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# BMJ Open

## The impact of Obesity on Postoperative Outcomes following cardiac Surgery (The OPOS trial) - Rationale and design of an investigator-initiated prospective trial

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Keywords:	inflammation, morbidity, Coronary artery bypass grafting, adipose tissue, atrial appendage, globesity

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Manuscripts

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3 1 **The impact of Obesity on Postoperative Outcomes following cardiac Surgery (The OPOS**  
4 **trial) - Rationale and design of an investigator-initiated prospective trial**  
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33 14 Abbreviated title: Obesity and cardiac surgical outcomes  
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**ABSTRACT:**

**Introduction:** Increasing levels of obesity worldwide have led to a rise in the prevalence of obesity-related complications including cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia. Health care providers believe that overweight and obese cardiac surgery patients are more likely to experience adverse post-operative outcomes. The body mass index (BMI) is the primary measure of obesity in clinical practice, without accounting for a patient's level of cardiopulmonary fitness or muscle mass.

**Methods and Analysis:** Patients between the ages of 18 and 75 years undergoing elective cardiac surgery are consented to participate in this prospective observational trial. Patients will be invited to participate in measures of obesity, functional capacity and exercise capacity assessments, quality of life questionnaires, and blood and tissue sampling for biomarker analysis. The endpoints evaluated are measures other than BMI that could be predictive of short-term and long-term post-operative outcomes. Clinical outcomes of interest are prolonged ventilation, hospital length of stay, renal failure and all-cause mortality. Biomarkers of interest will largely focus on metabolism (lipids, amino acids) and inflammation (adipokines, cytokines and chemokines).

**Ethics and Dissemination:** This study has been approved by the institutional review board at the Horizon Health Network. Upon completion of the trial, the results shall be disseminated through conference presentations and publications in peer-reviewed journals. Additionally, the report shall also be diffused more broadly to the general public and the cardiovascular community.

**Summary:** The results of this trial will provide an improved understanding and better definition of obesity beyond BMI. We hope to demonstrate how fitness capacity of obese cardiac surgical patients and biomarkers alone or in combination, will help identify patients at risk for adverse outcomes when undergoing cardiac surgery. This study will help clinicians better identify patients

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46 pre-operatively based on fitness levels and associated biomarkers in anticipation of implementing  
47 mitigating strategies.  
48 **Trial Registration:** NCT03248921 at [www.clinicaltrials.gov](http://www.clinicaltrials.gov)  
49 Protocol Version 7, dated 12 December 2017

For peer review only

## 50 **Strengths and limitations of this study**

- 51 • The results of this trial will present an improved understanding and better definition of  
52 obesity beyond BMI.
- 53 • Determination of the “fitness capacity” of obese cardiac surgical patients will help  
54 identify obese patients at risk for adverse outcomes.
- 55 • Identification of key biomarkers such as cytokines and adipokines will improve  
56 preoperative risk-assessment of obese patients.
- 57 • This observational study only assesses elective cardiac surgery patients, and excludes  
58 high-risk urgent and frail patients.
- 59 • This trial is limited in terms of overall enrolment of participants; and there is unequal  
60 representation of higher BMI categories especially females.

61  
62 **Keywords:** morbidity, CABG, valve replacement, valvuloplasty, adipose tissue, atrial appendage,  
63 clinical chemistry, inflammation, metaflammation, immunometabolism, globesity  
64

## 65 **BACKGROUND AND RATIONALE**

66 The global epidemic of overweight and obese patients - "globesity" - is steadily rising without  
67 abatement and more than one-third of U.S. adults are obese.(1) In the Canadian population, one  
68 quarter of the population is obese, with a two-fold higher obesity risk amongst Indigenous-  
69 Canadians.(2) It is estimated that each year approximately 66,000 Canadians die due to health  
70 complications associated with obesity.(3) Obese populations typically experience comorbid  
71 cardiovascular disease (CVD) often necessitating invasive cardiac surgical interventions.(4) These  
72 patients are at higher risk for intra-operative and post-operative adverse events, including  
73 mortality.(1, 5-12) However, recent studies show paradoxical results, wherein obese patients can  
74 experience fewer adverse events and lower mortality than patients with normal body mass index  
75 (BMI), suggesting a benefit to obesity for post-surgical outcomes.(13-17) Referred to as the  
76 "obesity paradox", the underlying mechanisms and clinical paradigms of this phenomenon remain  
77 to be defined.(18)

79 In part, this paradox may be attributable to over-reliance on singular anthropometric measures of  
80 obesity, namely BMI. BMI can be a poor predictor of clinical outcomes since it fails to account  
81 for variable whole-body adipose tissue distribution,(19, 20) or inflammatory state.(21, 22)  
82 Additionally, BMI does not address the physical ability or fitness of obese patients with respect to  
83 size. Thus, the question to be addressed with this trial is: Why do some obese patients have "good  
84 health-related quality of life" (QoL), maintain high physical ability, and have positive outcomes,  
85 while other obese patients and normal BMI patients have poor QoL, low physical ability and  
86 negative outcomes? Thus, we propose segregating obese patients into two populations: high-fit  
87 obese patients ("fit" obese or normally-able) and low fit obese patients ("non-fit" obese or less-

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3 88 able). This distinction could be of critical importance in determining which obese patients are  
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5 89 more likely to do well post-operatively.  
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10 91 Alternative measures to BMI have been proposed, including waist-to-hip ratios and waist-to-height  
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12 92 ratios and body adiposity index.(23-25) These measures of central obesity reflect visceral adiposity  
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14 93 and strongly predict cardiovascular risk, post-surgical outcomes, and resource utilization(26) but  
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16 94 are not often measured or easily calculated from routine patient histories. Beyond clinical  
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18 95 measures of obesity and functional capacity, levels of circulating hormones, inflammatory  
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20 96 cytokines(27), and the presence of insulin resistance and type-II diabetes are likely to influence  
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22 97 obese patient outcomes.(28) Developing a more complete understanding of biomarkers for obese  
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24 98 individuals that could improve operative risk-assessment is a priority.  
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31 100 Ultimately, the need exists to better differentiate obese patients who experience fewer  
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33 101 complications from those with increased rates of adverse events, and to determine if they  
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35 102 correspond with the physically distinct populations of “high-fit” vs. “low-fit” obese. This  
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38 103 distinction could be of critical importance in determining which obese patients are more likely to  
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40 104 do well post-operatively. Here, we describe a trial that will address this important knowledge gap,  
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42 105 “the impact of Obesity on Postoperative Outcomes following cardiac Surgery (OPOS) trial”.  
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## 46 47 107 **STUDY AIMS AND OUTCOME VARIABLES**

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49 108 The purpose of this trial is to identify non-BMI-related measures of obesity, functional capacity, and  
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51 109 molecular biomarkers that are capable of better defining risk for in-hospital, 30-day and 1-year  
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54 110 adverse events among obese patients undergoing cardiac surgery. We hypothesize that the  
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3 111 mechanisms by which obesity affects outcomes after cardiac surgery depend on a combination of a  
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5 112 patient's functional capacity, adipose tissue distribution and tissue/circulating metabolic-  
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8 113 inflammation status. We further hypothesize that by using this advanced approach, we may better  
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10 114 distinguish "high-fit" from "low-fit" obese patients to devise strategies that minimize poor clinical  
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12 115 outcomes.

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17 117 The primary outcome variable will be the composite of in-hospital mortality, prolonged ventilation  
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19 118 >24hrs, new-onset renal failure (defined as post-operative creatinine >176  $\mu\text{mol/L}$  in patients with  
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21  
22 119 normal baseline renal function) and wound infection. We have previously validated this composite  
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24 120 outcome by demonstrating a linear relationship between severity of obesity and adverse in-hospital  
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26 121 patient outcomes.(29) Secondary clinical outcomes include re-operation for any cause, stroke  
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28 122 (transient, permanent), respiratory complications (pleural effusion, pneumonia), atrial fibrillation,  
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31 123 post-operative length of stay and disposition on discharge (home, home with care, transfer to other  
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33 124 facility or expired), exercise or functional capacity (by walk-test or questionnaire).

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## 36 37 38 126 **METHODS**

### 39 40 127 **1. Research ethics approval**

41  
42 128 The OPOS trial protocol has been submitted and approved by the institutional committee on human  
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45 129 research at Horizon Health Network, Saint John Regional Hospital, New Brunswick Heart Centre &  
46  
47 130 the Nova Scotia Health Authority, Maritime Heart Centre. All aspects of this trial are in conformity  
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49 131 to the Canadian Tri-Council Policy Statement on ethical conduct for research involving humans  
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51 132 (TCPS-2-2014) and are in accordance with the World Medical Association Declaration of Helsinki  
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54 133 – ethical principles for medical research involving human subjects (2013). The trial has been  
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3 134 registered with the National Clinical Trials Database of the NIH ([www.clinicaltrials.gov](http://www.clinicaltrials.gov))  
4  
5 135 NCT03248921). We used the SPIRIT checklist when writing our report(30).  
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## 10 137 **2. Study population and subject selection**

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12 138 All patients scheduled for elective, first-time cardiac surgery at the New Brunswick Heart Centre in  
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14  
15 139 Saint John, New Brunswick, and the Maritime Heart Centre in Halifax, Nova Scotia, will be  
16  
17 140 considered. Patients with a BMI of less than 18.5 kg/m<sup>2</sup> are classified as underweight by the World  
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19 141 Health Organization and will be excluded. In addition, patients older than 75 years will be excluded  
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21  
22 142 to minimize the effect that frailty may have on exercise and functional capacity.  
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## 26 144 **3. Trial overview**

27  
28 145 Eligible patients will be screened by the research coordinator for potential enrolment prior to  
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31 146 surgery (**Fig.1**). Subjects fulfilling the inclusion and exclusion criteria will be approached by the  
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33 147 research coordinator and informed consent shall be obtained. Patients who convert from elective to  
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35 148 non-elective surgery or patients who choose to no longer participate are automatically withdrawn  
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37  
38 149 from the trial. Participants are not offered financial or non-financial incentives to participate in the  
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40 150 trial.  
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## 42 151 **4. Trial design**

43 152  
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46 153 The aims of this trial will be fulfilled using a prospective observational study design (**Fig.1**). Obese  
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48 154 patients awaiting elective cardiac surgery including coronary artery bypass grafting surgery with or  
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50 155 without valve surgery, aortic or mitral valve surgery will be identified. Consenting patients will be  
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53 156 invited to voluntarily participate in select measurements of obesity, testing of exercise capacity and  
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55 157 functional status, QoL questionnaires, as well as blood and tissue sampling for the purposes of  
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3 158 profiling circulating biomarkers and metabolic-inflammatory status (**Table-1, Fig.2**). Routinely  
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5 159 collected clinical data on baseline, intraoperative characteristics and post-operative outcomes will be  
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8 160 acquired from the New Brunswick Cardiac Surgery Registry (**Table-2**). Crude and risk-adjusted  
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10 161 analyses will be carried out to determine which of these non-traditional measures of obesity,  
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12 162 functional status, and metabolic-inflammatory status may have independent effects on rates of post-  
13  
14 163 operative adverse events among obese patients. Although adverse events related to the trial  
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16 164 procedure are unlikely (other than those related to cardiac surgery), all adverse events occurring  
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18 165 during the course of the trial will be reported to the REB.  
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23 167 **Table-1: Table of Determined Measures:**  
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Category	Variables
<b>Clinical</b>	Age (yrs)
	Hip, waist circumference (cm)
	Height (cm)
	Weight (kg)
	6-MWT (m)
<b>Calculated</b>	DASI, SF-12, PSMS (scores)
	BMI, waist-hip, waist-height, BAI, NYHF, NLR ratio
<b>Clinical Chemistry</b>	Na, K, Cl, HCO <sub>3</sub> , Ca, Urea, Creatinine, BNP, troponin, Cholesterol, triglycerides, Glucose, HbA1c, PT-INR, APTT, PaO <sub>2</sub> , PaCO <sub>2</sub> , Lactate, pH, Insulin
<b>Clinical Hematology</b>	CBC (Hb, Hct, RBC, WBC, Neu, Lym, Eos)
	Cell Phenotyping: (ex. Monocyte CD-14, CD-16)
<b>Experimental BioMarker Analyses</b>	Cardiac injury & Remodelling (ex. Galectin-3)
	Metabolism (ex. Amino acids, lysophospholipids)
	Inflammation (ex. sSRP, adiponectin, resistin, TNF $\alpha$ , interleukins)

<b>Physiology</b>	Functional Capacity (ex. EPO) HR, BP, Ejection Fraction, LVEDP, Doppler, ECG, SpO2, CVP, U/O
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**Table-2:** Socio-demographic, baseline clinical, intra-operative, and post-operative data available through New Brunswick Cardiac Surgery Registry

Category	Variables
<b>Socio-demographic</b>	Age, sex
<b>Baseline clinical characteristics</b>	Weight, height, body mass index, smoking history, hypertension, dyslipidemia, diabetes, peripheral vascular disease, cerebrovascular disease, renal insufficiency, chronic obstructive pulmonary disease, previous cardiac intervention (percutaneous coronary intervention/cardiac surgery), New York Heart Association classification, left ventricular ejection fraction, urgency
<b>Intra-operative details</b>	Procedure, cross clamp time, total bypass time, transfusion of blood products (packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate)
<b>In-hospital post-operative outcomes</b>	Re-operation for any cause, re-operation for bleeding, infection (leg, superficial sternal, deep sternal), stroke (transient, permanent), intensive care unit length of stay/readmission, time on mechanical ventilation, reintubation, BiPAP (Bilevel Positive Airway Pressure), pleural effusion, pneumonia, atrial fibrillation, renal failure, mortality, post-operative length of stay, disposition on discharge (home, home with extra mural home services, transfer to other facility, transfer to other service, expired)
<b>30-day and 1 year post-operative outcomes</b>	Complications (infection, stroke, pleural effusion, pneumonia, atrial fibrillation, renal failure, mortality) and/or readmission to hospital for any cause, occurring post-discharge from cardiac surgery service but within 30 days of surgery

### *Clinical assessment*

Consented patients will participate in various measures of obesity, exercise capacity, functional status, and QoL, and provide blood and tissue samples (**Fig.2**). In addition to BMI, alternate measures of obesity will include waist circumference, hip circumference, waist-to-hip ratio,(23) waist-to-height ratio,(24, 25) waist-to-hip-to-height ratio and body adiposity index.(31) Tests of

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3 179 exercise capacity, functional status and QoL exercise-capacity will include the Six-Minute Walk  
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5 180 Test (6MWT),(32) Duke Activity Status Index (DASI),(32) Physical Self-Maintenance Scale  
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8 181 (PSMS),(33) and the Short Form-12 (SF-12).(34) The 6MWT measures the distance an individual is  
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10 182 able to walk on a flat surface over a total of six minutes. The DASI measures a patient's functional  
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12 183 capacity and cardiopulmonary fitness by estimating a patient's peak oxygen uptake (surrogate  
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15 184 VO<sub>2</sub>max). The PSMS assesses a patient's ability to independently perform six personal care tasks.  
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17 185 The SF-12 addresses mental and physical function as it relates to QoL.  
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### 21 187 ***Blood collection***

22 188 Blood collection from each voluntarily consented participant will constitute 2 vials for plasma (vial  
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24 189 catalogue #365974; purple top) and 2 vials for serum (vial catalogue #365963; red top). The sample  
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26 190 will be labelled with a unique de-identification code and transferred to clinical chemistry or a  
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29 191 research laboratory for analysis. Patients may be sampled (8-10ml, venous in a non-fasted state) at  
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31 192 pre-operative consult and/or day prior to surgery for clinical hematology analysis (monocyte-  
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33 193 CD14/16)(35) and non-fasted retrospective comparative analyses of salient biomarkers. Otherwise,  
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36 194 standard of care pre-operative blood sampling will be performed and parameters charted (**Table-1**).  
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38 195 Patients will be sampled (8-10ml, arterial in a fasted state) 30 minutes prior to surgery, after  
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40 196 anaesthetic induction from the arterial central line alongside standard of care parameters that are  
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42 197 charted (**Table-2**). Patients will be sampled (8-10ml, venous in a non-fasted state) at post-operative  
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45 198 consultations at 1-3months for clinical hematology analysis and non-fasted prospective comparative  
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47 199 analyses of salient biomarkers (**Fig.2**). Investigative biomarker analysis will focus on cardiac injury  
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49 200 and remodelling (ex. galectin-3, sST2 etc.), metabolic (ex. amino acids, lysophospholipids etc),  
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3 201 inflammation (ex. adipokines, cytokines, interleukins etc) and functional capacity (ex.  
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5 202 erythropoietin, irisin, transferrin etc.) regulators.  
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### 8 203 ***Tissue collection***

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12 205 During surgery, adipose tissue from subcutaneous, pre-pericardial, epicardial and peri-aortic depots  
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14 206 will be collected in sterile specimen collection containers (**Fig.1**), labelled with a de-identification  
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16  
17 207 code and transferred to a research laboratory for analysis. The tissues will range in size from 0.5-1.5  
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19 208 cm in width (0.3-0.6 cm thick). The atrial appendage cardiac tissue will be isolated by clean cut  
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21 209 punch of the atria during bypass surgery and stored for further analysis (ex. metabolic and  
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24 210 inflammatory markers). Tissue protein and gene expression of various biomarkers (ex.  
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26 211 adipocytokines) in each of these tissue depots will be analyzed to determine whether current or  
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28 212 experimental biomarkers have prognostic relevance in distinguishing “high-fit” from “low-fit”  
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31 213 obese patients.  
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### 33 214

### 35 215 **5. Group assignment:**

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37 216 Despite the limitations of BMI as a measure of obesity, it remains an important starting point for  
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40 217 patient classification and comparisons given its widespread use and previous work by our  
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42 218 group.(36) Patients will be categorized into one of five BMI groups based on WHO definitions of  
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44 219 obesity class (**Table 3**).(37) WHO criteria consider any patient with a BMI  $\geq 25$  kg/m<sup>2</sup> as overweight,  
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46  
47 220 including both pre-obese and obese patients. Normal weight patients (BMI 18.5– 24.9 kg/m<sup>2</sup>) will  
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49 221 serve as the controls, while pre-obese (BMI 25.0-29.9), obese class I (BMI 30.0–34.9), II (BMI  
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51 222 35.0–39.9) and III (BMI  $\geq 40.0$ ) patients will form the study group.  
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**Table 3: World Health Organization obesity classification**

Obesity Classification	BMI (kg/m <sup>2</sup> )
Underweight	< 18.50
Normal range	18.50–24.99
Overweight	
<b>Pre-obese</b>	25.00–29.99
<b>Obese class I</b>	30.00–34.99
<b>Obese class II</b>	35.00–39.99
<b>Obese class III</b>	≥ 40.00

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## 6. Patient and Public involvement

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In addition to patient participation by recruitment, participants will be invited to part take in focus groups. Upon completion of the trial patients will be involved in disseminating the findings by sharing of the results with the public. Participant engagement will be raised through science fairs, seminars, research days, social media; and use of tools like posters, handouts and brochures.

