifies Dr. MacKay (PI) immediately in the event of an SAE or within seven days if the event is an AE
(3) Dr. MacKay will conduct an EMR review and/or make direct inquires with the medical care team, the patient, or designated family members to gather necessary additional information about the AE/SAE
(4) Dr. MacKay will report the AE/SAE to the Data Safety and Monitoring Board (DSMB) to aid in determining:
    a. Grade
    b. Trial relatedness
    c. Expectedness
    d. Severity
(5) Research staff will document the AE/SAE and DSMB determination in the study database. The report will be provided to the NHLBI Program Officer
(6) Dr. MacKay will prepare a report for the UPenn IRB per local, state, and federal reporting requirements.
(7) The DSMB will aid in planning measures to prevent future occurrences if warranted.
(8) Dr. MacKay will make changes to the trial protocol and/or informed consent form if needed.

19.1.1.3 Entities Responsible for Monitoring

(1) PI: Dr. Emily MacKay
(2) University of Pennsylvania IRB
(3) PPMC Cardiac Anesthesiology Chief (Dr. Ronak Shah)
(4) PPMC Cardiac Surgery Chief (Dr. Wilson Szeto)
(5) DSMB

19.1.1.4 Monitoring of Data

(1) Responsible parties for data and safety monitoring: As the PI for the trial, Dr. MacKay will be responsible for ensuring trial participants' safety on a daily basis. Both the Chief of Cardiac Anesthesiology at PPMC, Dr. Ronak Shah, and the Chief of Cardiac Surgery, Dr. Wilson Szeto, will be updated on the trial safety (including incidences of AEs/SAEs). The DSMB will act in an advisory capacity to monitor trial participants' safety, evaluate the progress of the study, review procedures to maintain confidentiality, review the quality of the data collected, management of the data, and the plans for data analyses.
(2) Frequency of data and safety monitoring: In addition to daily safety monitoring, Dr. MacKay will also perform weekly data audits to ensure the highest standards for data integrity. Specifically, this will involve checks to ensure complete data collection, identify data inaccuracies, and perform EMR audits to ensure data is

being correctly collected. Any data problems will be identified and corrected either by Dr. MacKay or by research staff. Logs of these data issues will be maintained to keep a record of problem areas with specific variables or with individual research team members to allow Dr. MacKay and the DSMB to proactively modify data collection procedures or re-train research team members. Logs of communications with study staff regarding data cleaning and management will also be maintained to keep track of corrected issues. Dr. MacKay will provide a weekly, trial safety report to both Dr. Ronak Shah (Chief of Cardiac Anesthesiology at PPMC) and mentor, Dr. Wilson Szeto (Chief of Cardiac Surgery at PPMC). The DSMB will annually, either in-person or by teleconference call to review study progress, data quality and participant safety alongside Dr. MacKay. Written safety reports will be sent to the both the UPenn IRB and the NHLBI Program Officer annually to provide detailed information on trial progress, safety issues, data collection, data management, and analysis.

(3) Content of Data and Safety Monitoring Report: The written progress report submitted to the DSMB, UPenn IRB, NHLBI Program Officer will include: (a) trial status dates and checkpoints; (b) reports on data completeness; (c) logs of AEs/SAEs; (d) logs of changes to the trial protocol; (e) anticipated trial timeline and deadlines for trial deliverables.

(4) DSMB Membership and Affiliation: DSMB members will be identified prior to start of the RCT. DSMB membership will be sent to the NHLBI. Should there be any questions regarding the independence of the DSMB, it will be addressed and corrected if necessary.

(5) Conflict of Interest for DSMB: The DSMB should have no direct involvement with the study investigators or intervention. Each DSMB member will sign a Conflict of Interest Statement which includes current affiliations, if any, with pharmaceutical and biotechnology companies (e.g., stockholder, consultant), and any other relationship that could be perceived as a conflict of interest related to the trial and/or associated with commercial interest pertinent to RCT objectives.

