Multimodal Prehabilitation and Perioperative Optimization of Cardiac Surgical Patients: A Retrospective Matched Cohort Chart Review

by

Pooja Sree Tallapaneni

BS, University of Pittsburgh, 2022

Submitted to the Graduate Faculty of the

School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Public Health

University of Pittsburgh

2023

UNIVERSITY OF PITTSBURGH

SCHOOL OF PUBLIC HEALTH

This essay is submitted

by

Pooja Sree Tallapaneni

on

April 28, 2023

and approved by

Nancy W. Glynn, PhD, FACSM, FGSA, Associated Professor, Department of Epidemiology, School of Public Health, University of Pittsburgh

Kathirvel Subramaniam, MD, MPH, FASE, Professor, Department of Anesthesiology and Perioperative Medicine, School of Medicine, University of Pittsburgh

Senthilkumar Sadhasivam, MD, MPH, MBA, FASA, Professor, Department of Anesthesiology and Perioperative Medicine, School of Medicine, University of Pittsburgh

Multimodal Prehabilitation and Perioperative Optimization of Cardiac Surgical Patients: A Retrospective Matched Cohort Chart Review

Pooja Sree Tallapaneni, MPH

University of Pittsburgh, 2023

Abstract

Prehabilitation typically consists of a set of personalized or general interventions designed and implemented with the intention of improving physiologic, psychologic, and metabolic response to the expected major stressor of surgery. Amongst cardiac surgical patients, there is currently only low quality evidence that prehabilitation may reduce risk of complications or length of stay after surgery. Furthermore, the great majority of studies are not multimodal or have only explored the effects of exercise or nutrition based prehabilitation interventions. This matched retrospective cohort chart review evaluated the first multimodal prehabilitation model in the United States which seeks to optimize patient status at large. The study analyzed 234 matched pairs who underwent major cardiac surgical procedures at the University of Pittsburgh Medical Center Healthcare System between 2021-2022. The treatment cohort were seen at least once prior to surgery by the Center for Perioperative Care in order to be optimized. The standardized core prehabilitation protocol consists of utilization of key clinical pathways and guidelines during preoperative visits to evaluate and optimize modifiable risk factors. Some key risk factors include obstructive sleep apnea, alcohol use, substance use, diabetes, obesity, anemia, frailty, malnutrition, respiratory disease, and depression. Propensity score matching was utilized to overcome baseline covariate imbalances. After matching, no significant differences were seen regarding the primary outcome measures of death or death within 30 days. A statistically significant difference in incidence of cardiac arrest ($p<0.005$), prolonger mechanical ventilation ($p=0.023$), and total hours

of mechanical ventilation (p=0.008) was seen between the two groups, with prehabilitated patients having worse outcomes. Our findings did not align with the initial hypothesis as patients in the prehabilitated group had higher incidences of complications compared to their control counterparts. To date, and to our knowledge, there has been no other published study that has explored a multimodal form of prehabilitation amongst major cardiac surgical patients in the US. The use of prehabilitation, and especially multimodal prehabilitation, is a somewhat novel intervention whose public health impact is not yet thoroughly known; this study offers further clarity regarding its potential value and impact on patient outcomes and health.

Table of Contents

Preface x

1.0 Introduction 1

1.1 Overview 1

1.1.1 Heart 1

1.1.2 Cardiac Surgery 2

1.1.3 Epidemiology of Cardiac Surgery 2

1.2 Modifiable Risk Factors 4

1.2.1 Anemia 5

1.2.2 Diabetes Mellitus 6

1.2.3 Obstructive Sleep Apnea 7

1.2.4 Smoking Cessation 8

1.2.5 Risky Alcohol Consumption 9

1.2.6 Pulmonary Diseases 9

1.3 Surgical Prehabilitation 10

1.4 Gaps In Knowledge 12

1.5 Public Health Significance 12

2.0 Objective 14

3.0 Methods 15

3.1 Study Design and Population 15

3.2 Prehabilitation Implementation 16

3.3 Outcome Measures 18

3.4 Statistical Analysis 19

4.0 Results 22

4.1 Preoperative and Procedural Characteristics of Full Cohort Sample 22

4.2 Postoperative Outcomes of Full Cohort Sample 25

4.3 Preoperative and Procedural Characteristics of Propensity Matched Sample 26

4.4 Postoperative Outcomes of Propensity Matched Sample 29

5.0 Discussion 32

Appendix A Risk Factor Optimization Clinical Pathways 36

Bibliography 45

List of Tables

Table 1. Preoperative and Procedural Characteristics of Full Cohort Sample Prior to Propensity Matching 23

Table 2. Postoperative Outcomes of Full Cohort Sample Prior to Propensity Matching 25

Table 3. Preoperative and Procedural Characteristics of Sample Matched by Propensity Score 27