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## Statistical methods

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We used the results from our previous study in which rates of the composite outcome (in-hospital mortality, prolonged ventilation >24hrs, new-onset renal failure and wound infection) were seen to increase with greater patient BMI (BMI 18.5-24.9kg/m<sup>2</sup>: 11.1%; BMI 25.0-29.9kg/m<sup>2</sup>: 11.8%; BMI 30.0-34.9kg/m<sup>2</sup>: 14.6%; BMI 35.0-39.9kg/m<sup>2</sup>: 19.4%; BMI ≥ 40.0 kg/m<sup>2</sup>: 28.5%; p<0.0001) to establish an expected effect size. Using the greatest observed difference in rates of the composite outcome in combination with a desired power of 80% and type I error rate of 0.01 (following 5-class Bonferroni correction), an estimated sample size of 122 patients per weight classification was derived (overall n=610). Patients' baseline, intra-operative, and post-operative clinical characteristics (**Tables 1 and 2**) will be compared by obesity class, using chi-squared tests for

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3 245 categorical variables and analysis of variance and Kruskal-Wallis tests for continuous variables.  
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5 246 Multivariable logistic regression will then be employed to construct a baseline model of the risk-  
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8 247 adjusted impact of obesity class, and the preoperative socio-demographic and clinical characteristics  
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10 248 and operative procedure (**Table 2**), on the composite outcome, based on our previous work.<sup>41</sup> A  
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12 249 fully adjusted regression model will initially include all predictor variables having an unadjusted  
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15 250 association of at least  $p \leq 0.20$  with the composite outcome. Backward selection will then be applied  
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17 251 to retain only those covariates having independent predictive power at a significance of  $p < 0.05$ .  
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19 252 Pearson and Spearman correlations for normally and non-normally distributed variables,  
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21  
22 253 respectively, among the non-traditional determined measures that are novel in this trial (**Table 1**)  
23  
24 254 will be assessed to avoid including collinear predictor variables in a more enhanced logistic  
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26 255 regression model. The ability of these measures to improve risk prediction over and above the  
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29 256 baseline model will be evaluated by comparing the c-statistics of the candidate enhanced model with  
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31 257 the baseline model. Analyses will be performed using SAS v 9.4 (SAS Institute Inc., Cary, NC,  
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33 258 USA), and R Statistical Software (<http://www.r-project.org/>).  
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### 35 259 36 37 38 260 **Data and safety monitoring**

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40 261 The quality of all data collected will be carefully supervised by the investigators. The research team  
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42 262 will be responsible for data collection and will be in close contact with the investigators for timely  
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45 263 follow-up of the study procedures, data update and corrections. An interim analysis will be  
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47 264 conducted when 50% of the patients have been recruited and have completed all data collection  
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49 265 procedures and follow-up.  
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### 51 266 52 53 54 267 **Intra data sharing**



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3 268 All Principal Investigators will be given access to the cleaned data sets. Data sets will be stored on  
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5 269 hospital secure drives at the site created for the study, and all data sets will be password protected.  
6  
7  
8 270 Paper files shall be stored at a secure location and kept locked at all times. To ensure confidentiality,  
9  
10 271 data dispersed to project team members will be blinded of any identifying participant information.  
11

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## 14 15 273 **DISCUSSION**

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17 274 The OPOS trial is novel in its design for classifying CVD patients by BMI, QoL measures and  
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19 275 functional capacity, and correlating these factors with molecular biomarkers of obesity at the  
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22 276 systemic and cellular level. Previous studies have been unable to completely elucidate the  
23  
24 277 mechanisms by which obesity affects post-operative outcomes. The proposed findings of this trial  
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26 278 should overcome, to a great extent, the limitations of BMI as a singular measure of obesity, the most  
27  
28 279 salient of which is its inability to account for muscle mass or functional capacity. While alternate  
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31 280 techniques can directly measure body composition, such as magnetic resonance imaging or dual-  
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33 281 energy X-ray absorptiometry(38), these are impractical in the clinical setting. Despite its limitations,  
34  
35 282 BMI is most familiar to clinicians and thus must serve as a comparative marker in this trial design.  
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38 283 Studies like this one are necessary to help segregate the high-risk obese patient likely to experience  
39  
40 284 adverse outcomes from the lower risk obese patient. Thus we plan to better define “high-fit” versus  
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42 285 “low-fit obese” patients in order to assist surgical planning and follow-up practices.  
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47 287 The assessments chosen for this trial are clinically validated, self-reported measures of functional  
48  
49 288 capacity and health related QoL. The SF-12 is considered a valid tool over SF-36 for its ease of  
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52 289 administration, reliability, validity and brevity acting as a reliable surrogate to more complex  
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54 290 analyses of life quality.(39) The PSMS is an effective tool determining independence of cardiac  
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3 291 patients to carry out activities of daily living. The utilization of both the SF-12 and the PSMS  
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5 292 allows us to determine which is more effective as a measure of QoL in this patient population and  
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8 293 provides the opportunity to compare or consolidate the two measures in determining “high-fit” vs  
9  
10 294 “low-fit” patient categorization. Similarly, the DASI is a valid measure of the functional capacity  
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12 295 measure for cardiac patients, determining the impact of the patient’s cardiovascular disease on self-  
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14 296 reported physical work capacity to estimate peak metabolic equivalents.(40) The DASI, as a self-  
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17 297 reported test, will be correlated with the objective measure of the 6MWT, another effective tool for  
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19 298 assessing functional capacity in patients with cardiovascular and pulmonary diseases.(41) These two  
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21  
22 299 tests in combination compensate for potential patient ineligibility due to disease burden for the  
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24 300 6MWT, or bias in self-reporting for the DASI. The order of administration may pose a limitation, as  
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26 301 the 6MWT test is administered prior to DASI and could influence the self-reporting. Interestingly,  
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28 302 many patients are accompanied by family and that strengthens the legitimacy of the DASI because  
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31 303 of two-person recall.

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33 304  
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35 305 Biomarkers are sensitive, specific objective measures that can be used alone or in combination and  
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37 306 are known to be predictive of outcomes.(42) Here we elected to design a trial amenable to  
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40 307 conventional and experimental biomarkers, to identify measures that are potentially highly sensitive,  
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42 308 translatable across centres and immutable to humanistic influences at the point of collection (**Table-**  
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44  
45 309 **1**). Recently, adipose depots in close proximity to the heart have emerged as regulators of cardiac  
46  
47 310 function and may likely influence the heart following cardiac surgery. Previous studies have shown  
48  
49 311 that perivascular, epicardial and cardiac adipose tissue depots are suggestive of visceral adiposity,  
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51 312 and are sensitive and specific markers of cardiovascular risk.(43, 44) Thus, it is important to  
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54 313 examine cytokines and chemokines in circulation, specifically adipokine expression in distinct  
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3 314 adipose tissues in an around the heart that may selectively influence cardiac cells via paracrine  
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5 315 secretion of biomolecules in close proximity to the heart.(45) With this trial we are building the  
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8 316 “OPOS Biobank” as a valuable and unique repository of adipose tissue from different depots and  
9  
10 317 blood samples from coronary artery bypass grafts and/or valve surgery patients. To this biobank we  
11  
12 318 can link clinical history and blood sample analyses with gene, protein and cellular expression  
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14  
15 319 profiles of critical regulators of cardiovascular and metabolic disease.(46, 47)

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17 320  
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19 321 The knowledge gained by consolidating this information for iterative utility would potentially help  
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21 322 identify new genes associated with a variety of clinical outcomes as well as new therapeutic targets.  
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24 323 Additionally, these patient samples provide opportunity to investigate associated disease processes  
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26 324 like coronary artery disease, chronic heart failure, calcified aortic valve disease, atrial fibrillation etc.  
27  
28 325 It has been shown that the power of two well characterized biomarkers can determine differences of  
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31 326 1-year mortality by more than 50% predictively.(42) Assessment of clinical and biomarker panels  
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33 327 could thus potentially help identify predictive biomarkers that would help clinicians treat cardiac  
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35 328 patients more effectively.

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38 329  
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40 330 Despite the novelty of the proposed trial, some investigations extend beyond our scope. Future  
41  
42 331 studies might include more comprehensive QoL assessments, including mental health assessments,  
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45 332 and socio-economic status, that contribute to health related QoL. Mental fortitude could be a  
46  
47 333 deterrent to QoL, independent of physical ability, and is not specifically accounted for in this trial.  
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49 334 Underweight patients were excluded due to the significantly higher risks associated with early major  
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51 335 adverse clinical outcomes.(48) Patients above the age of 75 were not included in this trial, to  
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53  
54 336 exclude the effect of frailty on physical capacity for recovery. Future studies could account for

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3 337 frailty as a confounding variable and incorporate this into a more complete assessment of surgical  
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5 338 fitness. Only elective patients are included in this trial, and high-risk urgent patients were excluded.  
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8 339 This was a practical and safety decision; however, the results of this trial should allow for more  
9  
10 340 open inclusion once the criterion to define surgical fitness is clear. Additional studies should  
11  
12 341 explore how best to treat and prevent adverse outcomes in at-risk obese patients in advance of their  
13  
14 342 surgery or thereafter in order to reduce their risk and to improve outcomes. These and additional  
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17 343 patient populations could be followed over a longer term to assess outcomes like 5-year mortality or  
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19 344 to compare retrospectively to past practices once a new paradigm is determined.(36) While our trial  
20  
21 345 is limited in terms of patients enrolled, future studies could also have higher enrollment targets that  
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23  
24 346 would allow for broader multivariate analyses.  
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## 26 347 27 28 348 **PRESENT STATUS**

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30 349 The OPOS trial began enrollment in December 2014 and as of March 2018, more than 365 patients  
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32  
33 350 have been enrolled with clinical data and tissue samples collected. 105 patients were withdrawn due  
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35 351 to change in patient's condition becoming more urgent, patients passing the age limit of 75 years,  
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38 352 and patients who decided to withdraw from the trial. The trial is expected to continue till 2022 until  
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40 353 enrolment targets have been achieved. Other potential strategies to improve enrolment are inclusion  
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42 354 of additional sites.  
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## 44 355 45 46 356 **DIRECTION**

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49 357 Fit or not, healthy or unhealthy, chronic obesity is strongly linked to metabolic deterioration, a  
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51 358 major risk factor for cardiovascular disease. The results of the OPOS trial will inform cardiac  
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54 359 surgeons and allied health care professionals on the important relationships that exist between  
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3 360 obesity and adverse outcomes after cardiac surgery. Upon completion of this trial, clinicians and  
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5 361 health care administrators will be better able to identify an obese patient who is more likely to  
6  
7  
8 362 experience adverse outcomes and require additional hospital resources in their recovery.  
9

10 363

## 11 12 364 **ACKNOWLEDGEMENTS and FUNDING**

13  
14  
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18  
19 367 of Surgery Clinical Research Scholarship grant, the New Brunswick Health Research Foundation,  
20  
21  
22 368 the New Brunswick Innovation Foundation, Canadian Diabetes Association and the Heart & Stroke  
23  
24 369 Foundation of Canada to members of the IMPART team (<https://www.impart.team>).  
25

26 370

## 27 371 **AUTHOR CONTRIBUTIONS**

28  
29  
30 372 JM, AY, AH, PK and KB contributed to trial design. TP and JFL provided significant intellectual  
31  
32 373 input. CA recruited patients and prepared the report. AH, JFL, CA and SM assisted with clinical  
33  
34 374 sample collection and processing. JM and AY contributed to statistical design. All authors have read  
35  
36  
37 375 and approved the article.  
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40  
41 377 **Declarations of interest:** none  
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**REFERENCES**

1. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah A. Effects of obesity and small body size on operative and long-term outcomes of coronary artery bypass surgery: a propensity-matched analysis. *The Annals of thoracic surgery*. 2005 Jun;79(6):1976-86. PubMed PMID: 15919295. Epub 2005/05/28. eng.
2. Ng C, Corey PN, Young TK. Divergent body mass index trajectories between Aboriginal and non-Aboriginal Canadians 1994-2009--an exploration of age, period, and cohort effects. *American journal of human biology : the official journal of the Human Biology Council*. 2012 Mar-Apr;24(2):170-6. PubMed PMID: 22275122. Epub 2012/01/26. eng.
3. Moubarac J-C, Batal M, Louzada ML, Martinez Steele E, Monteiro CA. Consumption of ultra-processed foods predicts diet quality in Canada. *Appetite*. 2017 1/1/;108:512-20.
4. Lastra G, Sowers JR. Obesity and cardiovascular disease: role of adipose tissue, inflammation, and the renin-angiotensin-aldosterone system. *Hormone molecular biology and clinical investigation*. 2013 Sep;15(2):49-57. PubMed PMID: 25436732.
5. Rahmanian PB, Adams DH, Castillo JG, Chikwe J, Bodian CA, Filsoufi F. Impact of body mass index on early outcome and late survival in patients undergoing coronary artery bypass grafting or valve surgery or both. *Am J Cardiol*. 2007 Dec 1;100(11):1702-8. PubMed PMID: 18036372. Epub 2007/11/27. eng.
6. Tyson GH, 3rd, Rodriguez E, Elci OC, Koutlas TC, Chitwood WR, Jr., Ferguson TB, et al. Cardiac procedures in patients with a body mass index exceeding 45: outcomes and long-term results. *The Annals of thoracic surgery*. 2007 Jul;84(1):3-9; discussion PubMed PMID: 17588372. Epub 2007/06/26. eng.
7. Sun X, Boyce SW, Hill PC, et al. Association of body mass index with new-onset atrial fibrillation after coronary artery bypass grafting operations. *Ann Thorac Surg*. 2011;91:1852-9.
8. van Straten AHM, Bramer S, Hamad MAS, et al. Effect of body mass index on early and late mortality after coronary artery bypass grafting. *Ann Thorac Surg*. 2010;89:30-7.
9. Tolpin DA, Collard CD, Lee V, Elayda MA, Pan W. Obesity is associated with increased morbidity after coronary artery bypass graft surgery in patients with renal insufficiency. *J Thorac Cardiovasc Surg*. 2009;138:873-9.
10. Choi JC, Bakaeen FG, Cornwell LD, et al. Morbid obesity is associated with increased resource utilization in coronary artery bypass grafting. *Ann Thorac Surg*. 2012;94:23-8.
11. Prabhakar G, Haan CK, Peterson ED, Coombs LP, Cruzzavala JL, Murray GF. The risks of moderate and extreme obesity for coronary artery bypass grafting outcomes: a study from the Society of Thoracic Surgeons' database. *The Annals of thoracic surgery*. 74(4):1125-31.
12. Ghanta RK, LaPar DJ, Zhang Q, Devarkonda V, Isbell JM, Yarboro LT, et al. Obesity Increases Risk-Adjusted Morbidity, Mortality, and Cost Following Cardiac Surgery. *Journal of the American Heart Association*. 2017 Mar 08;6(3). PubMed PMID: 28275064. Epub 2017/03/10. eng.
13. Gruberg L, Weissman NJ, Waksman R, et al. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol*. 2002;39:578-84.
14. Stamou SC, Nussbaum M, Stiegel RM, et al. Effect of body mass index on outcomes after cardiac surgery: is there an obesity paradox? *Ann Thorac Surg*. 2011;91:42-8.

- 1  
2  
3 422 15. Gruberg L, Mercado N, Milo S, et al. Impact of body mass index on the outcome of  
4 423 patients with multivessel disease randomized to either coronary artery bypass grafting or  
5 424 stenting in the ARTS trial: the obesity paradox II? *Am J Cardiol.* 2005;95:439-44.
- 7 425 16. Engel AM, McDonough S, Smith JM. Does an obese body mass index affect hospital  
8 426 outcomes after coronary artery bypass graft surgery? *Ann Thorac Surg.* 2009;88:1793-800.
- 9 427 17. Hartrumpf M, Kuehnel RU, Albes JM. The obesity paradox is still there: a risk analysis of  
10 428 over 15 000 cardiosurgical patients based on body mass index. *Interactive cardiovascular and*  
11 429 *thoracic surgery.* 2017 Mar 18. PubMed PMID: 28329172. Epub 2017/03/23. eng.
- 13 430 18. Uretsky S, Supariwala A, Gurram S, Bonda SL, Thota N, Bezwada P, et al. The interaction  
14 431 of exercise ability and body mass index upon long-term outcomes among patients undergoing  
15 432 stress-rest perfusion single-photon emission computed tomography imaging. *Am Heart J.*  
16 433 2013 Jul;166(1):127-33. PubMed PMID: 23816031. Epub 2013/07/03. eng.
- 17 434 19. Chasse M, Mathieu P, Voisine P, Despres JP, Pibarot P, Baillot R, et al. The  
18 435 Underestimated Belly Factor: Waist Circumference Is Linked to Significant Morbidity  
20 436 Following Isolated Coronary Artery Bypass Grafting. *The Canadian journal of cardiology.* 2015  
21 437 Jul 7. PubMed PMID: 26481079.
- 22 438 20. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total  
23 439 mortality and with cardiovascular events in coronary artery disease: a systematic review of  
24 440 cohort studies. *Lancet.* 2006;368(9536):666-78.
- 25 441 21. Baker AR, Silva NF, Quinn DW, Harte AL, Pagano D, Bonser RS, et al. Human epicardial  
27 442 adipose tissue expresses a pathogenic profile of adipocytokines in patients with  
28 443 cardiovascular disease. *Cardiovascular diabetology.* 2006 Jan 13;5:1. PubMed PMID:  
29 444 16412224. Pubmed Central PMCID: PMC1352345. Epub 2006/01/18. eng.
- 30 445 22. Kremen J, Dolinkova M, Krajickova J, Blaha J, Anderlova K, Lacinova Z, et al. Increased  
31 446 subcutaneous and epicardial adipose tissue production of proinflammatory cytokines in  
32 447 cardiac surgery patients: possible role in postoperative insulin resistance. *The Journal of*  
34 448 *clinical endocrinology and metabolism.* 2006 Nov;91(11):4620-7. PubMed PMID: 16895955.  
35 449 Epub 2006/08/10. eng.
- 36 450 23. Waist circumference and waist-hip ratio: report of a WHO expert consultation. Geneva:  
37 451 World Health Organization; 2008.
- 38 452 24. Schneider HJ, Friedrich N, Klotsche J, et al. The predictive value of different measures of  
39 453 obesity for incident cardiovascular events and mortality. *J Clin Endocrinol Metab.*  
41 454 2010;95:1777-85.
- 42 455 25. Lee CMY, Huxley RR, Wildman RP, Woodward M. Indices of abdominal obesity are  
43 456 better discriminators of cardiovascular risk factors than BMI: a meta-analysis. *J Clin Epidemiol.*  
44 457 2008;61:646-53.
- 45 458 26. Staiano AE, Reeder BA, Elliott S, Joffres MR, Pahwa P, Kirkland SA, et al. Body mass  
46 459 index versus waist circumference as predictors of mortality in Canadian adults. *International*  
48 460 *journal of obesity (2005).* 2012 Nov;36(11):1450-4. PubMed PMID: 22249224. Pubmed  
49 461 Central PMCID: PMC4120111. Epub 2012/01/18. eng.
- 50 462 27. Quante M, Dietrich A, ElKhal A, Tullius SG. Obesity-related immune responses and their  
51 463 impact on surgical outcomes. *International journal of obesity (2005).* 2015 Jun;39(6):877-83.  
52 464 PubMed PMID: 25697667. Epub 2015/02/24. eng.
- 54 465 28. Halkos ME, Puskas JD, Lattouf OM, Kilgo P, Kerendi F, Song HK, et al. Elevated  
55 466 preoperative hemoglobin A1c level is predictive of adverse events after coronary artery

- 1  
2  
3 467 bypass surgery. *The Journal of thoracic and cardiovascular surgery*. 2008 Sep;136(3):631-40.  
4 468 PubMed PMID: 18805264. Epub 2008/09/23. eng.
- 5 469 29. Hassan A, Yip AM, MacLeod JB, Lutchmedial S, Brown CD, Forgie R, et al. The effect of  
6 470 obesity on in-hospital outcomes following cardiac surgery in New Brunswick. *The Canadian*  
7 471 *journal of cardiology*. 2013;29(Suppl 10):S261-2.
- 8 472 30. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krle AJK, et al. SPIRIT 2013  
9 473 Statement: defining standard protocol items for clinical trials. *Revista panamericana de salud*  
10 474 *publica = Pan American journal of public health*. 2015 Dec;38(6):506-14. PubMed PMID:  
11 475 27440100. Pubmed Central PMCID: PMC5114122. Epub 2016/07/22. eng.
- 12 476 31. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue  
13 477 macrophage polarization. *The Journal of clinical investigation*. 2007 Jan;117(1):175-84.  
14 478 PubMed PMID: 17200717. Pubmed Central PMCID: PMC1716210. Epub 2007/01/04. eng.
- 15 479 32. O'Brien EC, Thomas LE. Untangling the paradox: Obesity as prognostic marker in  
16 480 prevalent cardiovascular disease. *American Heart Journal*. 2016 2//;172:170-2.
- 17 481 33. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental  
18 482 activities of daily living. *Gerontol*. 1969;9(3):179-86.
- 19 483 34. Li P, Liu S, Lu M, Bandyopadhyay G, Oh D, Imamura T, et al. Hematopoietic-Derived  
20 484 Galectin-3 Causes Cellular and Systemic Insulin Resistance. *Cell*. 2016 Nov 03;167(4):973-84  
21 485 e12. PubMed PMID: 27814523. Pubmed Central PMCID: PMC5179329. Epub 2016/11/05. eng.
- 22 486 35. Rogacev KS, Cremers B, Zawada AM, Seiler S, Binder N, Ege P, et al. CD14++CD16+  
23 487 monocytes independently predict cardiovascular events: a cohort study of 951 patients  
24 488 referred for elective coronary angiography. *Journal of the American College of Cardiology*.  
25 489 2012 Oct 16;60(16):1512-20. PubMed PMID: 22999728.
- 26 490 36. Rosvall BR, Forgie K, MacLeod JB, Yip AM, Aguiar C, Lutchmedial S, et al. Impact of  
27 491 Obesity on Intensive Care Unit Resource Utilization After Cardiac Operations. *The Annals of*  
28 492 *thoracic surgery*. 2017 Jul 24. PubMed PMID: 28803638.
- 29 493 37. WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO  
30 494 Expert Committee. World Health Organization technical report series. 1995;854:1-452.  
31 495 PubMed PMID: 8594834. Epub 1995/01/01. eng.
- 32 496 38. Rothney MP, Brychta RJ, Schaefer EV, Chen KY, Skarulis MC. Body Composition  
33 497 Measured by Dual-energy X-ray Absorptiometry Half-body Scans in Obese Adults. *Obesity*  
34 498 (Silver Spring, Md). 2009 02/19;17(6):1281-6. PubMed PMID: PMC2709755.
- 35 499 39. Muller-Nordhorn J, Roll S, Willich SN. Comparison of the short form (SF)-12 health  
36 500 status instrument with the SF-36 in patients with coronary heart disease. *Heart (British*  
37 501 *Cardiac Society)*. 2004 May;90(5):523-7. PubMed PMID: 15084550. Pubmed Central PMCID:  
38 502 PMC1768233. Epub 2004/04/16. eng.
- 39 503 40. Grodin JL, Hammadah M, Fan Y, Hazen SL, Tang WHW. Prognostic Value of Estimating  
40 504 Functional Capacity With the Use of the Duke Activity Status Index in Stable Patients With  
41 505 Chronic Heart Failure. *Journal of Cardiac Failure*. 21(1):44-50.
- 42 506 41. Society AT. ATS statement: guidelines for the six-minute walk test. *American journal of*  
43 507 *respiratory and critical care medicine*. 2002 Jul 01;166(1):111-7. PubMed PMID: 12091180.  
44 508 Epub 2002/07/02. eng.
- 45 509 42. Lassus J, Gayat E, Mueller C, Peacock WF, Spinar J, Harjola VP, et al. Incremental value of  
46 510 biomarkers to clinical variables for mortality prediction in acutely decompensated heart  
47 511 failure: the Multinational Observational Cohort on Acute Heart Failure (MOCA) study. *Int J*  
48 512 *Cardiol*. 2013 Oct 03;168(3):2186-94. PubMed PMID: 23538053.