(6) Responsibilities of the DSMB:

a. Review the trial protocol, informed consent documents and plans for data safety and monitoring.
b. Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk vs benefit, performance for the trials sites, and other factors potentially affecting study outcomes.
c. Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial.
d. Review study performance, make recommendations and assist in the resolution of problems reported by Dr. MacKay
e. Protect the safety of the study participants.
f. Report to NHLBI on the safety and progress of the trial.

g. Make recommendations to the NHLBI and the PI (MacKay) concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of intraoperative TEE as proposed in the trial protocol.
h. If appropriate, review interim analyses in accordance with stopping rules, which are clearly defined in advance of data analysis and have the approval of the DSMB.
i. Ensure the confidentiality of the study data and the results of monitoring.
j. Assist the NHLBI by commenting on any problems with study conduct or enrollment.

19.2 Recruitment and Retention Plan

19.2.1 Recruitment Plan

- Recruitment for the randomized controlled trial (RCT) will occur through the Penn Presbyterian Medical Center (PPMC) cardiac surgery clinic of the University of Pennsylvania Health System. Within our Institutional Review Board (IRB) protocol, we will request permission to access clinic and surgical schedules of potential isolated coronary artery bypass graft (CABG) patients in order to identify potential RCT subjects that meet inclusion and exclusion criteria for enrollment in the trial. Once a potential subject has been identified, he or she will be approached in-person, pre-procedure. After a brief introduction, either the research assistant (RA) or the principal investigator (PI) will approach these patient participants and ask if they would be interested in hearing about the trial. If they agree, the RA or PI will ask a series of additional screening questions to confirm that the patient meets eligibility criteria. If the patient is deemed eligible and expresses interest in learning more about the study, the RA or PI will review the intent of the study, present the current data regarding risks and benefits to using intraoperative transesophageal echocardiography (TEE) during isolated CABG surgery. Once the patient agrees to participate, the RA or PI will complete the enrollment process by providing an information packet, collecting basic demographic and health data, reviewing study timeline and protocols, and obtaining written informed consent that confirms the study subjects' agreement to participate in the RCT as specified in the trial protocol and the subjects' permission to allow the research team to access electronic medical records. Patients will receive an incentive for completing all phases of the study.The trial inclusion and exclusion criteria for subject participation listed in the above-protocol will be confirmed and finalized with Dr. Wilson Szeto prior to initiation of recruitment.

19.2.1.1 Estimated Rates of RCT Enrollment

- We will recruit up to 75 isolated CABG surgery patients who present to the cardiac surgery clinic(s) at either PPMC or the Hospital of the University of Pennsylvania The Division of Cardiovascular Surgery, within the University of Pennsylvania Health System is the largest cardiac surgery division in the State of Pennsylvania and receives over 250 isolated CABG referrals per year. This breaks down to approximately 20 patients per month. Assuming half of these patients meet inclusion criteria (i.e. 10 potential subjects per month), to meet our sample size of 22 isolated CABG surgery patients in year, we would need a 20% participation rate over 12 months; equating to approximately 2 – 3 study subjects per month. Although we do not anticipate difficulty in recruitment, if we are unable to achieve our

projected sample size goal within one year, we will extend the recruitment period six months.

19.2.1.2 Optimizing RCT Recruitment Strategy for Future Multicenter RCT

- Throughout the execution of this RCT, we will continually assess and document rates of recruitment of eligible participants to inform project timelines and improve our recruitment strategy for a future, multicenter, RCT. In particular, we will evaluate whether the verbal consent discussion and written materials provided to patients during the initial encounter were satisfactory and understandable to participating study subjects or whether additional improvements could be made to allow for higher study participation rates in the future