1

2

3 513 43. Fitzgibbons TP, Czech MP. Epicardial and perivascular adipose tissues and their  
 4 514 influence on cardiovascular disease: basic mechanisms and clinical associations. Journal of the  
 5 515 American Heart Association. 2014 Mar 04;3(2):e000582. PubMed PMID: 24595191. Pubmed  
 7 516 Central PMCID: 4187500.

8 517 44. Aldiss P, Davies G, Woods R, Budge H, Sacks HS, Symonds ME. 'Browning' the cardiac  
 9 518 and peri-vascular adipose tissues to modulate cardiovascular risk. Int J Cardiol. 2017 Feb  
 10 519 01;228:265-74. PubMed PMID: 27865196. Pubmed Central PMCID: 5236060.

11 520 45. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. Am Heart J. 2007  
 12 521 Jun;153(6):907-17. PubMed PMID: 17540190.

14 522 46. Falkenham A, Saraswat MK, Wong C, Gawdat K, Myers T, Begum J, et al. Recovery free of  
 15 523 heart failure after acute coronary syndrome and coronary revascularization. ESC heart failure.  
 16 524 2017 Jul 24. PubMed PMID: 28737273. Epub 2017/07/25. eng.

17 525 47. Trivedi PC, Bartlett JJ, Perez LJ, Brunt KR, Legare JF, Hassan A, et al. Glucolipotoxicity  
 18 526 diminishes cardiomyocyte TFEB and inhibits lysosomal autophagy during obesity and  
 19 527 diabetes. Biochimica et biophysica acta. 2016 Dec;1861(12 Pt A):1893-910. PubMed PMID:  
 21 528 27620487. Epub 2016/10/22. eng.

22 529 48. van Straten AH, Bramer S, Soliman Hamad MA, van Zundert AA, Martens EJ,  
 23 530 Schonberger JP, et al. Effect of body mass index on early and late mortality after coronary  
 24 531 artery bypass grafting. The Annals of thoracic surgery. 2010 Jan;89(1):30-7. PubMed PMID:  
 25 532 20103201. Epub 2010/01/28. eng.

27 533

#### 28 534 **FIGURE LEGENDS:**

29 535 **Fig. 1: Trial design flow-chart:** From left to right: Patients are admitted for surgical consultation  
 30 536 and cardiac catheterization. Consent may be obtained at this time as well as a venous blood sample  
 31 537 of 8-10ml collected. Consent could also be obtained at pre-operative admission for cardiac surgery,  
 32 538 as well as a venous blood sample of 8-10ml. (Surgery is elective and typically is scheduled between  
 33 539 2months to 1 year after surgical consult but not time-restrictive to participation). Patients are  
 35 540 admitted 24hours prior to surgery, and a 30 min pre-op arterial blood sample is collected. Tissue  
 36 541 sampling is carried out intra-operatively. At the early post-operative follow-up appointment  
 37 542 (occurring between 6 weeks to 3 months), a non-fasting venous blood sample may be collected. At  
 38 543 the late post-operative follow-up appointment (approximately 1 year post-operatively) telephone  
 39 544 follow-up by questionnaire are conducted.

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 43 546 **Figure 2:** Flowchart showing protocol for the OPOS trial.

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#### 45 548 **Date and Version Identifier:**

46 549 *Issue Date:* 28 November, 2014

47 550 *Protocol Version Number:* 7 dated 12 December 2017

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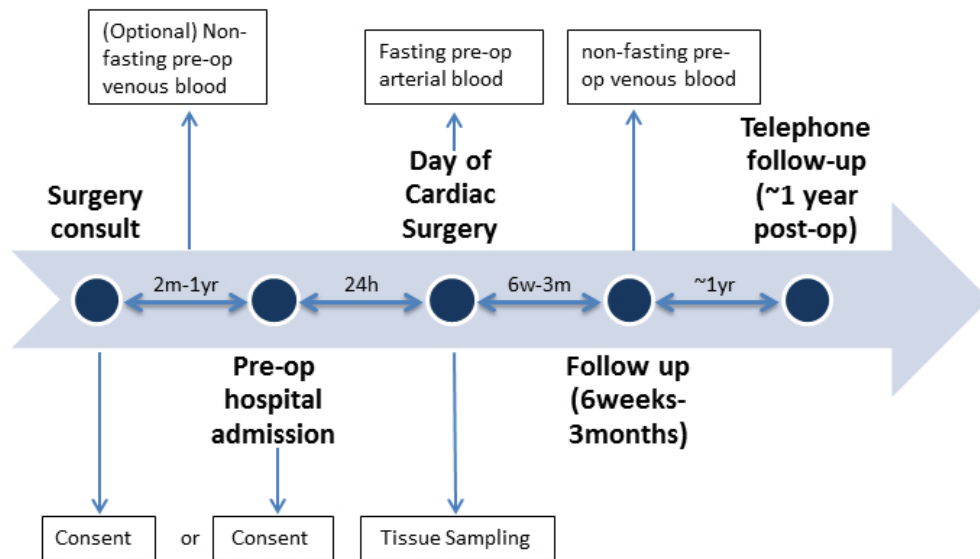
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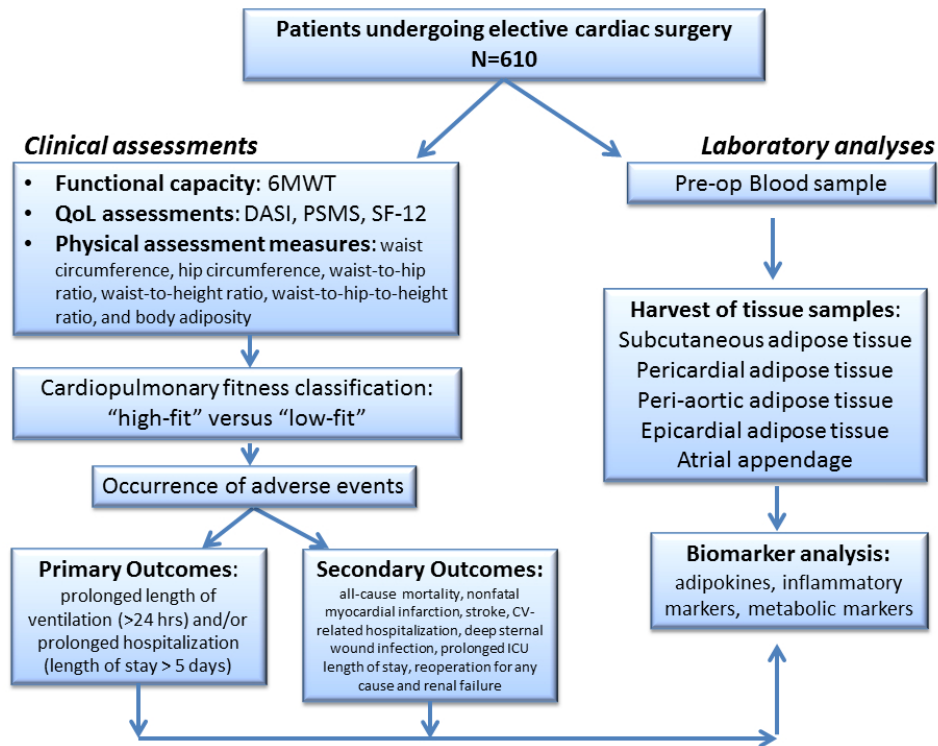
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Trial design flow-chart: From left to right: Patients are admitted for surgical consultation and cardiac catheterization. Consent may be obtained at this time as well as a venous blood sample of 8-10ml collected. Consent could also be obtained at pre-operative admission for cardiac surgery, as well as a venous blood sample of 8-10ml. (Surgery is elective and typically is scheduled between 2months to 1 year after surgical consult but not time-restrictive to participation). Patients are admitted 24hours prior to surgery, and a 30 min pre-op arterial blood sample is collected. Tissue sampling is carried out intra-operatively. At the early post-operative follow-up appointment (occurring between 6 weeks to 3 months), a non-fasting venous blood sample may be collected. At the late post-operative follow-up appointment (approximately 1 year post-operatively) telephone follow-up by questionnaire are conducted.

58x33mm (300 x 300 DPI)



Flowchart showing protocol for the OPOS trial.

81x60mm (300 x 300 DPI)

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	17

1	sponsor contact			
2	information			
3				
4	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	NA
5	responsibilities:		collection, management, analysis, and interpretation of	
6	sponsor and funder		data; writing of the report; and the decision to submit the	
7			report for publication, including whether they will have	
8			ultimate authority over any of these activities	
9				
10				
11				
12	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	NA
13	responsibilities:		centre, steering committee, endpoint adjudication	
14	committees		committee, data management team, and other individuals or	
15			groups overseeing the trial, if applicable (see Item 21a for	
16			data monitoring committee)	
17				
18				
19				
20	Background and	#6a	Description of research question and justification for	3,4
21	rationale		undertaking the trial, including summary of relevant studies	
22			(published and unpublished) examining benefits and harms	
23			for each intervention	
24				
25				
26				
27	Background and	#6b	Explanation for choice of comparators	4,5
28	rationale: choice of			
29	comparators			
30				
31				
32	Objectives	#7	Specific objectives or hypotheses	4,5
33				
34				
35	Trial design	#8	Description of trial design including type of trial (eg, parallel	6,7
36			group, crossover, factorial, single group), allocation ratio,	
37			and framework (eg, superiority, equivalence, non-inferiority,	
38			exploratory)	
39				
40				
41				
42	Study setting	#9	Description of study settings (eg, community clinic,	5
43			academic hospital) and list of countries where data will be	
44			collected. Reference to where list of study sites can be	
45			obtained	
46				
47				
48	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	6
49			eligibility criteria for study centres and individuals who will	
50			perform the interventions (eg, surgeons, psychotherapists)	
51				
52				
53				
54	Interventions:	#11a	Interventions for each group with sufficient detail to allow	9-11
55	description		replication, including how and when they will be	
56			administered	
57				
58				
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1	Interventions:	#11b	Criteria for discontinuing or modifying allocated	9-11
2	modifications		interventions for a given trial participant (eg, drug dose	
3			change in response to harms, participant request, or	
4			improving / worsening disease)	
5				
6				
7	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	NA
8	adherence		and any procedures for monitoring adherence (eg, drug	
9			tablet return; laboratory tests)	
10				
11				
12	Interventions:	#11d	Relevant concomitant care and interventions that are	NA
13	concomitant care		permitted or prohibited during the trial	
14				
15				
16	Outcomes	#12	Primary, secondary, and other outcomes, including the	4,5
17			specific measurement variable (eg, systolic blood pressure),	
18			analysis metric (eg, change from baseline, final value, time	
19			to event), method of aggregation (eg, median, proportion),	
20			and time point for each outcome. Explanation of the clinical	
21			relevance of chosen efficacy and harm outcomes is strongly	
22			recommended	
23				
24				
25				
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27				
28	Participant timeline	#13	Time schedule of enrolment, interventions (including any	Fig.1
29			run-ins and washouts), assessments, and visits for	
30			participants. A schematic diagram is highly recommended	
31			(see Figure)	
32				
33				
34				
35	Sample size	#14	Estimated number of participants needed to achieve study	12
36			objectives and how it was determined, including clinical and	
37			statistical assumptions supporting any sample size	
38			calculations	
39				
40				
41				
42	Recruitment	#15	Strategies for achieving adequate participant enrolment to	16
43			reach target sample size	
44				
45				
46	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	NA
47	generation		computer-generated random numbers), and list of any	
48			factors for stratification. To reduce predictability of a random	
49			sequence, details of any planned restriction (eg, blocking)	
50			should be provided in a separate document that is	
51			unavailable to those who enrol participants or assign	
52			interventions	
53				
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57	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	NA
58	concealment		central telephone; sequentially numbered, opaque, sealed	
59				

1	mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
2				
3				
4	Allocation:	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
5	implementation			
6				
7				
8				
9	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
10				
11				
12				
13				
14	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
15	emergency			
16	unblinding			
17				
18				
19				
20	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9,12
21				
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31	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
32	retention			
33				
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38	Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
39				
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46	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
47				
48				
49				
50				
51	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
52	analyses			
53				
54				
55	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
56	population and			
57	missing data			
58				
59				

1	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	NA
2	formal committee		of its role and reporting structure; statement of whether it is	
3			independent from the sponsor and competing interests; and	
4			reference to where further details about its charter can be	
5			found, if not in the protocol. Alternatively, an explanation of	
6			why a DMC is not needed	
7				
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9				
10	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	12
11	interim analysis		including who will have access to these interim results and	
12			make the final decision to terminate the trial	
13				
14				
15	Harms	#22	Plans for collecting, assessing, reporting, and managing	7
16			solicited and spontaneously reported adverse events and	
17			other unintended effects of trial interventions or trial conduct	
18				
19				
20				
21	Auditing	#23	Frequency and procedures for auditing trial conduct, if any,	NA
22			and whether the process will be independent from	
23			investigators and the sponsor	
24				
25				
26				
27	Research ethics	#24	Plans for seeking research ethics committee / institutional	5
28	approval		review board (REC / IRB) approval	
29				
30				
31	Protocol	#25	Plans for communicating important protocol modifications	5
32	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
33			relevant parties (eg, investigators, REC / IRBs, trial	
34			participants, trial registries, journals, regulators)	
35				
36				
37	Consent or assent	#26a	Who will obtain informed consent or assent from potential	5
38			trial participants or authorised surrogates, and how (see	
39			Item 32)	
40				
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42				
43	Consent or assent:	#26b	Additional consent provisions for collection and use of	9,10
44	ancillary studies		participant data and biological specimens in ancillary	
45			studies, if applicable	
46				
47				
48	Confidentiality	#27	How personal information about potential and enrolled	NA
49			participants will be collected, shared, and maintained in	
50			order to protect confidentiality before, during, and after the	
51			trial	
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54				
55	Declaration of	#28	Financial and other competing interests for principal	17
56	interests		investigators for the overall trial and each study site	
57				
58				
59	Data access	#29	Statement of who will have access to the final trial dataset,	NA
60				



			and disclosure of contractual agreements that limit such access for investigators	
	Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
	Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
	Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA
	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9,10

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# BMJ Open

## The impact of Obesity on Postoperative Outcomes following cardiac Surgery (The OPOS trial) - Rationale and design of an investigator-initiated prospective cohort trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023418.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Oct-2018
Complete List of Authors:	<p>Aguiar, Christie; Saint John Regional Hospital, Cardiovascular Research New Brunswick  MacLeod, Jeffrey ; Saint John Regional Hospital, Cardiovascular Research New Brunswick  Yip, Alexandra; Saint John Regional Hospital, Cardiovascular Research New Brunswick  Melville, Sarah; Dalhousie Medicine New Brunswick  Légaré, Jean-Francois ; Saint John Regional Hospital, Cardiovascular Research New Brunswick, and Cardiac Surgery  Pulinilkunnil, Thomas; Dalhousie Medicine New Brunswick, Biochemistry and Molecular Biology  Kienesberger, Petra; Dalhousie Medicine New Brunswick, Biochemistry and Molecular Biology  Brunt, Keith; Dalhousie Medicine New Brunswick, Department of Pharmacology  Hassan, Ansar; Saint John Regional Hospital, Cardiovascular Research New Brunswick and Cardiac Surgery</p>
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Research methods
Keywords:	inflammation, morbidity, Coronary artery bypass grafting, adipose tissue, atrial appendage, globesity

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Manuscripts

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3 1 **The impact of Obesity on Postoperative Outcomes following cardiac Surgery (The OPOS**  
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5 2 **trial) - Rationale and design of an investigator-initiated prospective cohort trial**  
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9  
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33 14 Abbreviated title: Obesity and cardiac surgical outcomes  
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47 20  
48  
49 21 **Word Count:** 3,464  
50

**ABSTRACT:**

**Introduction:** Increasing levels of obesity worldwide have led to a rise in the prevalence of obesity-related complications including cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia. Health care providers believe that overweight and obese cardiac surgery patients are more likely to experience adverse post-operative outcomes. The body mass index (BMI) is the primary measure of obesity in clinical practice, without accounting for a patient's level of cardiopulmonary fitness or muscle mass.

**Methods and Analysis:** Patients between the ages of 18 and 75 years undergoing elective cardiac surgery are consented to participate in this prospective observational trial. Patients will be invited to participate in measures of obesity, functional capacity and exercise capacity assessments, quality of life questionnaires, and blood and tissue sampling for biomarker analysis. The endpoints evaluated are measures other than BMI that could be predictive of short-term and long-term post-operative outcomes. Clinical outcomes of interest are prolonged ventilation, hospital length of stay, renal failure and all-cause mortality. Biomarkers of interest will largely focus on metabolism (lipids, amino acids) and inflammation (adipokines, cytokines and chemokines).

**Ethics and Dissemination:** This study has been approved by the institutional review board at the Horizon Health Network. Upon completion of the trial, the results shall be disseminated through conference presentations and publications in peer-reviewed journals. Additionally, the report shall also be diffused more broadly to the general public and the cardiovascular community.

**Summary:** The results of this trial will provide an improved understanding and better definition of obesity beyond BMI. We hope to demonstrate how fitness capacity of obese cardiac surgical patients and biomarkers alone or in combination, will help identify patients at risk for adverse outcomes when undergoing cardiac surgery. This study will help clinicians better identify patients

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46 pre-operatively based on fitness levels and associated biomarkers in anticipation of implementing  
47 mitigating strategies.  
48 **Trial Registration:** NCT03248921 at [www.clinicaltrials.gov](http://www.clinicaltrials.gov)  
49 Protocol Version 7, dated 12 December 2017

For peer review only

## 50 **Strengths and limitations of this study**

- 51 •The results of this prospective trial will present an improved understanding and better  
52 definition of obesity beyond BMI by identifying key biomarkers such as cytokines and  
53 adipokines
- 54 •This trial will determine the “fitness capacity” of obese cardiac surgical patients by  
55 segregating patients into “high-fit” and “low-fit” categories. This observational study  
56 only assesses elective cardiac surgery patients, and excludes high-risk urgent and frail  
57 patients.
- 58 •This trial is limited in terms of overall enrolment of participants; and there is unequal  
59 representation of higher BMI categories especially females.

61 **Keywords:** morbidity, CABG, valve replacement, valvuloplasty, adipose tissue, atrial appendage,  
62 clinical chemistry, inflammation, metaflammation, immunometabolism, globesity

## 64 BACKGROUND AND RATIONALE

65 The global epidemic of overweight and obese patients - "globesity" - is steadily rising without  
66 abatement and more than one-third of U.S. adults are obese.(1) In the Canadian population, one  
67 quarter of the population is obese, with a two-fold higher obesity risk amongst Indigenous-  
68 Canadians.(2) It is estimated that each year approximately 66,000 Canadians die due to health  
69 complications associated with obesity.(3) Obese populations typically experience comorbid  
70 cardiovascular disease (CVD) often necessitating invasive cardiac surgical interventions.(4) These  
71 patients are at higher risk for intra-operative and post-operative adverse events, including  
72 mortality.(1, 5-12) However, recent studies show paradoxical results, wherein obese patients can  
73 experience fewer adverse events and lower mortality than patients with normal body mass index  
74 (BMI), suggesting a benefit to obesity for post-surgical outcomes.(13-17) Referred to as the  
75 "obesity paradox", the underlying mechanisms and clinical paradigms of this phenomenon remain  
76 to be defined.(18)

77  
78 In part, this paradox may be attributable to over-reliance on singular anthropometric measures of  
79 obesity, namely BMI. BMI can be a poor predictor of clinical outcomes since it fails to account  
80 for variable whole-body adipose tissue distribution,(19, 20) or inflammatory state.(21, 22)  
81 Additionally, BMI does not address the physical ability or fitness of obese patients with respect to  
82 size. Thus, the question to be addressed with this trial is: Why do some obese patients have "good  
83 health-related quality of life" (QoL), maintain high physical ability, and have positive outcomes,  
84 while other obese patients and normal BMI patients have poor QoL, low physical ability and  
85 negative outcomes? Thus, we propose segregating obese patients into two populations: high-fit  
86 obese patients ("fit" obese or normally-able) and low fit obese patients ("non-fit" obese or less-

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2  
3 87 able). This distinction could be of critical importance in determining which obese patients are  
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5 88 more likely to do well post-operatively.  
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8 89  
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10 90 Alternative measures to BMI have been proposed, including waist-to-hip ratios and waist-to-height  
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12 91 ratios and body adiposity index.(23-25) These measures of central obesity reflect visceral adiposity  
13  
14  
15 92 and strongly predict cardiovascular risk, post-surgical outcomes, and resource utilization(26)' but  
16  
17 93 are not often measured or easily calculated from routine patient histories. Beyond clinical  
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19 94 measures of obesity and functional capacity, levels of circulating hormones, inflammatory  
20  
21 95 cytokines(27), and the presence of insulin resistance and type-II diabetes are likely to influence  
22  
23  
24 96 obese patient outcomes.(28) Developing a more complete understanding of biomarkers for obese  
25  
26 97 individuals that could improve operative risk-assessment is a priority.  
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28 98  
29  
30  
31 99 Ultimately, the need exists to better differentiate obese patients who experience fewer  
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33 100 complications from those with increased rates of adverse events, and to determine if they  
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35 101 correspond with the physically distinct populations of “high-fit” vs. “low-fit” obese. This  
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37  
38 102 distinction could be of critical importance in determining which obese patients are more likely to  
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40 103 do well post-operatively. Crude and risk-adjusted analyses will be carried out to determine which  
41  
42 104 non-traditional measures of obesity, functional status, and metabolic-inflammatory status may  
43  
44 105 have independent effects on rates of post-operative adverse events among obese patients. Here, we  
45  
46  
47 106 describe a trial that will address this important knowledge gap, “the impact of Obesity on  
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49 107 Postoperative Outcomes following cardiac Surgery (OPOS) trial”.  
50

## 51 108 52 53 109 **STUDY AIMS AND OUTCOME VARIABLES** 54 55



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3 110 The purpose of this trial is to identify non-BMI-related measures of obesity, functional capacity, and  
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5 111 molecular biomarkers that are capable of better defining risk for in-hospital, 30-day and 1-year  
6  
7 112 adverse events among obese patients undergoing cardiac surgery. We hypothesize that the  
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10 113 mechanisms by which obesity affects outcomes after cardiac surgery depend on a combination of a  
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12 114 patient's functional capacity, adipose tissue distribution and tissue/circulating metabolic-  
13  
14 115 inflammation status. We further hypothesize that by using this advanced approach, we may better  
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16  
17 116 distinguish "high-fit" from "low-fit" obese patients to devise strategies that minimize poor clinical  
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19 117 outcomes.

20  
21  
22 118  
23  
24 119 The primary outcome variable will be the composite of in-hospital mortality, prolonged ventilation  
25  
26 120 >24hrs, new-onset renal failure (The Society of Thoracic Surgeons score for renal failure is defined  
27  
28 121 as an increase in serum creatinine levels 4 mg/dL or greater (176.8 mmol/L), a 50% or greater  
29  
30  
31 122 increase in serum creatinine levels over the baseline preoperative value, or a new requirement for  
32  
33 123 dialysis) and wound infection. We have previously validated this composite outcome by  
34  
35 124 demonstrating a linear relationship between severity of obesity and adverse in-hospital patient  
36  
37  
38 125 outcomes.(29) Secondary clinical outcomes include re-operation for any cause, stroke (transient,  
39  
40 126 permanent), respiratory complications (pleural effusion, pneumonia), atrial fibrillation, post-  
41  
42 127 operative length of stay and disposition on discharge (home, home with care, transfer to other  
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44 128 facility or expired), exercise or functional capacity (by walk-test or questionnaire).

## 46 47 129 48 49 130 **METHODS**

### 50 51 131 **1. Research ethics approval**

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3 132 The OPOS trial protocol has been submitted and approved by the institutional committee on human  
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5 133 research at Horizon Health Network, Saint John Regional Hospital, New Brunswick Heart Centre &  
6  
7  
8 134 the Nova Scotia Health Authority, Maritime Heart Centre. All aspects of this trial are in conformity  
9  
10 135 to the Canadian Tri-Council Policy Statement on ethical conduct for research involving humans  
11  
12 136 (TCPS-2-2014) and are in accordance with the World Medical Association Declaration of Helsinki  
13  
14  
15 137 – ethical principles for medical research involving human subjects (2013). The trial has been  
16  
17 138 registered with the National Clinical Trials Database of the NIH ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)  
18  
19 139 NCT03248921). We used the SPIRIT checklist when writing our report(30).  
20  
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## 24 141 **2. Study population and subject selection**

25  
26 142 All patients scheduled for elective, first-time cardiac surgery at the New Brunswick Heart Centre in  
27  
28 143 Saint John, New Brunswick, and the Maritime Heart Centre in Halifax, Nova Scotia, will be  
29  
30  
31 144 considered. Patients with a BMI of less than  $18.5 \text{ kg/m}^2$  are classified as underweight by the World  
32  
33 145 Health Organization and will be excluded. In addition, patients older than 75 years will be excluded  
34  
35 146 to minimize the effect that frailty may have on exercise and functional capacity.  
36  
37  
38 147

## 40 148 **3. Trial overview**

41  
42 149 Eligible patients will be screened by the research coordinator for potential enrolment prior to  
43  
44 150 surgery (**Fig.1**). Subjects fulfilling the inclusion and exclusion criteria will be approached by the  
45  
46  
47 151 research coordinator and informed consent shall be obtained. Patients who convert from elective to  
48  
49 152 non-elective surgery or patients who choose to no longer participate are automatically withdrawn  
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51 153 from the trial. Participants are not offered financial or non-financial incentives to participate in the  
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54 154 trial.  
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#### 4. Trial design

The aims of this trial will be fulfilled using a prospective observational study design (**Fig.1**). Obese patients awaiting elective cardiac surgery including coronary artery bypass grafting surgery with or without valve surgery, aortic or mitral valve surgery will be identified. Consenting patients will be invited to voluntarily participate in select measurements of obesity, testing of exercise capacity and functional status, QoL questionnaires, as well as blood and tissue sampling for the purposes of profiling circulating biomarkers and metabolic-inflammatory status (**Table-1, Fig.2**). Routinely collected clinical data on baseline, intraoperative characteristics and post-operative outcomes will be acquired from the New Brunswick Cardiac Surgery Registry (**Table-2**). Although adverse events related to the trial procedure are unlikely (other than those related to cardiac surgery), all adverse events occurring during the course of the trial will be reported to the REB.

**Table-1: Table of Determined Measures:**

Category	Variables
<b>Clinical</b>	Age (yrs)
	Hip, waist circumference (cm)
	Height (cm)
	Weight (kg)
	6-MWT (m)
<b>Calculated</b>	DASI, SF-12, PSMS (scores)
	BMI, waist-hip, waist-height, BAI, NYHF, NLR ratio
<b>Clinical Chemistry</b>	Na, K, Cl, HCO <sub>3</sub> , Ca, Urea, Creatinine, BNP, troponin, Cholesterol, triglycerides, Glucose, HbA1c, PT-INR, APTT, PaO <sub>2</sub> , PaCO <sub>2</sub> , Lactate, pH, Insulin
<b>Clinical Hematology</b>	CBC (Hb, Hct, RBC, WBC, Neu, Lym, Eos)
	Cell Phenotyping: (ex. Monocyte CD-14, CD-16)

<b>Experimental BioMarker Analyses</b>	Cardiac injury & Remodelling (ex. Galectin-3) Metabolism (ex. Amino acids, lysophospholipids) Inflammation (ex. sSRP, adiponectin, resistin, TNF $\alpha$ , interleukins)
<b>Physiology</b>	Functional Capacity (ex. EPO) HR, BP, Ejection Fraction, LVEDP, Doppler, ECG, SpO <sub>2</sub> , CVP, U/O

**Table-2:** Socio-demographic, baseline clinical, intra-operative, and post-operative data available through New Brunswick Cardiac Surgery Registry

Category	Variables
<b>Socio-demographic</b>	Age, sex
<b>Baseline clinical characteristics</b>	Weight, height, body mass index, smoking history, hypertension, dyslipidemia, diabetes, peripheral vascular disease, cerebrovascular disease, renal insufficiency, chronic obstructive pulmonary disease, previous cardiac intervention (percutaneous coronary intervention/cardiac surgery), New York Heart Association classification, left ventricular ejection fraction, urgency
<b>Intra-operative details</b>	Procedure, cross clamp time, total bypass time, transfusion of blood products (packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate)
<b>In-hospital post-operative outcomes</b>	Re-operation for any cause, re-operation for bleeding, infection (leg, superficial sternal, deep sternal), stroke (transient, permanent), intensive care unit length of stay/readmission, time on mechanical ventilation, reintubation, BiPAP (Bilevel Positive Airway Pressure), pleural effusion, pneumonia, atrial fibrillation, renal failure, mortality, post-operative length of stay, disposition on discharge (home, home with extra mural home services, transfer to other facility, transfer to other service, expired)
<b>30-day and 1 year post-operative outcomes</b>	Complications (infection, stroke, pleural effusion, pneumonia, atrial fibrillation, renal failure, mortality) and/or readmission to hospital for any cause, occurring post-discharge from cardiac surgery service but within 30 days of surgery

### *Clinical assessment*

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3 176 Consented patients will participate in various measures of obesity, exercise capacity, functional  
4  
5 177 status, and QoL, and provide blood and tissue samples (**Fig.2**). In addition to BMI, alternate  
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8 178 measures of obesity will include waist circumference, hip circumference, waist-to-hip ratio,(23)  
9  
10 179 waist-to-height ratio,(24, 25) waist-to-hip-to-height ratio and body adiposity index.(31) Tests of  
11  
12 180 exercise capacity, functional status and QoL exercise-capacity will include the Six-Minute Walk  
13  
14 181 Test (6MWT),(32) Duke Activity Status Index (DASI),(32) Physical Self-Maintenance Scale  
15  
16 182 (PSMS),(33) and the Short Form-12 (SF-12).(34) The 6MWT measures the distance an individual is  
17  
18 183 able to walk on a flat surface over a total of six minutes. The DASI measures a patient's functional  
19  
20 184 capacity and cardiopulmonary fitness by estimating a patient's peak oxygen uptake (surrogate  
21  
22 185 VO<sub>2</sub>max). The PSMS assesses a patient's ability to independently perform six personal care tasks.  
23  
24 186 The SF-12 addresses mental and physical function as it relates to QoL.  
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### 30 188 **Blood collection**

31  
32  
33 189 Blood collection from each voluntarily consented participant will constitute 2 vials for plasma (vial  
34  
35 190 catalogue #365974; purple top) and 2 vials for serum (vial catalogue #365963; red top). The sample  
36  
37 191 will be labelled with a unique de-identification code and transferred to clinical chemistry or a  
38  
39  
40 192 research laboratory for analysis. Patients may be sampled (8-10ml, venous in a non-fasted state) at  
41  
42 193 pre-operative consult and/or day prior to surgery for clinical hematology analysis (monocyte-  
43  
44 194 CD14/16)(35) and non-fasted retrospective comparative analyses of salient biomarkers. Otherwise,  
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46 195 standard of care pre-operative blood sampling will be performed and parameters charted (**Table-1**).  
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49 196 Patients will be sampled (8-10ml, arterial in a fasted state) 30 minutes prior to surgery, after  
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51 197 anaesthetic induction from the arterial central line alongside standard of care parameters that are  
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53 198 charted (**Table-2**). Patients will be sampled (8-10ml, venous in a non-fasted state) at post-operative  
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199 consultations at 1-3months for clinical hematology analysis and non-fasted prospective comparative  
200 analyses of salient biomarkers (**Fig.2**). Investigative biomarker analysis will focus on cardiac injury  
201 and remodelling (ex. galectin-3, sST2 etc.), metabolic (ex. amino acids, lysophospholipids etc),  
202 inflammation (ex. adipokines, cytokines, interleukins etc) and functional capacity (ex.  
203 erythropoietin, irisin, transferrin etc.) regulators.

204

### 205 ***Tissue collection***

206 During surgery, adipose tissue from subcutaneous, pre-pericardial, epicardial and peri-aortic depots  
207 will be collected in sterile specimen collection containers (**Fig.1**), labelled with a de-identification  
208 code and transferred to a research laboratory for analysis. The tissues will range in size from 0.5-1.5  
209 cm in width (0.3-0.6 cm thick). The atrial appendage cardiac tissue will be isolated by clean cut  
210 punch of the atria during bypass surgery and stored for further analysis (ex. metabolic and  
211 inflammatory markers). Tissue protein and gene expression of various biomarkers (ex.  
212 adipocytokines) in each of these tissue depots will be analyzed to determine whether current or  
213 experimental biomarkers have prognostic relevance in distinguishing “high-fit” from “low-fit”  
214 obese patients.

215

### 216 **5. Group assignment:**

217 Despite the limitations of BMI as a measure of obesity, it remains an important starting point for  
218 patient classification and comparisons given its widespread use and previous work by our  
219 group.(36) Patients will be categorized into one of five BMI groups based on WHO definitions of  
220 obesity class (**Table 3**).(37) WHO criteria consider any patient with a BMI  $\geq 25$  kg/m<sup>2</sup> as overweight,  
221 including both pre-obese and obese patients. Normal weight patients (BMI 18.5– 24.9 kg/m<sup>2</sup>) will

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3 222 serve as the controls, while pre-obese (BMI 25.0-29.9), obese class I (BMI 30.0–34.9), II (BMI  
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5 223 35.0–39.9) and III (BMI  $\geq$  40.0) patients will form the study group.  
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**Table 3: World Health Organization obesity classification**

Obesity Classification	BMI (kg/m <sup>2</sup> )
Underweight	< 18.50
Normal range	18.50–24.99
Overweight	
<b>Pre-obese</b>	25.00–29.99
<b>Obese class I</b>	30.00–34.99
<b>Obese class II</b>	35.00–39.99
<b>Obese class III</b>	$\geq$ 40.00

## 6. Patient and Public involvement

Upon completion of the trial patients will be involved in disseminating the findings by sharing of the results with the public. Participant engagement will be raised through science fairs, seminars, research days, social media; and use of tools like posters, handouts and brochures.

## Statistical methods

We used the results from our previous study in which rates of the composite outcome (in-hospital mortality, prolonged ventilation >24hrs, new-onset renal failure and wound infection) were seen to increase with greater patient BMI (BMI 18.5-24.9kg/m<sup>2</sup>: 11.1%; BMI 25.0-29.9kg/m<sup>2</sup>: 11.8%; BMI 30.0-34.9kg/m<sup>2</sup>: 14.6%; BMI 35.0-39.9kg/m<sup>2</sup>: 19.4%; BMI  $\geq$  40.0 kg/m<sup>2</sup>: 28.5%;  $p < 0.0001$ )(38) to establish an expected effect size. Using the greatest observed difference in rates of the composite outcome in combination with a desired power of 80% and type I error rate of 0.0125 (following 5-class Bonferroni correction), an estimated sample size of 116 patients per weight classification was

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3 243 derived (overall n=580). Patients' baseline, intra-operative, and post-operative clinical  
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5 244 characteristics (**Tables 1 and 2**) will be compared by obesity class, using chi-squared tests for  
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8 245 categorical variables and analysis of variance and Kruskal-Wallis tests for continuous variables.  
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10 246 Multivariable logistic regression will then be employed to construct a baseline model of the risk-  
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12 247 adjusted impact of obesity class, and the preoperative socio-demographic and clinical characteristics  
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14 248 and operative procedure (**Table 2**), on the composite outcome, based on our previous work.(38).  
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17 249 Similar to the primary outcome of interest, separate multivariable regression models will be  
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19 250 employed to explore the secondary outcomes of interest and adjust for potential confounders.  
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21 251 Multiple logistic regression modeling will be used for categorical outcomes and multiple linear  
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23 252 regression modeling will be used for continuous variables. In the instance where missing data are  
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26 253 present, we will either remove patients with incomplete data from the analysis or employ a  
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28 254 sensitivity analysis.  
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30 255 A fully adjusted regression model will initially include all predictor variables having an unadjusted  
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32 256 association of at least  $p \leq 0.20$  with the composite outcome. Pearson and Spearman correlations for  
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34 257 normally and non-normally distributed variables, respectively, among the non-traditional  
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36 258 determined measures that are novel in this trial (Table 1) will be assessed to avoid including  
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38 259 collinear predictor variables in a more enhanced logistic regression model. The ability of these  
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40 260 measures to improve risk prediction over and above the baseline model will be evaluated by  
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42 261 comparing the c-statistics of the candidate enhanced model with the baseline model. Analyses will  
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44 262 be performed using SAS v 9.4 (SAS Institute Inc., Cary, NC, USA), and R Statistical Software  
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46 263 (<http://www.r-project.org/>).  
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### **Data and safety monitoring**



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3 266 The quality of all data collected will be carefully supervised by the investigators. The research team  
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5 267 will be responsible for data collection and will be in close contact with the investigators for timely  
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8 268 follow-up of the study procedures, data update and corrections. An interim analysis will be  
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10 269 conducted when 50% of the patients have been recruited and have completed all data collection  
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12 270 procedures and follow-up. The purpose of the interim analysis will be to re-evaluate the sample size  
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14 271 calculation and to test/refine the statistical models as needed. The statistical evaluations to be  
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17 272 performed at this interim point are identical to the ones have been proposed following the  
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19 273 completion of patient recruitment.  
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### 23 24 275 **Intra data sharing**

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26 276 All Principal Investigators will be given access to the cleaned data sets. Data sets will be stored on  
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28 277 hospital secure drives at the site created for the study, and all data sets will be password protected.  
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31 278 Paper files shall be stored at a secure location and kept locked at all times. To ensure confidentiality,  
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33 279 data dispersed to project team members will be blinded of any identifying participant information.  
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### 37 38 281 **DISCUSSION**

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40 282 The OPOS trial is novel in its design for classifying CVD patients by BMI, QoL measures and  
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42 283 functional capacity, and correlating these factors with molecular biomarkers of obesity at the  
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44 284 systemic and cellular level. Previous studies have been unable to completely elucidate the  
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47 285 mechanisms by which obesity affects post-operative outcomes. The proposed findings of this trial  
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49 286 should overcome, to a great extent, the limitations of BMI as a singular measure of obesity, the most  
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51 287 salient of which is its inability to account for muscle mass or functional capacity. While alternate  
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54 288 techniques can directly measure body composition, such as magnetic resonance imaging or dual-

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3 289 energy X-ray absorptiometry(39), these are impractical in the clinical setting. Despite its limitations,  
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5 290 BMI is most familiar to clinicians and thus must serve as a comparative marker in this trial design.  
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8 291 Studies like this one are necessary to help segregate the high-risk obese patient likely to experience  
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10 292 adverse outcomes from the lower risk obese patient. Thus we plan to better define “high-fit” versus  
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12 293 “low-fit obese” patients in order to assist surgical planning and follow-up practices.  
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17 295 The assessments chosen for this trial are clinically validated, self-reported measures of functional  
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19 296 capacity and health related QoL. The SF-12 is considered a valid tool over SF-36 for its ease of  
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21 297 administration, reliability, validity and brevity acting as a reliable surrogate to more complex  
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24 298 analyses of life quality.(40) The PSMS is an effective tool determining independence of cardiac  
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26 299 patients to carry out activities of daily living. The utilization of both the SF-12 and the PSMS  
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28 300 allows us to determine which is more effective as a measure of QoL in this patient population and  
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31 301 provides the opportunity to compare or consolidate the two measures in determining “high-fit” vs  
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33 302 “low-fit” patient categorization. Similarly, the DASI is a valid measure of the functional capacity  
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35 303 measure for cardiac patients, determining the impact of the patient’s cardiovascular disease on self-  
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37 304 reported physical work capacity to estimate peak metabolic equivalents.(41) The DASI, as a self-  
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40 305 reported test, will be correlated with the objective measure of the 6MWT, another effective tool for  
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42 306 assessing functional capacity in patients with cardiovascular and pulmonary diseases.(42) These two  
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44 307 tests in combination compensate for potential patient ineligibility due to disease burden for the  
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47 308 6MWT, or bias in self-reporting for the DASI. The order of administration may pose a limitation, as  
48  
49 309 the 6MWT test is administered prior to DASI and could influence the self-reporting. Interestingly,  
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51 310 many patients are accompanied by family and that strengthens the legitimacy of the DASI because  
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53 311 of two-person recall.  
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5 313 Biomarkers are sensitive, specific objective measures that can be used alone or in combination and  
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8 314 are known to be predictive of outcomes.(43) Here we elected to design a trial amenable to  
9  
10 315 conventional and experimental biomarkers, to identify measures that are potentially highly sensitive,  
11  
12 316 translatable across centres and immutable to humanistic influences at the point of collection (**Table-**  
13  
14  
15 317 **1**). Recently, adipose depots in close proximity to the heart have emerged as regulators of cardiac  
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17 318 function and may likely influence the heart following cardiac surgery. Previous studies have shown  
18  
19 319 that perivascular, epicardial and cardiac adipose tissue depots are suggestive of visceral adiposity,  
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21 320 and are sensitive and specific markers of cardiovascular risk.(44, 45) Thus, it is important to  
22  
23 321 examine cytokines and chemokines in circulation, specifically adipokine expression in distinct  
24  
25 322 adipose tissues in an around the heart that may selectively influence cardiac cells via paracrine  
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27 323 secretion of biomolecules in close proximity to the heart.(46) With this trial we are building the  
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29 324 “OPOS Biobank” as a valuable and unique repository of adipose tissue from different depots and  
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31 325 blood samples from coronary artery bypass grafts and/or valve surgery patients. To this biobank we  
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33 326 can link clinical history and blood sample analyses with gene, protein and cellular expression  
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35 327 profiles of critical regulators of cardiovascular and metabolic disease.(47, 48)  
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42 329 The knowledge gained by consolidating this information for iterative utility would potentially help  
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44 330 identify new genes associated with a variety of clinical outcomes as well as new therapeutic targets.  
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46  
47 331 Additionally, these patient samples provide opportunity to investigate associated disease processes  
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49 332 like coronary artery disease, chronic heart failure, calcified aortic valve disease, atrial fibrillation etc.  
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51 333 It has been shown that the power of two well characterized biomarkers can determine differences of  
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53 334 1-year mortality by more than 50% predictively.(43) Assessment of clinical and biomarker panels  
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335 could thus potentially help identify predictive biomarkers that would help clinicians treat cardiac  
336 patients more effectively.