19.2.2 RCT Retention Plan

- To ensure optimal retention of RCT participants, we will follow an enhanced retention approach that includes collecting contact information (e.g. physical address, mobile phone numbers, email address, etc.) from each participant. We will also ask the participant to designate one other individual to allow researchers to locate and communicate with participants in the event that the participant cannot be reached directly.
- During the trial, the RCT protocol will involve a member of the research team conducting in-person interviews post-CABG surgery with each study participant. Interview questions will cover incidence of clinical adverse sequelae (e.g. difficulty or painful swallowing, hoarseness, etc.) in each trial arm and will also involve asking open-ended questions regarding the study protocol to allow participants to provide feedback to research team personnel on how to optimize the study protocol for participating subjects. We will encourage study participants to consider themselves essential members of the study team with valuable information that is critical to the success of a future trial. At the end of the study, we will invite patients to consider staying on as representative stakeholders to serve on a monitoring board for a future, multicenter RCT comparing default vs as-needed intraoperative TEE during isolated CABG surgery.
- During the course of the study, we will encourage patients to directly contact research team personnel or the PI (MacKay) at any point before, during, or following RCT completion. To facilitate this level of open communication, participating RCT subjects will be provided the PI (MacKay's) mobile phone number in the information packed. Subjects will be told they can contact the PI directly 24/7 to answer questions or address concerns regarding RCT participation.

19.3 Structure of the RCT Study Team

19.3.1 Study Team Roles and Responsibilities

- The trial PI, Dr. MacKay will provide overall management and supervision of this RCT as proposed in aim 3 of the Research Approach. A dedicated research assistant will assist Dr. MacKay with all aspects of trial execution including subject recruitment, enrollment, and data collection. Dr. MacKay's primary mentor (Dr. Peter Groeneveld), trial methodologic mentor (Dr. Mark Neuman), and cardiac surgeon and trialist scientific advisor (Dr. Wilson Szeto) will provide regular guidance and support throughout the RCT. Dr. MacKay will analyze trial data with the help of her Biostatistical collaborator Dr. Bo Zhang, with input from statistical content advisor Dr. Dylan Small.

19.3.2 Governance and Organizational Structure

- Dr. MacKay, her grant administrator Ms. Rene Wick, and the University of Pennsylvania will be responsible for the overall administration of the K23 grant funds for this trial. Dr. MacKay will serve as the primary contact and be responsible for submission of all trial progress reports to (and communication with) the NHLBI at the NIH.

19.3.3 Dissemination of Findings and Scientific Responsibilities

- Dr. MacKay will hold primary responsibility for data analysis and dissemination of research findings, including analysis of trial data (in consultation with collaborator Dr. Bo Zhang), presentation at scientific meetings, and manuscript drafting and submitting for peer review.

19.3.4 Funding Allocation

- Funding allocation will be carried out in accordance with the policies and procedures outlined by the University of Pennsylvania and the NIH. The Department of Anesthesiology and Critical Care is committed to the success of the applicant as an independent investigator and will provide all the resources required for the trial success (please see Institutional Commitment Letter for details).

19.4 Copy of the K23 Funded by the NHLBI of the NIH

- A copy of the K23 grant funded by NHLBI of the NIH is provided as an addendum to this protocol.

19.5 Statistical Design and Power Analysis for the RCT

19.5.1 Statistical Analysis

- Descriptive statistics and frequency distributions will be calculated for: presurgical comorbidities, surgical characteristics, and perioperative factors for patients in each trial arm. Clinical data will be analyzed via intention-to-treat by Chi-squared and Wilcoxon rank-sum tests. Results from patient and cardiac surgeon satisfaction questionnaires will be collated and summarized using descriptive statistics. Means and proportions will be plotted to compare surgeon satisfaction with each trial arm.

19.5.2 Power Analysis

- Because the goal of this RCT is to assess study feasibility of a future trial, rather than efficacy comparisons, we did not conduct a formal power calculation. Rather, we established a sample size of 22 patients based on clinical expertise, annual PPMC isolated CABG surgical volume, and knowledge of operating room procedures. Given this low number of projected trial enrollment (n=22), this feasibility RCT will be underpowered to detect a difference in cardiac surgical outcomes. Nevertheless, we plan to review the electronic medical record for each study arm of the trial to compare any potential differences in clinical outcomes between the default and the as-needed intraoperative TEE trial arms.