337  
338 Despite the novelty of the proposed trial, some investigations extend beyond our scope. Future  
339 studies might include more comprehensive QoL assessments, including mental health assessments,  
340 and socio-economic status, that contribute to health related QoL. Mental fortitude could be a  
341 deterrent to QoL, independent of physical ability, and is not specifically accounted for in this trial.  
342 Underweight patients were excluded due to the significantly higher risks associated with early major  
343 adverse clinical outcomes.(49) Patients above the age of 75 were not included in this trial, to  
344 exclude the effect of frailty on physical capacity for recovery. Future studies could account for  
345 frailty as a confounding variable and incorporate this into a more complete assessment of surgical  
346 fitness. Only elective patients are included in this trial, and high-risk urgent patients were excluded.  
347 This was a practical and safety decision; however, the results of this trial should allow for more  
348 open inclusion once the criterion to define surgical fitness is clear. Additional studies should  
349 explore how best to treat and prevent adverse outcomes in at-risk obese patients in advance of their  
350 surgery or thereafter in order to reduce their risk and to improve outcomes. These and additional  
351 patient populations could be followed over a longer term to assess outcomes like 5-year mortality or  
352 to compare retrospectively to past practices once a new paradigm is determined.(36) While our trial  
353 is limited in terms of patients enrolled, future studies could also have higher enrollment targets that  
354 would allow for broader multivariate analyses.

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356 Fit or not, healthy or unhealthy, chronic obesity is strongly linked to metabolic deterioration, a  
357 major risk factor for cardiovascular disease. The results of the OPOS trial will inform cardiac

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3 358 surgeons and allied health care professionals on the important relationships that exist between  
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5 359 obesity and adverse outcomes after cardiac surgery. Upon completion of this trial, clinicians and  
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8 360 health care administrators will be better able to identify an obese patient who is more likely to  
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10 361 experience adverse outcomes and require additional hospital resources in their recovery.  
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## 14 363 **PRESENT STATUS**

16  
17 364 The OPOS trial began enrollment in December 2014 and as of March 2018, more than 365 patients  
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19 365 have been enrolled with clinical data and tissue samples collected. 105 patients were withdrawn due  
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21 366 to change in patient's condition becoming more urgent, patients passing the age limit of 75 years,  
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23  
24 367 and patients who decided to withdraw from the trial. The trial is expected to continue till 2022 until  
25  
26 368 enrolment targets have been achieved. Other potential strategies to improve enrolment are inclusion  
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28 369 of additional sites.  
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38  
39  
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41  
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43  
44 376 the New Brunswick Innovation Foundation, Canadian Diabetes Association and the Heart & Stroke  
45  
46  
47 377 Foundation of Canada to members of the IMPART team (<https://www.impart.team>).  
48

## 49 378 **AUTHOR CONTRIBUTIONS**

50 379  
51  
52 380 JM, AY, AH, PK and KB contributed to trial design. TP and JFL provided significant intellectual  
53  
54  
55 381 input. CA recruited patients and prepared the report. AH, JFL, CA and SM assisted with clinical  
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382 sample collection and processing. JM and AY contributed to statistical design. All authors have read  
383 and approved the article.

384

385 **Declarations of interest:** none

For peer review only

**REFERENCES**

- 1.Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah A. Effects of obesity and small body size on operative and long-term outcomes of coronary artery bypass surgery: a propensity-matched analysis. *The Annals of thoracic surgery*. 2005 Jun;79(6):1976-86. PubMed PMID: 15919295. Epub 2005/05/28. eng.
- 2.Ng C, Corey PN, Young TK. Divergent body mass index trajectories between Aboriginal and non-Aboriginal Canadians 1994-2009--an exploration of age, period, and cohort effects. *American journal of human biology : the official journal of the Human Biology Council*. 2012 Mar-Apr;24(2):170-6. PubMed PMID: 22275122. Epub 2012/01/26. eng.
- 3.Moubarac J-C, Batal M, Louzada ML, Martinez Steele E, Monteiro CA. Consumption of ultra-processed foods predicts diet quality in Canada. *Appetite*. 2017 1/1/;108:512-20.
- 4.Lastra G, Sowers JR. Obesity and cardiovascular disease: role of adipose tissue, inflammation, and the renin-angiotensin-aldosterone system. *Hormone molecular biology and clinical investigation*. 2013 Sep;15(2):49-57. PubMed PMID: 25436732.
- 5.Rahmanian PB, Adams DH, Castillo JG, Chikwe J, Bodian CA, Filsoufi F. Impact of body mass index on early outcome and late survival in patients undergoing coronary artery bypass grafting or valve surgery or both. *Am J Cardiol*. 2007 Dec 1;100(11):1702-8. PubMed PMID: 18036372. Epub 2007/11/27. eng.
- 6.Tyson GH, 3rd, Rodriguez E, Elci OC, Koutlas TC, Chitwood WR, Jr., Ferguson TB, et al. Cardiac procedures in patients with a body mass index exceeding 45: outcomes and long-term results. *The Annals of thoracic surgery*. 2007 Jul;84(1):3-9; discussion PubMed PMID: 17588372. Epub 2007/06/26. eng.
- 7.Sun X, Boyce SW, Hill PC, et al. Association of body mass index with new-onset atrial fibrillation after coronary artery bypass grafting operations. *Ann Thorac Surg*. 2011;91:1852-9.
- 8.van Straten AHM, Bramer S, Hamad MAS, et al. Effect of body mass index on early and late mortality after coronary artery bypass grafting. *Ann Thorac Surg*. 2010;89:30-7.
- 9.Tolpin DA, Collard CD, Lee V, Elayda MA, Pan W. Obesity is associated with increased morbidity after coronary artery bypass graft surgery in patients with renal insufficiency. *J Thorac Cardiovasc Surg*. 2009;138:873-9.
10. Choi JC, Bakaeen FG, Cornwell LD, et al. Morbid obesity is associated with increased resource utilization in coronary artery bypass grafting. *Ann Thorac Surg*. 2012;94:23-8.
11. Prabhakar G, Haan CK, Peterson ED, Coombs LP, Cruzzavala JL, Murray GF. The risks of moderate and extreme obesity for coronary artery bypass grafting outcomes: a study from the Society of Thoracic Surgeons' database. *The Annals of thoracic surgery*. 74(4):1125-31.
12. Ghanta RK, LaPar DJ, Zhang Q, Devarkonda V, Isbell JM, Yarboro LT, et al. Obesity Increases Risk-Adjusted Morbidity, Mortality, and Cost Following Cardiac Surgery. *Journal of the American Heart Association*. 2017 Mar 08;6(3). PubMed PMID: 28275064. Epub 2017/03/10. eng.
13. Gruberg L, Weissman NJ, Waksman R, et al. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol*. 2002;39:578-84.
14. Stamou SC, Nussbaum M, Stiegel RM, et al. Effect of body mass index on outcomes after cardiac surgery: is there an obesity paradox? *Ann Thorac Surg*. 2011;91:42-8.

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2  
3 430 15. Gruberg L, Mercado N, Milo S, et al. Impact of body mass index on the outcome of  
4 431 patients with multivessel disease randomized to either coronary artery bypass grafting or  
5 432 stenting in the ARTS trial: the obesity paradox II? *Am J Cardiol.* 2005;95:439-44.
- 7 433 16. Engel AM, McDonough S, Smith JM. Does an obese body mass index affect hospital  
8 434 outcomes after coronary artery bypass graft surgery? *Ann Thorac Surg.* 2009;88:1793-800.
- 9 435 17. Hartrumpf M, Kuehnel RU, Albes JM. The obesity paradox is still there: a risk analysis of  
10 436 over 15 000 cardiosurgical patients based on body mass index. *Interactive cardiovascular and*  
11 437 *thoracic surgery.* 2017 Mar 18. PubMed PMID: 28329172. Epub 2017/03/23. eng.
- 13 438 18. Uretsky S, Supariwala A, Gurram S, Bonda SL, Thota N, Bezwada P, et al. The interaction  
14 439 of exercise ability and body mass index upon long-term outcomes among patients undergoing  
15 440 stress-rest perfusion single-photon emission computed tomography imaging. *Am Heart J.*  
16 441 2013 Jul;166(1):127-33. PubMed PMID: 23816031. Epub 2013/07/03. eng.
- 17 442 19. Chasse M, Mathieu P, Voisine P, Despres JP, Pibarot P, Baillot R, et al. The  
18 443 Underestimated Belly Factor: Waist Circumference Is Linked to Significant Morbidity  
20 444 Following Isolated Coronary Artery Bypass Grafting. *The Canadian journal of cardiology.* 2015  
21 445 Jul 7. PubMed PMID: 26481079.
- 22 446 20. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total  
23 447 mortality and with cardiovascular events in coronary artery disease: a systematic review of  
24 448 cohort studies. *Lancet.* 2006;368(9536):666-78.
- 25 449 21. Baker AR, Silva NF, Quinn DW, Harte AL, Pagano D, Bonser RS, et al. Human epicardial  
27 450 adipose tissue expresses a pathogenic profile of adipocytokines in patients with  
28 451 cardiovascular disease. *Cardiovascular diabetology.* 2006 Jan 13;5:1. PubMed PMID:  
29 452 16412224. Pubmed Central PMCID: PMC1352345. Epub 2006/01/18. eng.
- 30 453 22. Kremen J, Dolinkova M, Krajickova J, Blaha J, Anderlova K, Lacinova Z, et al. Increased  
31 454 subcutaneous and epicardial adipose tissue production of proinflammatory cytokines in  
32 455 cardiac surgery patients: possible role in postoperative insulin resistance. *The Journal of*  
33 456 *clinical endocrinology and metabolism.* 2006 Nov;91(11):4620-7. PubMed PMID: 16895955.  
34 457 Epub 2006/08/10. eng.
- 36 458 23. Waist circumference and waist-hip ratio: report of a WHO expert consultation. Geneva:  
37 459 World Health Organization; 2008.
- 38 460 24. Schneider HJ, Friedrich N, Klotsche J, et al. The predictive value of different measures of  
39 461 obesity for incident cardiovascular events and mortality. *J Clin Endocrinol Metab.*  
40 462 2010;95:1777-85.
- 42 463 25. Lee CMY, Huxley RR, Wildman RP, Woodward M. Indices of abdominal obesity are  
43 464 better discriminators of cardiovascular risk factors than BMI: a meta-analysis. *J Clin Epidemiol.*  
44 465 2008;61:646-53.
- 45 466 26. Staiano AE, Reeder BA, Elliott S, Joffres MR, Pahwa P, Kirkland SA, et al. Body mass  
46 467 index versus waist circumference as predictors of mortality in Canadian adults. *International*  
48 468 *journal of obesity (2005).* 2012 Nov;36(11):1450-4. PubMed PMID: 22249224. Pubmed  
49 469 Central PMCID: PMC4120111. Epub 2012/01/18. eng.
- 50 470 27. Quante M, Dietrich A, ElKhal A, Tullius SG. Obesity-related immune responses and their  
51 471 impact on surgical outcomes. *International journal of obesity (2005).* 2015 Jun;39(6):877-83.  
52 472 PubMed PMID: 25697667. Epub 2015/02/24. eng.
- 53 473 28. Halkos ME, Puskas JD, Lattouf OM, Kilgo P, Kerendi F, Song HK, et al. Elevated  
54 474 preoperative hemoglobin A1c level is predictive of adverse events after coronary artery  
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3 475 bypass surgery. *The Journal of thoracic and cardiovascular surgery*. 2008 Sep;136(3):631-40.  
4 476 PubMed PMID: 18805264. Epub 2008/09/23. eng.
- 5 477 29. Hassan A, Yip AM, MacLeod JB, Lutchmedial S, Brown CD, Forgie R, et al. The effect of  
6 478 obesity on in-hospital outcomes following cardiac surgery in New Brunswick. *The Canadian*  
7 479 *journal of cardiology*. 2013;29(Suppl 10):S261-2.
- 8 480 30. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krle AJK, et al. SPIRIT 2013  
9 481 Statement: defining standard protocol items for clinical trials. *Revista panamericana de salud*  
10 482 *publica = Pan American journal of public health*. 2015 Dec;38(6):506-14. PubMed PMID:  
11 483 27440100. Pubmed Central PMCID: PMC5114122. Epub 2016/07/22. eng.
- 12 484 31. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue  
13 485 macrophage polarization. *The Journal of clinical investigation*. 2007 Jan;117(1):175-84.  
14 486 PubMed PMID: 17200717. Pubmed Central PMCID: PMC1716210. Epub 2007/01/04. eng.
- 15 487 32. O'Brien EC, Thomas LE. Untangling the paradox: Obesity as prognostic marker in  
16 488 prevalent cardiovascular disease. *American Heart Journal*. 2016 2//;172:170-2.
- 17 489 33. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental  
18 490 activities of daily living. *Gerontol*. 1969;9(3):179-86.
- 19 491 34. Li P, Liu S, Lu M, Bandyopadhyay G, Oh D, Imamura T, et al. Hematopoietic-Derived  
20 492 Galectin-3 Causes Cellular and Systemic Insulin Resistance. *Cell*. 2016 Nov 03;167(4):973-84  
21 493 e12. PubMed PMID: 27814523. Pubmed Central PMCID: PMC5179329. Epub 2016/11/05. eng.
- 22 494 35. Rogacev KS, Cremers B, Zawada AM, Seiler S, Binder N, Ege P, et al. CD14++CD16+  
23 495 monocytes independently predict cardiovascular events: a cohort study of 951 patients  
24 496 referred for elective coronary angiography. *Journal of the American College of Cardiology*.  
25 497 2012 Oct 16;60(16):1512-20. PubMed PMID: 22999728.
- 26 498 36. Rosvall BR, Forgie K, MacLeod JB, Yip AM, Aguiar C, Lutchmedial S, et al. Impact of  
27 499 Obesity on Intensive Care Unit Resource Utilization After Cardiac Operations. *The Annals of*  
28 500 *thoracic surgery*. 2017 Jul 24. PubMed PMID: 28803638.
- 29 501 37. WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO  
30 502 Expert Committee. World Health Organization technical report series. 1995;854:1-452.  
31 503 PubMed PMID: 8594834. Epub 1995/01/01. eng.
- 32 504 38. Hassan A, Yip AM, MacLeod JB, Lutchmedial S, Brown CD, Forgie R, et al. The Effect of  
33 505 Obesity on In-Hospital Outcomes Following Cardiac Surgery in New Brunswick. *Canadian*  
34 506 *Journal of Cardiology*. 2013;29(10):S261-S2.
- 35 507 39. Rothney MP, Brychta RJ, Schaefer EV, Chen KY, Skarulis MC. Body Composition  
36 508 Measured by Dual-energy X-ray Absorptiometry Half-body Scans in Obese Adults. *Obesity*  
37 509 (Silver Spring, Md). 2009 02/19;17(6):1281-6. PubMed PMID: PMC2709755.
- 38 510 40. Muller-Nordhorn J, Roll S, Willich SN. Comparison of the short form (SF)-12 health  
39 511 status instrument with the SF-36 in patients with coronary heart disease. *Heart (British*  
40 512 *Cardiac Society)*. 2004 May;90(5):523-7. PubMed PMID: 15084550. Pubmed Central PMCID:  
41 513 PMC1768233. Epub 2004/04/16. eng.
- 42 514 41. Grodin JL, Hammadah M, Fan Y, Hazen SL, Tang WHW. Prognostic Value of Estimating  
43 515 Functional Capacity With the Use of the Duke Activity Status Index in Stable Patients With  
44 516 Chronic Heart Failure. *Journal of Cardiac Failure*. 21(1):44-50.
- 45 517 42. Society AT. ATS statement: guidelines for the six-minute walk test. *American journal of*  
46 518 *respiratory and critical care medicine*. 2002 Jul 01;166(1):111-7. PubMed PMID: 12091180.  
47 519 Epub 2002/07/02. eng.
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3 520 43. Lassus J, Gayat E, Mueller C, Peacock WF, Spinar J, Harjola VP, et al. Incremental value of  
4 521 biomarkers to clinical variables for mortality prediction in acutely decompensated heart  
5 522 failure: the Multinational Observational Cohort on Acute Heart Failure (MOCA) study. *Int J*  
6 523 *Cardiol.* 2013 Oct 03;168(3):2186-94. PubMed PMID: 23538053.
- 8 524 44. Fitzgibbons TP, Czech MP. Epicardial and perivascular adipose tissues and their  
9 525 influence on cardiovascular disease: basic mechanisms and clinical associations. *Journal of the*  
10 526 *American Heart Association.* 2014 Mar 04;3(2):e000582. PubMed PMID: 24595191. Pubmed  
11 527 Central PMCID: 4187500.
- 13 528 45. Aldiss P, Davies G, Woods R, Budge H, Sacks HS, Symonds ME. 'Browning' the cardiac  
14 529 and peri-vascular adipose tissues to modulate cardiovascular risk. *Int J Cardiol.* 2017 Feb  
15 530 01;228:265-74. PubMed PMID: 27865196. Pubmed Central PMCID: 5236060.
- 16 531 46. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. *Am Heart J.* 2007  
17 532 Jun;153(6):907-17. PubMed PMID: 17540190.
- 18 533 47. Falkenham A, Saraswat MK, Wong C, Gawdat K, Myers T, Begum J, et al. Recovery free of  
19 534 heart failure after acute coronary syndrome and coronary revascularization. *ESC heart failure.*  
21 535 2017 Jul 24. PubMed PMID: 28737273. Epub 2017/07/25. eng.
- 22 536 48. Trivedi PC, Bartlett JJ, Perez LJ, Brunt KR, Legare JF, Hassan A, et al. Glucolipototoxicity  
23 537 diminishes cardiomyocyte TFE8 and inhibits lysosomal autophagy during obesity and  
24 538 diabetes. *Biochimica et biophysica acta.* 2016 Dec;1861(12 Pt A):1893-910. PubMed PMID:  
25 539 27620487. Epub 2016/10/22. eng.
- 27 540 49. van Straten AH, Bramer S, Soliman Hamad MA, van Zundert AA, Martens EJ,  
28 541 Schonberger JP, et al. Effect of body mass index on early and late mortality after coronary  
29 542 artery bypass grafting. *The Annals of thoracic surgery.* 2010 Jan;89(1):30-7. PubMed PMID:  
30 543 20103201. Epub 2010/01/28. eng.

### 32 545 **FIGURE LEGENDS:**

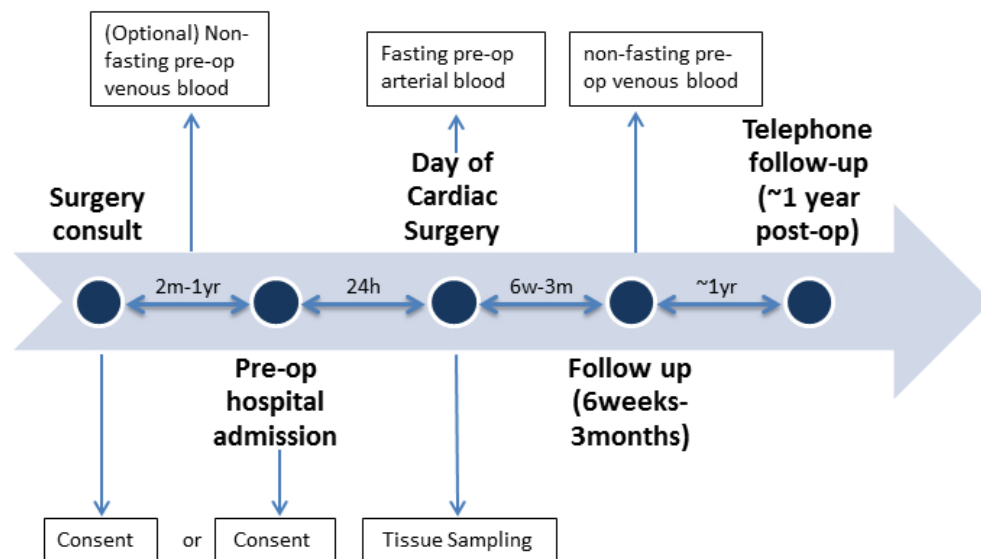
34 546 **Fig. 1: Trial design flow-chart:** From left to right: Patients are admitted for surgical consultation  
35 547 and cardiac catheterization. Consent may be obtained at this time as well as a venous blood sample  
36 548 of 8-10ml collected. Consent could also be obtained at pre-operative admission for cardiac surgery,  
37 549 as well as a venous blood sample of 8-10ml. (Surgery is elective and typically is scheduled between  
38 550 2months to 1 year after surgical consult but not time-restrictive to participation). Patients are  
39 551 admitted 24hours prior to surgery, and a 30 min pre-op arterial blood sample is collected. Tissue  
40 552 sampling is carried out intra-operatively. At the early post-operative follow-up appointment  
41 553 (occurring between 6 weeks to 3 months), a non-fasting venous blood sample may be collected. At  
42 554 the late post-operative follow-up appointment (approximately 1 year post-operatively) telephone  
43 555 follow-up by questionnaire are conducted.

47 557 **Figure 2:** Flowchart showing protocol for the OPOS trial.

### 50 559 **Date and Version Identifier:**

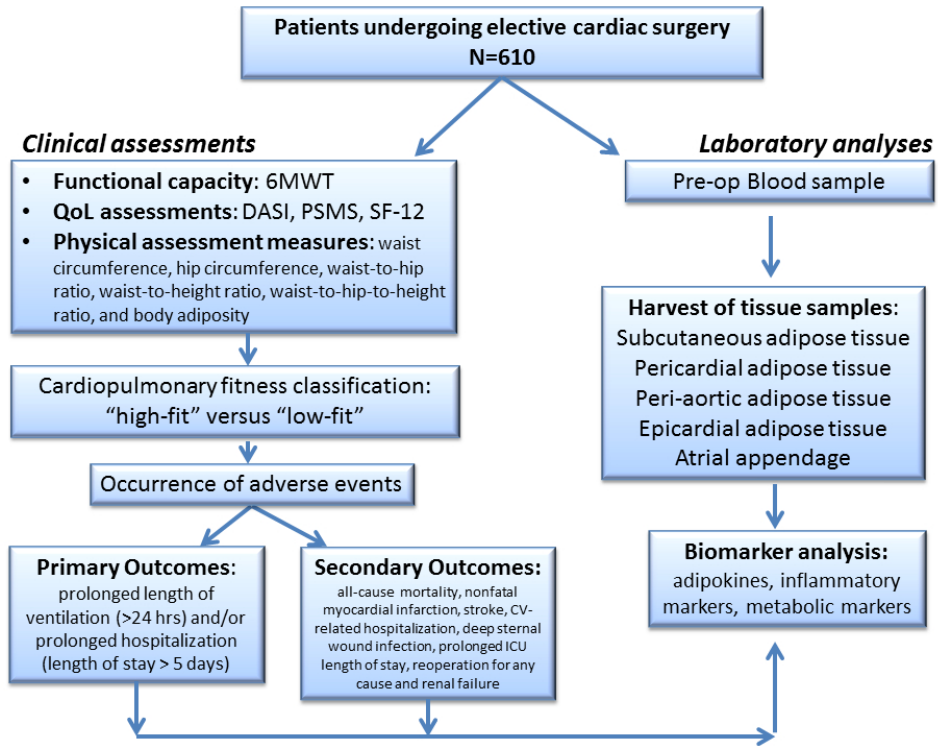
51 560 *Issue Date:* 28 November, 2014

52 561 *Protocol Version Number:* 7 dated 12 December 2017



Trial design flow-chart: From left to right: Patients are admitted for surgical consultation and cardiac catheterization. Consent may be obtained at this time as well as a venous blood sample of 8-10ml collected. Consent could also be obtained at pre-operative admission for cardiac surgery, as well as a venous blood sample of 8-10ml. (Surgery is elective and typically is scheduled between 2months to 1 year after surgical consult but not time-restrictive to participation). Patients are admitted 24hours prior to surgery, and a 30 min pre-op arterial blood sample is collected. Tissue sampling is carried out intra-operatively. At the early post-operative follow-up appointment (occurring between 6 weeks to 3 months), a non-fasting venous blood sample may be collected. At the late post-operative follow-up appointment (approximately 1 year post-operatively) telephone follow-up by questionnaire are conducted.

58x33mm (300 x 300 DPI)



Flowchart showing protocol for the OPOS trial.

81x60mm (300 x 300 DPI)

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	17

1	sponsor contact			
2	information			
3				
4	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	NA
5	responsibilities:		collection, management, analysis, and interpretation of	
6	sponsor and funder		data; writing of the report; and the decision to submit the	
7			report for publication, including whether they will have	
8			ultimate authority over any of these activities	
9				
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12	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	NA
13	responsibilities:		centre, steering committee, endpoint adjudication	
14	committees		committee, data management team, and other individuals or	
15			groups overseeing the trial, if applicable (see Item 21a for	
16			data monitoring committee)	
17				
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19				
20	Background and	#6a	Description of research question and justification for	3,4
21	rationale		undertaking the trial, including summary of relevant studies	
22			(published and unpublished) examining benefits and harms	
23			for each intervention	
24				
25				
26				
27	Background and	#6b	Explanation for choice of comparators	4,5
28	rationale: choice of			
29	comparators			
30				
31				
32	Objectives	#7	Specific objectives or hypotheses	4,5
33				
34				
35	Trial design	#8	Description of trial design including type of trial (eg, parallel	6,7
36			group, crossover, factorial, single group), allocation ratio,	
37			and framework (eg, superiority, equivalence, non-inferiority,	
38			exploratory)	
39				
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41				
42	Study setting	#9	Description of study settings (eg, community clinic,	5
43			academic hospital) and list of countries where data will be	
44			collected. Reference to where list of study sites can be	
45			obtained	
46				
47				
48	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	6
49			eligibility criteria for study centres and individuals who will	
50			perform the interventions (eg, surgeons, psychotherapists)	
51				
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53				
54	Interventions:	#11a	Interventions for each group with sufficient detail to allow	9-11
55	description		replication, including how and when they will be	
56			administered	
57				
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1	Interventions:	#11b	Criteria for discontinuing or modifying allocated	9-11
2	modifications		interventions for a given trial participant (eg, drug dose	
3			change in response to harms, participant request, or	
4			improving / worsening disease)	
5				
6				
7	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	NA
8	adherence		and any procedures for monitoring adherence (eg, drug	
9			tablet return; laboratory tests)	
10				
11				
12	Interventions:	#11d	Relevant concomitant care and interventions that are	NA
13	concomitant care		permitted or prohibited during the trial	
14				
15				
16	Outcomes	#12	Primary, secondary, and other outcomes, including the	4,5
17			specific measurement variable (eg, systolic blood pressure),	
18			analysis metric (eg, change from baseline, final value, time	
19			to event), method of aggregation (eg, median, proportion),	
20			and time point for each outcome. Explanation of the clinical	
21			relevance of chosen efficacy and harm outcomes is strongly	
22			recommended	
23				
24				
25				
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27				
28	Participant timeline	#13	Time schedule of enrolment, interventions (including any	Fig.1
29			run-ins and washouts), assessments, and visits for	
30			participants. A schematic diagram is highly recommended	
31			(see Figure)	
32				
33				
34				
35	Sample size	#14	Estimated number of participants needed to achieve study	12
36			objectives and how it was determined, including clinical and	
37			statistical assumptions supporting any sample size	
38			calculations	
39				
40				
41				
42	Recruitment	#15	Strategies for achieving adequate participant enrolment to	16
43			reach target sample size	
44				
45				
46	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	NA
47	generation		computer-generated random numbers), and list of any	
48			factors for stratification. To reduce predictability of a random	
49			sequence, details of any planned restriction (eg, blocking)	
50			should be provided in a separate document that is	
51			unavailable to those who enrol participants or assign	
52			interventions	
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57	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	NA
58	concealment		central telephone; sequentially numbered, opaque, sealed	
59				
60				

1	mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
2				
3				
4	Allocation:	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
5	implementation			
6				
7				
8				
9	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
10				
11				
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14	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
15	emergency			
16	unblinding			
17				
18				
19				
20	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9,12
21				
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31	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
32	retention			
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38	Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
39				
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46	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
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51	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
52	analyses			
53				
54				
55	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
56	population and			
57	missing data			
58				
59				



1	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	NA
2	formal committee		of its role and reporting structure; statement of whether it is	
3			independent from the sponsor and competing interests; and	
4			reference to where further details about its charter can be	
5			found, if not in the protocol. Alternatively, an explanation of	
6			why a DMC is not needed	
7				
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9				
10	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	12
11	interim analysis		including who will have access to these interim results and	
12			make the final decision to terminate the trial	
13				
14				
15	Harms	#22	Plans for collecting, assessing, reporting, and managing	7
16			solicited and spontaneously reported adverse events and	
17			other unintended effects of trial interventions or trial conduct	
18				
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21	Auditing	#23	Frequency and procedures for auditing trial conduct, if any,	NA
22			and whether the process will be independent from	
23			investigators and the sponsor	
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27	Research ethics	#24	Plans for seeking research ethics committee / institutional	5
28	approval		review board (REC / IRB) approval	
29				
30				
31	Protocol	#25	Plans for communicating important protocol modifications	5
32	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
33			relevant parties (eg, investigators, REC / IRBs, trial	
34			participants, trial registries, journals, regulators)	
35				
36				
37	Consent or assent	#26a	Who will obtain informed consent or assent from potential	5
38			trial participants or authorised surrogates, and how (see	
39			Item 32)	
40				
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43	Consent or assent:	#26b	Additional consent provisions for collection and use of	9,10
44	ancillary studies		participant data and biological specimens in ancillary	
45			studies, if applicable	
46				
47				
48	Confidentiality	#27	How personal information about potential and enrolled	NA
49			participants will be collected, shared, and maintained in	
50			order to protect confidentiality before, during, and after the	
51			trial	
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55	Declaration of	#28	Financial and other competing interests for principal	17
56	interests		investigators for the overall trial and each study site	
57				
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59	Data access	#29	Statement of who will have access to the final trial dataset,	NA
60				

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9,10

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# BMJ Open

## The impact of Obesity on Postoperative Outcomes following cardiac Surgery (The OPOS trial) - Rationale and design of an investigator-initiated prospective cohort trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023418.R2
Article Type:	Protocol
Date Submitted by the Author:	27-Nov-2018
Complete List of Authors:	<p>Aguiar, Christie; Saint John Regional Hospital, Cardiovascular Research New Brunswick  MacLeod, Jeffrey ; Saint John Regional Hospital, Cardiovascular Research New Brunswick  Yip, Alexandra; Saint John Regional Hospital, Cardiovascular Research New Brunswick  Melville, Sarah; Dalhousie Medicine New Brunswick  Légaré, Jean-Francois ; Saint John Regional Hospital, Cardiovascular Research New Brunswick, and Cardiac Surgery  Pulinilkunnil, Thomas; Dalhousie Medicine New Brunswick, Biochemistry and Molecular Biology  Kienesberger, Petra; Dalhousie Medicine New Brunswick, Biochemistry and Molecular Biology  Brunt, Keith; Dalhousie Medicine New Brunswick, Department of Pharmacology  Hassan, Ansar; Saint John Regional Hospital, Cardiovascular Research New Brunswick and Cardiac Surgery</p>
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Research methods
Keywords:	inflammation, morbidity, Coronary artery bypass grafting, adipose tissue, atrial appendage, globesity

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1 **The impact of Obesity on Postoperative Outcomes following cardiac Surgery (The OPOS**  
2 **trial) - Rationale and design of an investigator-initiated prospective cohort trial**

3  
4 **Authors:** C. M. Aguiar, PhD<sup>1,2</sup>, J. B. MacLeod<sup>1,2</sup>, BSc, A.M. Yip<sup>1,2</sup>, MSc, S. Melville, BSc  
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14 Abbreviated title: Obesity and cardiac surgical outcomes

15  
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20  
21 **Word Count:** 3,464

1  
2  
3 **ABSTRACT:**  
4

5 **Introduction:** Increasing levels of obesity worldwide have led to a rise in the prevalence of obesity-  
6  
7 related complications including cardiovascular risk factors such as diabetes, hypertension, and  
8  
9 dyslipidemia. Health care providers believe that overweight and obese cardiac surgery patients are  
10  
11 more likely to experience adverse post-operative outcomes. The body mass index (BMI) is the  
12  
13 primary measure of obesity in clinical practice, without accounting for a patient's level of  
14  
15 cardiopulmonary fitness or muscle mass. The objective of this trial is to determine if fitness capacity  
16  
17 of obese cardiac surgical patients and biomarkers, alone or in combination, will help identify  
18  
19 patients at risk for adverse outcomes when undergoing cardiac surgery.  
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23  
24 **Methods and Analysis:** Patients between the ages of 18 and 75 years undergoing elective cardiac  
25  
26 surgery are consented to participate in this prospective observational trial. Patients will be invited to  
27  
28 participate in measures of obesity, functional capacity and exercise capacity assessments, quality of  
29  
30 life questionnaires, and blood and tissue sampling for biomarker analysis. The endpoints evaluated  
31  
32 are measures other than BMI that could be predictive of short-term and long-term post-operative  
33  
34 outcomes. Clinical outcomes of interest are prolonged ventilation, hospital length of stay, renal  
35  
36 failure and all-cause mortality. Biomarkers of interest will largely focus on metabolism (lipids,  
37  
38 amino acids) and inflammation (adipokines, cytokines and chemokines).  
39  
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41  
42 **Ethics and Dissemination:** This study has been approved by the institutional review board at the  
43  
44 Horizon Health Network. Upon completion of the trial, the results shall be disseminated through  
45  
46 conference presentations and publications in peer-reviewed journals. Additionally, the report shall  
47  
48 also be diffused more broadly to the general public and the cardiovascular community.  
49  
50

51 **Trial Registration:** NCT03248921 at [www.clinicaltrials.gov](http://www.clinicaltrials.gov)  
52  
53 Protocol Version 7, dated 12 December 2017  
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56  
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## Strengths and limitations of this study

- The results of this prospective trial will present an improved understanding and better definition of obesity beyond BMI by identifying key biomarkers such as cytokines and adipokines.
- Patients will undergo a clinical assessment consisting of functional capacity, quality of life, and physical assessment measures. Laboratory analyses include blood sample and cardiac adipose tissue analyses for predictive biomarkers.
- This trial will determine the “fitness capacity” of obese cardiac surgical patients by segregating patients into “high-fit” and “low-fit” categories. This observational study only assesses elective cardiac surgery patients, and excludes high-risk urgent and frail patients.
- This trial is limited in terms of overall enrolment of participants; and there is unequal representation of higher BMI categories especially females.

**Keywords:** morbidity, CABG, valve replacement, valvuloplasty, adipose tissue, atrial appendage, clinical chemistry, inflammation, metaflammation, immunometabolism, globesity

## 63 BACKGROUND AND RATIONALE

64 The global epidemic of overweight and obese patients - "globesity" - is steadily rising without  
65 abatement and more than one-third of U.S. adults are obese.(1) In the Canadian population, one  
66 quarter of the population is obese, with a two-fold higher obesity risk amongst Indigenous-  
67 Canadians.(2) It is estimated that each year approximately 66,000 Canadians die due to health  
68 complications associated with obesity.(3) Obese populations typically experience comorbid  
69 cardiovascular disease (CVD) often necessitating invasive cardiac surgical interventions.(4) These  
70 patients are at higher risk for intra-operative and post-operative adverse events, including  
71 mortality.(1, 5-12) However, recent studies show paradoxical results, wherein obese patients can  
72 experience fewer adverse events and lower mortality than patients with normal body mass index  
73 (BMI), suggesting a benefit to obesity for post-surgical outcomes.(13-17) Referred to as the  
74 "obesity paradox", the underlying mechanisms and clinical paradigms of this phenomenon remain  
75 to be defined.(18)

76  
77 In part, this paradox may be attributable to over-reliance on singular anthropometric measures of  
78 obesity, namely BMI. BMI can be a poor predictor of clinical outcomes since it fails to account  
79 for variable whole-body adipose tissue distribution,(19, 20) or inflammatory state.(21, 22)  
80 Additionally, BMI does not address the physical ability or fitness of obese patients with respect to  
81 size. Thus, the question to be addressed with this trial is: Why do some obese patients have "good  
82 health-related quality of life" (QoL), maintain high physical ability, and have positive outcomes,  
83 while other obese patients and normal BMI patients have poor QoL, low physical ability and  
84 negative outcomes? Thus, we propose segregating obese patients into two populations: high-fit  
85 obese patients ("fit" obese or normally-able) and low fit obese patients ("non-fit" obese or less-

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3 86 able). This distinction could be of critical importance in determining which obese patients are  
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5 87 more likely to do well post-operatively.  
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10 89 Alternative measures to BMI have been proposed, including waist-to-hip ratios and waist-to-height  
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12 90 ratios and body adiposity index.(23-25) These measures of central obesity reflect visceral adiposity  
13  
14 91 and strongly predict cardiovascular risk, post-surgical outcomes, and resource utilization(26) but  
15  
16 92 are not often measured or easily calculated from routine patient histories. Beyond clinical  
17  
18 93 measures of obesity and functional capacity, levels of circulating hormones, inflammatory  
19  
20 94 cytokines(27), and the presence of insulin resistance and type-II diabetes are likely to influence  
21  
22 95 obese patient outcomes.(28) Developing a more complete understanding of biomarkers for obese  
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24 96 individuals that could improve operative risk-assessment is a priority.  
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29 97  
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31 98 Ultimately, the need exists to better differentiate obese patients who experience fewer  
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33 99 complications from those with increased rates of adverse events, and to determine if they  
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35 100 correspond with the physically distinct populations of “high-fit” vs. “low-fit” obese. This  
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38 101 distinction could be of critical importance in determining which obese patients are more likely to  
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40 102 do well post-operatively. Crude and risk-adjusted analyses will be carried out to determine which  
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42 103 non-traditional measures of obesity, functional status, and metabolic-inflammatory status may  
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44 104 have independent effects on rates of post-operative adverse events among obese patients. Here, we  
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47 105 describe a trial that will address this important knowledge gap, “the impact of Obesity on  
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49 106 Postoperative Outcomes following cardiac Surgery (OPOS) trial”.

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## 52 53 54 108 **STUDY AIMS AND OUTCOME VARIABLES**



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3 109 The purpose of this trial is to identify non-BMI-related measures of obesity, functional capacity, and  
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5 110 molecular biomarkers that are capable of better defining risk for in-hospital, 30-day and 1-year  
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8 111 adverse events among obese patients undergoing cardiac surgery. We hypothesize that the  
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10 112 mechanisms by which obesity affects outcomes after cardiac surgery depend on a combination of a  
11  
12 113 patient's functional capacity, adipose tissue distribution and tissue/circulating metabolic-  
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14  
15 114 inflammation status. We further hypothesize that by using this advanced approach, we may better  
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17 115 distinguish "high-fit" from "low-fit" obese patients to devise strategies that minimize poor clinical  
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19 116 outcomes.

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22 117  
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24 118 The primary outcome variable will be the composite of in-hospital mortality, prolonged ventilation  
25  
26 119 >24hrs, new-onset renal failure (The Society of Thoracic Surgeons score for renal failure is defined  
27  
28 120 as an increase in serum creatinine levels 4 mg/dL or greater (176.8 mmol/L), a 50% or greater  
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31 121 increase in serum creatinine levels over the baseline preoperative value, or a new requirement for  
32  
33 122 dialysis) and wound infection. We have previously validated this composite outcome by  
34  
35 123 demonstrating a linear relationship between severity of obesity and adverse in-hospital patient  
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37  
38 124 outcomes.(29) Secondary clinical outcomes include re-operation for any cause, stroke (transient,  
39  
40 125 permanent), respiratory complications (pleural effusion, pneumonia), atrial fibrillation, post-  
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42 126 operative length of stay and disposition on discharge (home, home with care, transfer to other  
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45 127 facility or expired), exercise or functional capacity (by walk-test or questionnaire).

## 46 47 128 48 49 129 **METHODS**

### 50 51 130 **1. Research ethics approval**

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3 131 The OPOS trial protocol has been submitted and approved by the institutional committee on human  
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5 132 research at Horizon Health Network, Saint John Regional Hospital, New Brunswick Heart Centre &  
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7  
8 133 the Nova Scotia Health Authority, Maritime Heart Centre. All aspects of this trial are in conformity  
9  
10 134 to the Canadian Tri-Council Policy Statement on ethical conduct for research involving humans  
11  
12 135 (TCPS-2-2014) and are in accordance with the World Medical Association Declaration of Helsinki  
13  
14  
15 136 – ethical principles for medical research involving human subjects (2013). The trial has been  
16  
17 137 registered with the National Clinical Trials Database of the NIH ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)  
18  
19 138 NCT03248921). We used the SPIRIT checklist when writing our report(30).  
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22 139

## 24 140 **2. Study population and subject selection**

25  
26 141 All patients scheduled for elective, first-time cardiac surgery at the New Brunswick Heart Centre in  
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28 142 Saint John, New Brunswick, and the Maritime Heart Centre in Halifax, Nova Scotia, will be  
29  
30  
31 143 considered. Patients with a BMI of less than 18.5 kg/m<sup>2</sup> are classified as underweight by the World  
32  
33 144 Health Organization and will be excluded. In addition, patients older than 75 years will be excluded  
34  
35 145 to minimize the effect that frailty may have on exercise and functional capacity.  
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38 146

## 40 147 **3. Trial overview**

41  
42 148 Eligible patients will be screened by the research coordinator for potential enrolment prior to  
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44 149 surgery (**Fig.1**). Subjects fulfilling the inclusion and exclusion criteria will be approached by the  
45  
46  
47 150 research coordinator and informed consent shall be obtained. Patients who convert from elective to  
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49 151 non-elective surgery or patients who choose to no longer participate are automatically withdrawn  
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51 152 from the trial. Participants are not offered financial or non-financial incentives to participate in the  
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54 153 trial.  
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#### 4. Trial design

The aims of this trial will be fulfilled using a prospective observational study design (**Fig.1**). Obese patients awaiting elective cardiac surgery including coronary artery bypass grafting surgery with or without valve surgery, aortic or mitral valve surgery will be identified. Consenting patients will be invited to voluntarily participate in select measurements of obesity, testing of exercise capacity and functional status, QoL questionnaires, as well as blood and tissue sampling for the purposes of profiling circulating biomarkers and metabolic-inflammatory status (**Table-1, Fig.2**). Routinely collected clinical data on baseline, intraoperative characteristics and post-operative outcomes will be acquired from the New Brunswick Cardiac Surgery Registry (**Table-2**). Although adverse events related to the trial procedure are unlikely (other than those related to cardiac surgery), all adverse events occurring during the course of the trial will be reported to the REB.

**Table-1: Table of Determined Measures:**

Category	Variables
<b>Clinical</b>	Age (yrs)
	Hip, waist circumference (cm)
	Height (cm)
	Weight (kg)
	6-MWT (m)
<b>Calculated</b>	DASI, SF-12, PSMS (scores)
	BMI, waist-hip, waist-height, BAI, NYHF, NLR ratio
<b>Clinical Chemistry</b>	Na, K, Cl, HCO <sub>3</sub> , Ca, Urea, Creatinine, BNP, troponin, Cholesterol, triglycerides, Glucose, HbA1c, PT-INR, APTT, PaO <sub>2</sub> , PaCO <sub>2</sub> , Lactate, pH, Insulin
<b>Clinical Hematology</b>	CBC (Hb, Hct, RBC, WBC, Neu, Lym, Eos)
	Cell Phenotyping: (ex. Monocyte CD-14, CD-16)

<b>Experimental BioMarker Analyses</b>	Cardiac injury & Remodelling (ex. Galectin-3) Metabolism (ex. Amino acids, lysophospholipids) Inflammation (ex. sSRP, adiponectin, resistin, TNF $\alpha$ , interleukins)
<b>Physiology</b>	Functional Capacity (ex. EPO) HR, BP, Ejection Fraction, LVEDP, Doppler, ECG, SpO <sub>2</sub> , CVP, U/O

**Table-2:** Socio-demographic, baseline clinical, intra-operative, and post-operative data available through New Brunswick Cardiac Surgery Registry

Category	Variables
<b>Socio-demographic</b>	Age, sex
<b>Baseline clinical characteristics</b>	Weight, height, body mass index, smoking history, hypertension, dyslipidemia, diabetes, peripheral vascular disease, cerebrovascular disease, renal insufficiency, chronic obstructive pulmonary disease, previous cardiac intervention (percutaneous coronary intervention/cardiac surgery), New York Heart Association classification, left ventricular ejection fraction, urgency
<b>Intra-operative details</b>	Procedure, cross clamp time, total bypass time, transfusion of blood products (packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate)
<b>In-hospital post-operative outcomes</b>	Re-operation for any cause, re-operation for bleeding, infection (leg, superficial sternal, deep sternal), stroke (transient, permanent), intensive care unit length of stay/readmission, time on mechanical ventilation, reintubation, BiPAP (Bilevel Positive Airway Pressure), pleural effusion, pneumonia, atrial fibrillation, renal failure, mortality, post-operative length of stay, disposition on discharge (home, home with extra mural home services, transfer to other facility, transfer to other service, expired)
<b>30-day and 1 year post-operative outcomes</b>	Complications (infection, stroke, pleural effusion, pneumonia, atrial fibrillation, renal failure, mortality) and/or readmission to hospital for any cause, occurring post-discharge from cardiac surgery service but within 30 days of surgery

### Clinical assessment

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3 175 Consented patients will participate in various measures of obesity, exercise capacity, functional  
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5 176 status, and QoL, and provide blood and tissue samples (**Fig.2**). In addition to BMI, alternate  
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8 177 measures of obesity will include waist circumference, hip circumference, waist-to-hip ratio,(23)  
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10 178 waist-to-height ratio,(24, 25) waist-to-hip-to-height ratio and body adiposity index.(31) Tests of  
11  
12 179 exercise capacity, functional status and QoL exercise-capacity will include the Six-Minute Walk  
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14  
15 180 Test (6MWT),(32) Duke Activity Status Index (DASI),(32) Physical Self-Maintenance Scale  
16  
17 181 (PSMS),(33) and the Short Form-12 (SF-12).(34) The 6MWT measures the distance an individual is  
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19 182 able to walk on a flat surface over a total of six minutes. The DASI measures a patient's functional  
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22 183 capacity and cardiopulmonary fitness by estimating a patient's peak oxygen uptake (surrogate  
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24 184 VO<sub>2</sub>max). The PSMS assesses a patient's ability to independently perform six personal care tasks.  
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26 185 The SF-12 addresses mental and physical function as it relates to QoL.  
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29 186

### 30 31 187 **Blood collection**

32  
33 188 Blood collection from each voluntarily consented participant will constitute 2 vials for plasma (vial  
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35 189 catalogue #365974; purple top) and 2 vials for serum (vial catalogue #365963; red top). The sample  
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37  
38 190 will be labelled with a unique de-identification code and transferred to clinical chemistry or a  
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40 191 research laboratory for analysis. Patients may be sampled (8-10ml, venous in a non-fasted state) at  
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42 192 pre-operative consult and/or day prior to surgery for clinical hematology analysis (monocyte-  
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45 193 CD14/16)(35) and non-fasted retrospective comparative analyses of salient biomarkers. Otherwise,  
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47 194 standard of care pre-operative blood sampling will be performed and parameters charted (**Table-1**).  
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49 195 Patients will be sampled (8-10ml, arterial in a fasted state) 30 minutes prior to surgery, after  
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52 196 anaesthetic induction from the arterial central line alongside standard of care parameters that are  
53  
54 197 charted (**Table-2**). Patients will be sampled (8-10ml, venous in a non-fasted state) at post-operative  
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3 198 consultations at 1-3months for clinical hematology analysis and non-fasted prospective comparative  
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5 199 analyses of salient biomarkers (**Fig.2**). Investigative biomarker analysis will focus on cardiac injury  
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8 200 and remodelling (ex. galectin-3, sST2 etc.), metabolic (ex. amino acids, lysophospholipids etc),  
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10 201 inflammation (ex. adipokines, cytokines, interleukins etc) and functional capacity (ex.  
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12 202 erythropoietin, irisin, transferrin etc.) regulators.

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15 203

### 16 17 204 ***Tissue collection***

18  
19 205 During surgery, adipose tissue from subcutaneous, pre-pericardial, epicardial and peri-aortic depots  
20  
21 206 will be collected in sterile specimen collection containers (**Fig.1**), labelled with a de-identification  
22  
23  
24 207 code and transferred to a research laboratory for analysis. The tissues will range in size from 0.5-1.5  
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26 208 cm in width (0.3-0.6 cm thick). The atrial appendage cardiac tissue will be isolated by clean cut  
27  
28 209 punch of the atria during bypass surgery and stored for further analysis (ex. metabolic and  
29  
30  
31 210 inflammatory markers). Tissue protein and gene expression of various biomarkers (ex.  
32  
33 211 adipocytokines) in each of these tissue depots will be analyzed to determine whether current or  
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35 212 experimental biomarkers have prognostic relevance in distinguishing “high-fit” from “low-fit”  
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37  
38 213 obese patients.

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### 41 42 215 **5. Group assignment:**

43  
44 216 Despite the limitations of BMI as a measure of obesity, it remains an important starting point for  
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47 217 patient classification and comparisons given its widespread use and previous work by our  
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49 218 group.(36) Patients will be categorized into one of five BMI groups based on WHO definitions of  
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51 219 obesity class (**Table 3**).(37) WHO criteria consider any patient with a BMI  $\geq 25$  kg/m<sup>2</sup> as  
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53  
54 220 overweight, including both pre-obese and obese patients. Normal weight patients (BMI 18.5– 24.9  
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kg/m<sup>2</sup>) will serve as the controls, while pre-obese (BMI 25.0-29.9), obese class I (BMI 30.0–34.9), II (BMI 35.0–39.9) and III (BMI ≥ 40.0) patients will form the study group.

**Table 3: World Health Organization obesity classification**

Obesity Classification	BMI (kg/m <sup>2</sup> )
Underweight	< 18.50
Normal range	18.50–24.99
Overweight	
Pre-obese	25.00–29.99
Obese class I	30.00–34.99
Obese class II	35.00–39.99
Obese class III	≥ 40.00

## 6. Patient and Public involvement

Upon completion of the trial patients will be involved in disseminating the findings by sharing of the results with the public. Participant engagement will be raised through science fairs, seminars, research days, social media; and use of tools like posters, handouts and brochures.

## Statistical methods

We used the results from our previous study in which rates of the composite outcome (in-hospital mortality, prolonged ventilation >24hrs, new-onset renal failure and wound infection) were seen to increase with greater patient BMI (BMI 18.5-24.9kg/m<sup>2</sup>: 11.1%; BMI 25.0-29.9kg/m<sup>2</sup>: 11.8%; BMI 30.0-34.9kg/m<sup>2</sup>: 14.6%; BMI 35.0-39.9kg/m<sup>2</sup>: 19.4%; BMI ≥ 40.0 kg/m<sup>2</sup>: 28.5%; p<0.0001)(38) to establish an expected effect size. Using the greatest observed difference in rates of the composite outcome in combination with a desired power of 80% and type I error rate of 0.0125 (following Bonferroni correction), an estimated sample size of 116 patients per weight classification was

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3 242 derived (overall n=580). Patients' baseline, intra-operative, and post-operative clinical  
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5 243 characteristics (**Tables 1 and 2**) will be compared by obesity class, using chi-squared tests for  
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7  
8 244 categorical variables and analysis of variance and Kruskal-Wallis tests for continuous variables.  
9  
10 245 Multivariable logistic regression will then be employed to construct a baseline model of the risk-  
11  
12 246 adjusted impact of obesity class, and the preoperative socio-demographic and clinical characteristics  
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14  
15 247 and operative procedure (**Table 2**), on the composite outcome, based on our previous work.(38).  
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17 248 Similar to the primary outcome of interest, separate multivariable regression models will be  
18  
19 249 employed to explore the secondary outcomes of interest and adjust for potential confounders.  
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21  
22 250 Multiple logistic regression modeling will be used for categorical outcomes and multiple linear  
23  
24 251 regression modeling will be used for continuous variables. In the instance where missing data are  
25  
26 252 present, we will either remove patients with incomplete data from the analysis or employ a  
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28  
29 253 sensitivity analysis.  
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31 254 A fully adjusted regression model will initially include all predictor variables having an unadjusted  
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33 255 association of at least  $p \leq 0.20$  with the composite outcome. Pearson and Spearman correlations for  
34  
35 256 normally and non-normally distributed variables, respectively, among the non-traditional  
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38 257 determined measures that are novel in this trial (Table 1) will be assessed to avoid including  
39  
40 258 collinear predictor variables in a more enhanced logistic regression model. The ability of these  
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42 259 measures to improve risk prediction over and above the baseline model will be evaluated by  
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44  
45 260 comparing the c-statistics of the candidate enhanced model with the baseline model. Analyses will  
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47 261 be performed using SAS v 9.4 (SAS Institute Inc., Cary, NC, USA), and R Statistical Software  
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49 262 (<http://www.r-project.org/>).  
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### 53 54 264 **Data and safety monitoring**

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3 265 The quality of all data collected will be carefully supervised by the investigators. The research team  
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5 266 will be responsible for data collection and will be in close contact with the investigators for timely  
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8 267 follow-up of the study procedures, data update and corrections. An interim analysis will be  
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10 268 conducted when 50% of the patients have been recruited and have completed all data collection  
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12 269 procedures and follow-up. The purpose of the interim analysis will be to re-evaluate the sample size  
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14 270 calculation and to test/refine the statistical models as needed. The statistical evaluations to be  
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17 271 performed at this interim point are identical to the ones have been proposed following the  
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19 272 completion of patient recruitment.  
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### 23 24 274 **Intra data sharing**

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26 275 All Principal Investigators will be given access to the cleaned data sets. Data sets will be stored on  
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28 276 hospital secure drives at the site created for the study, and all data sets will be password protected.  
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30  
31 277 Paper files shall be stored at a secure location and kept locked at all times. To ensure confidentiality,  
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33 278 data dispersed to project team members will be blinded of any identifying participant information.  
34

### 35 279 36 37 38 280 **DISCUSSION**

39  
40 281 The OPOS trial is novel in its design for classifying CVD patients by BMI, QoL measures and  
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42 282 functional capacity, and correlating these factors with molecular biomarkers of obesity at the  
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44 283 systemic and cellular level. Previous studies have been unable to completely elucidate the  
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47 284 mechanisms by which obesity affects post-operative outcomes. The proposed findings of this trial  
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49 285 should overcome, to a great extent, the limitations of BMI as a singular measure of obesity, the most  
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51 286 salient of which is its inability to account for muscle mass or functional capacity. While alternate  
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54 287 techniques can directly measure body composition, such as magnetic resonance imaging or dual-  
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3 288 energy X-ray absorptiometry(39), these are impractical in the clinical setting. Despite its limitations,  
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5 289 BMI is most familiar to clinicians and thus must serve as a comparative marker in this trial design.  
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8 290 Studies like this one are necessary to help segregate the high-risk obese patient likely to experience  
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10 291 adverse outcomes from the lower risk obese patient. Thus we plan to better define “high-fit” versus  
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12 292 “low-fit obese” patients in order to assist surgical planning and follow-up practices.  
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15 293  
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17 294 The assessments chosen for this trial are clinically validated, self-reported measures of functional  
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19 295 capacity and health related QoL. The SF-12 is considered a valid tool over SF-36 for its ease of  
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22 296 administration, reliability, validity and brevity acting as a reliable surrogate to more complex  
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24 297 analyses of life quality.(40) The PSMS is an effective tool determining independence of cardiac  
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26 298 patients to carry out activities of daily living. The utilization of both the SF-12 and the PSMS  
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28  
29 299 allows us to determine which is more effective as a measure of QoL in this patient population and  
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31 300 provides the opportunity to compare or consolidate the two measures in determining “high-fit” vs  
32  
33 301 “low-fit” patient categorization. Similarly, the DASI is a valid measure of the functional capacity  
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35 302 measure for cardiac patients, determining the impact of the patient’s cardiovascular disease on self-  
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37  
38 303 reported physical work capacity to estimate peak metabolic equivalents.(41) The DASI, as a self-  
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40 304 reported test, will be correlated with the objective measure of the 6MWT, another effective tool for  
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42 305 assessing functional capacity in patients with cardiovascular and pulmonary diseases.(42) These two  
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44  
45 306 tests in combination compensate for potential patient ineligibility due to disease burden for the  
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47 307 6MWT, or bias in self-reporting for the DASI. The order of administration may pose a limitation, as  
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49 308 the 6MWT test is administered prior to DASI and could influence the self-reporting. Interestingly,  
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52 309 many patients are accompanied by family and that strengthens the legitimacy of the DASI because  
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54 310 of two-person recall.  
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5 312 Biomarkers are sensitive, specific objective measures that can be used alone or in combination and  
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8 313 are known to be predictive of outcomes.(43) Here we elected to design a trial amenable to  
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10 314 conventional and experimental biomarkers, to identify measures that are potentially highly sensitive,  
11  
12 315 translatable across centres and immutable to humanistic influences at the point of collection (**Table-**  
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14  
15 316 **1**). Recently, adipose depots in close proximity to the heart have emerged as regulators of cardiac  
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17 317 function and may likely influence the heart following cardiac surgery. Previous studies have shown  
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19 318 that perivascular, epicardial and cardiac adipose tissue depots are suggestive of visceral adiposity,  
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21  
22 319 and are sensitive and specific markers of cardiovascular risk.(44, 45) Thus, it is important to  
23  
24 320 examine cytokines and chemokines in circulation, specifically adipokine expression in distinct  
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26 321 adipose tissues in an around the heart that may selectively influence cardiac cells via paracrine  
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29 322 secretion of biomolecules in close proximity to the heart.(46) With this trial we are building the  
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31 323 “OPOS Biobank” as a valuable and unique repository of adipose tissue from different depots and  
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33 324 blood samples from coronary artery bypass grafts and/or valve surgery patients. To this biobank we  
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35 325 can link clinical history and blood sample analyses with gene, protein and cellular expression  
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37  
38 326 profiles of critical regulators of cardiovascular and metabolic disease.(47, 48)  
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42 328 The knowledge gained by consolidating this information for iterative utility would potentially help  
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45 329 identify new genes associated with a variety of clinical outcomes as well as new therapeutic targets.  
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47 330 Additionally, these patient samples provide opportunity to investigate associated disease processes  
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49 331 like coronary artery disease, chronic heart failure, calcified aortic valve disease, atrial fibrillation  
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51  
52 332 etc. It has been shown that the power of two well characterized biomarkers can determine  
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54 333 differences of 1-year mortality by more than 50% predictively.(43) Assessment of clinical and  
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3 334 biomarker panels could thus potentially help identify predictive biomarkers that would help  
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5 335 clinicians treat cardiac patients more effectively.  
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10 337 Despite the novelty of the proposed trial, some investigations extend beyond our scope. Future  
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12 338 studies might include more comprehensive QoL assessments, including mental health assessments,  
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14  
15 339 and socio-economic status, that contribute to health related QoL. Mental fortitude could be a  
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17 340 deterrent to QoL, independent of physical ability, and is not specifically accounted for in this trial.  
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19 341 Underweight patients were excluded due to the significantly higher risks associated with early major  
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21 342 adverse clinical outcomes.(49) Patients above the age of 75 were not included in this trial, to  
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24 343 exclude the effect of frailty on physical capacity for recovery. Future studies could account for  
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26 344 frailty as a confounding variable and incorporate this into a more complete assessment of surgical  
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28 345 fitness. Only elective patients are included in this trial, and high-risk urgent patients were excluded.  
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31 346 This was a practical and safety decision; however, the results of this trial should allow for more  
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33 347 open inclusion once the criterion to define surgical fitness is clear. Additional studies should  
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35 348 explore how best to treat and prevent adverse outcomes in at-risk obese patients in advance of their  
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37  
38 349 surgery or thereafter in order to reduce their risk and to improve outcomes. These and additional  
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40 350 patient populations could be followed over a longer term to assess outcomes like 5-year mortality or  
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42 351 to compare retrospectively to past practices once a new paradigm is determined.(36) While our trial  
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45 352 is limited in terms of patients enrolled, future studies could also have higher enrollment targets that  
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47 353 would allow for broader multivariate analyses.  
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51 355 Fit or not, healthy or unhealthy, chronic obesity is strongly linked to metabolic deterioration, a  
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54 356 major risk factor for cardiovascular disease. The results of the OPOS trial will inform cardiac  
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3 357 surgeons and allied health care professionals on the important relationships that exist between  
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5 358 obesity and adverse outcomes after cardiac surgery. Upon completion of this trial, clinicians and  
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8 359 health care administrators will be better able to identify an obese patient who is more likely to  
9  
10 360 experience adverse outcomes and require additional hospital resources in their recovery.  
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## 12 361 13 14 **PRESENT STATUS**

15 362  
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17 363 The OPOS trial began enrollment in December 2014 and as of March 2018, more than 365 patients  
18  
19 364 have been enrolled with clinical data and tissue samples collected. 105 patients were withdrawn due  
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21  
22 365 to change in patient's condition becoming more urgent, patients passing the age limit of 75 years,  
23  
24 366 and patients who decided to withdraw from the trial. The trial is expected to continue till 2022 until  
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26 367 enrolment targets have been achieved. Other potential strategies to improve enrolment are inclusion  
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28  
29 368 of additional sites.  
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## 31 369 32 33 370 34 35 **ACKNOWLEDGEMENTS and FUNDING**

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37  
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39  
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41  
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43  
44  
45 375 the New Brunswick Innovation Foundation, Canadian Diabetes Association and the Heart & Stroke  
46  
47 376 Foundation of Canada to members of the IMPART team (<https://www.impart.team>).  
48

## 49 377 50 **AUTHOR CONTRIBUTIONS**

51 378  
52  
53 379 JM, AY, AH, PK and KB contributed to trial design. TP and JFL provided significant intellectual  
54  
55 380 input. CA recruited patients and prepared the report. AH, JFL, CA and SM assisted with clinical  
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381 sample collection and processing. JM and AY contributed to statistical design. All authors have read  
382 and approved the article.

383  
384 **Declarations of interest:** none declared

For peer review only

**REFERENCES**

1. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah A. Effects of obesity and small body size on operative and long-term outcomes of coronary artery bypass surgery: a propensity-matched analysis. *The Annals of thoracic surgery*. 2005 Jun;79(6):1976-86. PubMed PMID: 15919295. Epub 2005/05/28. eng.
2. Ng C, Corey PN, Young TK. Divergent body mass index trajectories between Aboriginal and non-Aboriginal Canadians 1994-2009--an exploration of age, period, and cohort effects. *American journal of human biology : the official journal of the Human Biology Council*. 2012 Mar-Apr;24(2):170-6. PubMed PMID: 22275122. Epub 2012/01/26. eng.
3. Moubarac J-C, Batal M, Louzada ML, Martinez Steele E, Monteiro CA. Consumption of ultra-processed foods predicts diet quality in Canada. *Appetite*. 2017 1/1/;108:512-20.
4. Lastra G, Sowers JR. Obesity and cardiovascular disease: role of adipose tissue, inflammation, and the renin-angiotensin-aldosterone system. *Hormone molecular biology and clinical investigation*. 2013 Sep;15(2):49-57. PubMed PMID: 25436732.
5. Rahmanian PB, Adams DH, Castillo JG, Chikwe J, Bodian CA, Filsoufi F. Impact of body mass index on early outcome and late survival in patients undergoing coronary artery bypass grafting or valve surgery or both. *Am J Cardiol*. 2007 Dec 1;100(11):1702-8. PubMed PMID: 18036372. Epub 2007/11/27. eng.
6. Tyson GH, 3rd, Rodriguez E, Elci OC, Koutlas TC, Chitwood WR, Jr., Ferguson TB, et al. Cardiac procedures in patients with a body mass index exceeding 45: outcomes and long-term results. *The Annals of thoracic surgery*. 2007 Jul;84(1):3-9; discussion PubMed PMID: 17588372. Epub 2007/06/26. eng.
7. Sun X, Boyce SW, Hill PC, et al. Association of body mass index with new-onset atrial fibrillation after coronary artery bypass grafting operations. *Ann Thorac Surg*. 2011;91:1852-9.
8. van Straten AHM, Bramer S, Hamad MAS, et al. Effect of body mass index on early and late mortality after coronary artery bypass grafting. *Ann Thorac Surg*. 2010;89:30-7.
9. Tolpin DA, Collard CD, Lee V, Elayda MA, Pan W. Obesity is associated with increased morbidity after coronary artery bypass graft surgery in patients with renal insufficiency. *J Thorac Cardiovasc Surg*. 2009;138:873-9.
10. Choi JC, Bakaeen FG, Cornwell LD, et al. Morbid obesity is associated with increased resource utilization in coronary artery bypass grafting. *Ann Thorac Surg*. 2012;94:23-8.
11. Prabhakar G, Haan CK, Peterson ED, Coombs LP, Cruzzavala JL, Murray GF. The risks of moderate and extreme obesity for coronary artery bypass grafting outcomes: a study from the Society of Thoracic Surgeons' database. *The Annals of thoracic surgery*. 74(4):1125-31.
12. Ghanta RK, LaPar DJ, Zhang Q, Devarkonda V, Isbell JM, Yarboro LT, et al. Obesity Increases Risk-Adjusted Morbidity, Mortality, and Cost Following Cardiac Surgery. *Journal of the American Heart Association*. 2017 Mar 08;6(3). PubMed PMID: 28275064. Epub 2017/03/10. eng.
13. Gruberg L, Weissman NJ, Waksman R, et al. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol*. 2002;39:578-84.
14. Stamou SC, Nussbaum M, Stiegel RM, et al. Effect of body mass index on outcomes after cardiac surgery: is there an obesity paradox? *Ann Thorac Surg*. 2011;91:42-8.

- 1  
2  
3 429 15. Gruberg L, Mercado N, Milo S, et al. Impact of body mass index on the outcome of  
4 430 patients with multivessel disease randomized to either coronary artery bypass grafting or  
5 431 stenting in the ARTS trial: the obesity paradox II? *Am J Cardiol.* 2005;95:439-44.  
6 432 16. Engel AM, McDonough S, Smith JM. Does an obese body mass index affect hospital  
7 433 outcomes after coronary artery bypass graft surgery? *Ann Thorac Surg.* 2009;88:1793-800.  
8 434 17. Hartrumpf M, Kuehnel RU, Albes JM. The obesity paradox is still there: a risk analysis of  
9 435 over 15 000 cardiosurgical patients based on body mass index. *Interactive cardiovascular and*  
10 436 *thoracic surgery.* 2017 Mar 18. PubMed PMID: 28329172. Epub 2017/03/23. eng.  
11 437 18. Uretsky S, Supariwala A, Gurram S, Bonda SL, Thota N, Bezwada P, et al. The interaction  
12 438 of exercise ability and body mass index upon long-term outcomes among patients undergoing  
13 439 stress-rest perfusion single-photon emission computed tomography imaging. *Am Heart J.*  
14 440 2013 Jul;166(1):127-33. PubMed PMID: 23816031. Epub 2013/07/03. eng.  
15 441 19. Chasse M, Mathieu P, Voisine P, Despres JP, Pibarot P, Baillot R, et al. The  
16 442 Underestimated Belly Factor: Waist Circumference Is Linked to Significant Morbidity  
17 443 Following Isolated Coronary Artery Bypass Grafting. *The Canadian journal of cardiology.* 2015  
18 444 Jul 7. PubMed PMID: 26481079.  
19 445 20. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total  
20 446 mortality and with cardiovascular events in coronary artery disease: a systematic review of  
21 447 cohort studies. *Lancet.* 2006;368(9536):666-78.  
22 448 21. Baker AR, Silva NF, Quinn DW, Harte AL, Pagano D, Bonser RS, et al. Human epicardial  
23 449 adipose tissue expresses a pathogenic profile of adipocytokines in patients with  
24 450 cardiovascular disease. *Cardiovascular diabetology.* 2006 Jan 13;5:1. PubMed PMID:  
25 451 16412224. Pubmed Central PMCID: PMC1352345. Epub 2006/01/18. eng.  
26 452 22. Kremen J, Dolinkova M, Krajickova J, Blaha J, Anderlova K, Lacinova Z, et al. Increased  
27 453 subcutaneous and epicardial adipose tissue production of proinflammatory cytokines in  
28 454 cardiac surgery patients: possible role in postoperative insulin resistance. *The Journal of*  
29 455 *clinical endocrinology and metabolism.* 2006 Nov;91(11):4620-7. PubMed PMID: 16895955.  
30 456 Epub 2006/08/10. eng.  
31 457 23. Waist circumference and waist-hip ratio: report of a WHO expert consultation. Geneva:  
32 458 World Health Organization; 2008.  
33 459 24. Schneider HJ, Friedrich N, Klotsche J, et al. The predictive value of different measures of  
34 460 obesity for incident cardiovascular events and mortality. *J Clin Endocrinol Metab.*  
35 461 2010;95:1777-85.  
36 462 25. Lee CMY, Huxley RR, Wildman RP, Woodward M. Indices of abdominal obesity are  
37 463 better discriminators of cardiovascular risk factors than BMI: a meta-analysis. *J Clin*  
38 464 *Epidemiol.* 2008;61:646-53.  
39 465 26. Staiano AE, Reeder BA, Elliott S, Joffres MR, Pahwa P, Kirkland SA, et al. Body mass  
40 466 index versus waist circumference as predictors of mortality in Canadian adults. *International*  
41 467 *journal of obesity (2005).* 2012 Nov;36(11):1450-4. PubMed PMID: 22249224. Pubmed  
42 468 Central PMCID: PMC4120111. Epub 2012/01/18. eng.  
43 469 27. Quante M, Dietrich A, ElKhal A, Tullius SG. Obesity-related immune responses and their  
44 470 impact on surgical outcomes. *International journal of obesity (2005).* 2015 Jun;39(6):877-83.  
45 471 PubMed PMID: 25697667. Epub 2015/02/24. eng.  
46 472 28. Halkos ME, Puskas JD, Lattouf OM, Kilgo P, Kerendi F, Song HK, et al. Elevated  
47 473 preoperative hemoglobin A1c level is predictive of adverse events after coronary artery  
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57  
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2  
3 474 bypass surgery. *The Journal of thoracic and cardiovascular surgery*. 2008 Sep;136(3):631-40.  
4 475 PubMed PMID: 18805264. Epub 2008/09/23. eng.
- 5 476 29. Hassan A, Yip AM, MacLeod JB, Lutchmedial S, Brown CD, Forgie R, et al. The effect of  
6 477 obesity on in-hospital outcomes following cardiac surgery in New Brunswick. *The Canadian*  
7 478 *journal of cardiology*. 2013;29(Suppl 10):S261-2.
- 9 479 30. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krle AJK, et al. SPIRIT 2013  
10 480 Statement: defining standard protocol items for clinical trials. *Revista panamericana de salud*  
11 481 *publica = Pan American journal of public health*. 2015 Dec;38(6):506-14. PubMed PMID:  
12 482 27440100. Pubmed Central PMCID: PMC5114122. Epub 2016/07/22. eng.
- 14 483 31. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue  
15 484 macrophage polarization. *The Journal of clinical investigation*. 2007 Jan;117(1):175-84.  
16 485 PubMed PMID: 17200717. Pubmed Central PMCID: PMC1716210. Epub 2007/01/04. eng.
- 17 486 32. O'Brien EC, Thomas LE. Untangling the paradox: Obesity as prognostic marker in  
18 487 prevalent cardiovascular disease. *American Heart Journal*. 2016 2//;172:170-2.
- 20 488 33. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental  
21 489 activities of daily living. *Gerontol*. 1969;9(3):179-86.
- 22 490 34. Li P, Liu S, Lu M, Bandyopadhyay G, Oh D, Imamura T, et al. Hematopoietic-Derived  
23 491 Galectin-3 Causes Cellular and Systemic Insulin Resistance. *Cell*. 2016 Nov 03;167(4):973-84  
24 492 e12. PubMed PMID: 27814523. Pubmed Central PMCID: PMC5179329. Epub 2016/11/05. eng.
- 25 493 35. Rogacev KS, Cremers B, Zawada AM, Seiler S, Binder N, Ege P, et al. CD14++CD16+  
27 494 monocytes independently predict cardiovascular events: a cohort study of 951 patients  
28 495 referred for elective coronary angiography. *Journal of the American College of Cardiology*.  
29 496 2012 Oct 16;60(16):1512-20. PubMed PMID: 22999728.
- 30 497 36. Rosvall BR, Forgie K, MacLeod JB, Yip AM, Aguiar C, Lutchmedial S, et al. Impact of  
31 498 Obesity on Intensive Care Unit Resource Utilization After Cardiac Operations. *The Annals of*  
32 499 *thoracic surgery*. 2017 Jul 24. PubMed PMID: 28803638.
- 34 500 37. WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO  
35 501 Expert Committee. World Health Organization technical report series. 1995;854:1-452.  
36 502 PubMed PMID: 8594834. Epub 1995/01/01. eng.
- 37 503 38. Hassan A, Yip AM, MacLeod JB, Lutchmedial S, Brown CD, Forgie R, et al. The Effect of  
38 504 Obesity on In-Hospital Outcomes Following Cardiac Surgery in New Brunswick. *Canadian*  
39 505 *Journal of Cardiology*. 2013;29(10):S261-S2.
- 41 506 39. Rothney MP, Brychta RJ, Schaefer EV, Chen KY, Skarulis MC. Body Composition  
42 507 Measured by Dual-energy X-ray Absorptiometry Half-body Scans in Obese Adults. *Obesity*  
43 508 (Silver Spring, Md). 2009 02/19;17(6):1281-6. PubMed PMID: PMC2709755.
- 44 509 40. Muller-Nordhorn J, Roll S, Willich SN. Comparison of the short form (SF)-12 health  
45 510 status instrument with the SF-36 in patients with coronary heart disease. *Heart (British*  
46 511 *Cardiac Society)*. 2004 May;90(5):523-7. PubMed PMID: 15084550. Pubmed Central PMCID:  
48 512 PMC1768233. Epub 2004/04/16. eng.
- 49 513 41. Grodin JL, Hammadah M, Fan Y, Hazen SL, Tang WHW. Prognostic Value of Estimating  
50 514 Functional Capacity With the Use of the Duke Activity Status Index in Stable Patients With  
51 515 Chronic Heart Failure. *Journal of Cardiac Failure*. 21(1):44-50.
- 52 516 42. Society AT. ATS statement: guidelines for the six-minute walk test. *American journal of*  
53 517 *respiratory and critical care medicine*. 2002 Jul 01;166(1):111-7. PubMed PMID: 12091180.  
55 518 Epub 2002/07/02. eng.

- 1  
2  
3 519 43. Lasso J, Gayat E, Mueller C, Peacock WF, Spinar J, Harjola VP, et al. Incremental value  
4 520 of biomarkers to clinical variables for mortality prediction in acutely decompensated heart  
5 521 failure: the Multinational Observational Cohort on Acute Heart Failure (MOCA) study. *Int J*  
6 522 *Cardiol.* 2013 Oct 03;168(3):2186-94. PubMed PMID: 23538053.
- 8 523 44. Fitzgibbons TP, Czech MP. Epicardial and perivascular adipose tissues and their  
9 524 influence on cardiovascular disease: basic mechanisms and clinical associations. *Journal of the*  
10 525 *American Heart Association.* 2014 Mar 04;3(2):e000582. PubMed PMID: 24595191. Pubmed  
11 526 Central PMCID: 4187500.
- 13 527 45. Aldiss P, Davies G, Woods R, Budge H, Sacks HS, Symonds ME. 'Browning' the cardiac  
14 528 and peri-vascular adipose tissues to modulate cardiovascular risk. *Int J Cardiol.* 2017 Feb  
15 529 01;228:265-74. PubMed PMID: 27865196. Pubmed Central PMCID: 5236060.
- 16 530 46. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. *Am Heart J.* 2007  
17 531 Jun;153(6):907-17. PubMed PMID: 17540190.
- 18 532 47. Falkenham A, Saraswat MK, Wong C, Gawdat K, Myers T, Begum J, et al. Recovery free of  
19 533 heart failure after acute coronary syndrome and coronary revascularization. *ESC heart failure.*  
20 534 2017 Jul 24. PubMed PMID: 28737273. Epub 2017/07/25. eng.
- 22 535 48. Trivedi PC, Bartlett JJ, Perez LJ, Brunt KR, Legare JF, Hassan A, et al. Glucolipotoxicity  
23 536 diminishes cardiomyocyte TFE8 and inhibits lysosomal autophagy during obesity and  
24 537 diabetes. *Biochimica et biophysica acta.* 2016 Dec;1861(12 Pt A):1893-910. PubMed PMID:  
25 538 27620487. Epub 2016/10/22. eng.
- 27 539 49. van Straten AH, Bramer S, Soliman Hamad MA, van Zundert AA, Martens EJ,  
28 540 Schonberger JP, et al. Effect of body mass index on early and late mortality after coronary  
29 541 artery bypass grafting. *The Annals of thoracic surgery.* 2010 Jan;89(1):30-7. PubMed PMID:  
30 542 20103201. Epub 2010/01/28. eng.

### 31 543 32 544 **FIGURE LEGENDS:**

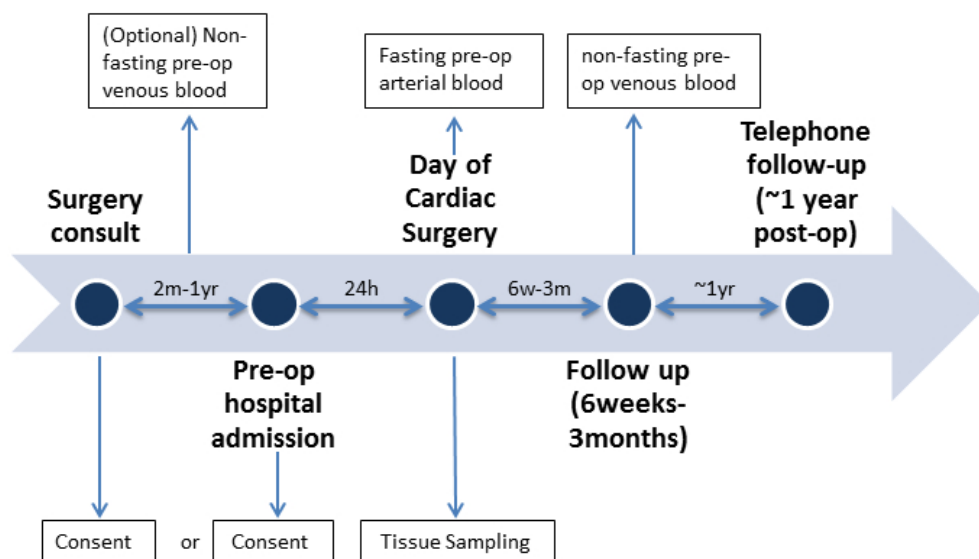
34 545 **Fig. 1: Trial design flow-chart:** From left to right: Patients are admitted for surgical consultation  
35 546 and cardiac catheterization. Consent may be obtained at this time as well as a venous blood sample  
36 547 of 8-10ml collected. Consent could also be obtained at pre-operative admission for cardiac surgery,  
37 548 as well as a venous blood sample of 8-10ml. (Surgery is elective and typically is scheduled between  
38 549 2months to 1 year after surgical consult but not time-restrictive to participation). Patients are  
39 550 admitted 24hours prior to surgery, and a 30 min pre-op arterial blood sample is collected. Tissue  
40 551 sampling is carried out intra-operatively. At the early post-operative follow-up appointment  
42 552 (occurring between 6 weeks to 3 months), a non-fasting venous blood sample may be collected. At  
43 553 the late post-operative follow-up appointment (approximately 1 year post-operatively) telephone  
44 554 follow-up by questionnaire are conducted.

46  
47 556 **Figure 2:** Flowchart showing protocol for the OPOS trial.

### 50 558 **Date and Version Identifier:**

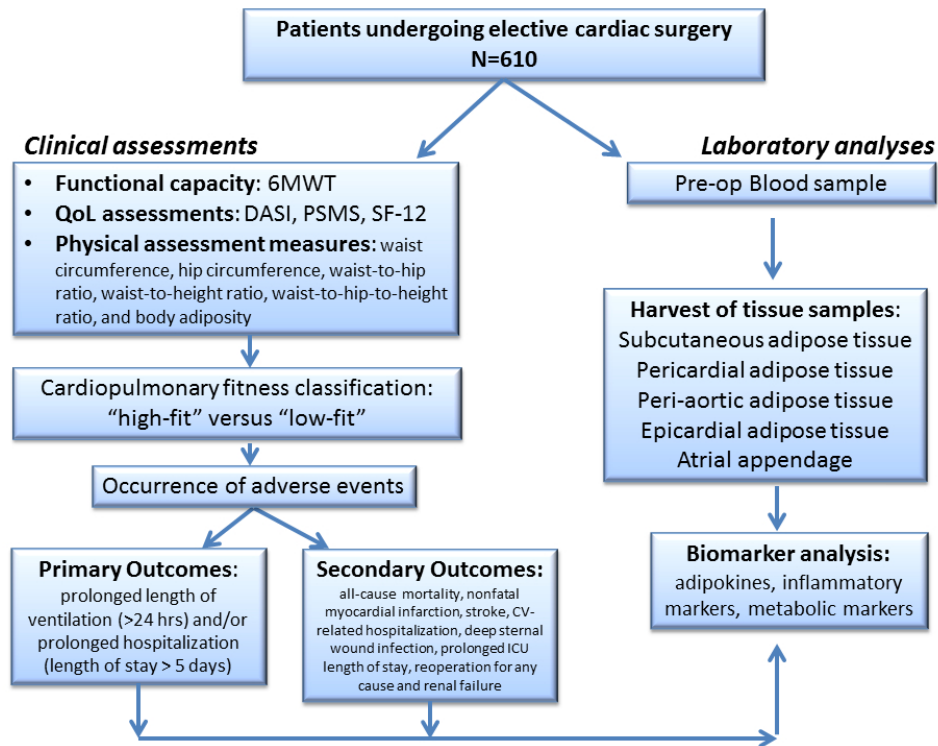
51 559 *Issue Date:* 28 November, 2014

52 560 *Protocol Version Number:* 7 dated 12 December 2017



Trial design flow-chart: From left to right: Patients are admitted for surgical consultation and cardiac catheterization. Consent may be obtained at this time as well as a venous blood sample of 8-10ml collected. Consent could also be obtained at pre-operative admission for cardiac surgery, as well as a venous blood sample of 8-10ml. (Surgery is elective and typically is scheduled between 2months to 1 year after surgical consult but not time-restrictive to participation). Patients are admitted 24hours prior to surgery, and a 30 min pre-op arterial blood sample is collected. Tissue sampling is carried out intra-operatively. At the early post-operative follow-up appointment (occurring between 6 weeks to 3 months), a non-fasting venous blood sample may be collected. At the late post-operative follow-up appointment (approximately 1 year post-operatively) telephone follow-up by questionnaire are conducted.

58x33mm (300 x 300 DPI)



Flowchart showing protocol for the OPOS trial.

81x60mm (300 x 300 DPI)