Table 4. Postoperative Outcomes of Sample Matched by Propensity Score 30

List of Figures

Figure 1. Anemia Clinical Evaluation and Optimization Pathway 17

Figure 2. Diagram of Study Sample Selection and Matching 21

Figure 3. Endocrinology Clinical Evaluation and Optimization Pathway 36

Figure 4. Smoking Cessation Clinical Evaluation and Optimization Pathway 37

Figure 5. Substance Use Clinical Evaluation and Optimization Pathway 38

Figure 6. Alcohol Use Clinical Evaluation and Optimization Pathway 39

Figure 7. Social Work Needs Evaluation and Optimization Pathway 40

Figure 8. Pulmonary Clinical Evaluation and Optimization Pathway 40

Figure 9. Nutrition Evaluation and Optimization Pathway 41

Figure 10. Obesity Clinical Evaluation and Optimization Pathway 42

Figure 11. Frailty Clinical Evaluation and Optimization Pathway 43

Figure 12. Chronic Pain Clinical Evaluation and Optimization Pathway 44

Preface

I would like to thank my family and academic advisors for their unwavering support and invaluable help throughout not only this process, but my academic career thus far at large.

1.0 Introduction

1.1 Overview

1.1.1 Heart

The heart is the main organ of the cardiovascular and circulatory systems, which pump blood throughout the body using a system of blood vessels. The primary anatomy of a heart consists of chambers, walls (myocardium, endo and epicardium), valves, blood vessels and an electrical conduction system with nodes and bundles of electrical fibers. It contains four main chambers made of muscle tissue that are constantly contracting and relaxing based on a series of electrical impulses that move through the tissue. These impulses are directed by the brain and nervous system and allow for control over blood pressure as well as the heart rhythm and heart rate. The heart also works in coordination with the endocrine system as various hormones can either dilate or constrict blood vessels, and thus impact blood pressure.

Due to the extremely critical role it plays, suboptimal heart function has very serious health consequences and can certainly lead to death. In fact, heart disease is currently the leading cause of death across genders and for most ethnic groups. Some of the most common conditions include congestive heart failure, coronary artery disease, myocardial infarction, and arrythmias.

1.1.2 Cardiac Surgery

To treat these conditions, heart surgery is often pursued after lifestyle changes, medication regimens, and other less invasive treatment methods have been exhausted. However, not all cardiac surgery is extremely invasive, like open-heart surgery, and evolution in the field has allowed for minimally invasive cardiac surgery (MICS) to be developed over time. Operative mortality generally has decreased to roughly 2-3% and the number of adverse events and need for reoperation has also markedly decreased[1].

The most common conditions treated by heart surgery include coronary artery disease, valve disease, aortic aneurysm, arrhythmias, atrial fibrillation, and end stage heart failure. The most common cardiac procedures include coronary artery bypass graft (CABG), aortic valve replacement (AVR), combined CABG and AVR, mitral valve repair and replacement (MVR), and aortic aneurysm repair[2].

1.1.3 Epidemiology of Cardiac Surgery

In 2020 alone roughly 19 million deaths were attributed to cardiovascular disease (CVD) globally, which signifies an 18.7% increase from 2010[3]. Furthermore, over 697,000 people in the United States died from heart disease in 2020; this resulted in 1 in every 5 total deaths being attributed directly to heart disease[4]. Clearly, the burden of cardiac health issues is quite significant on both a national and global scale.

To address these cardiac health issues, over 300,000 cardiac surgery procedures are performed each year in the US[4]. Furthermore, there has been a 3.3% increase in procedures over the past decade[3], indicating that the frequency of surgery is stable and if anything, increasing with

time. The most performed cardiac surgery over the past decade has remained the isolated coronary artery bypass graft (CABG), which made up over 70% of total cardiac procedures performed in 2021[2].

However, it is important to note that there are certainly disparities in outcome based on the nonmodifiable risk factors of race, sex, and age. Black patients who have undergone CABG consistently and empirically have higher rates of death, infection, pneumonia, post-operative stroke and 30-day mortality compared to their risk matched white counterparts[5]. Certainly, there are several factors that may affect and contribute to this overall trend, including hospital quality, cultural differences, insurance status and coverage, biological differences, and baseline health status. However, even after controlling for socioeconomic status and hospital quality, non-white patients undergoing CABG still have at least a 16% higher mortality risk[6].

A similar disparity can be seen between men and women undergoing major cardiac surgery as well. Some key biologic factors that account for a portion of the difference in outcomes include that women on average live longer, have smaller coronary arteries, and have consistent exposure to estrogen, which in turn delays atherosclerosis[7]. While the postoperative mortality gap between men and women after CABG has begun to close over the past 20 years, the postoperative morbidity burden is still empirically and significantly higher in women[8].

Another important nonmodifiable risk factor for disparate surgical outcomes is age. This is of particular importance as the number of older individuals undergoing major cardiac procedures is steadily increasing over time as the population ages because CVD is the leading cause of morbidity and mortality amongst older people[9-10]. Amongst adults, typically increasing age is associated with worse health outcomes at large regardless of procedure. This trend remains true as patients under 60 have comparatively lower rates of cardiac-related mortality and overall mortality

compared to their matched counterparts following CABG[11]. Exploring further, amongst patients who are over 60 there are significant differences in outcome amongst Septuagenarians (≥70) versus Octogenarians (≥80). Octogenarians are more likely to develop more cardiac, renal, respiratory, and infectious complications post-surgery and thus have significantly worse overall outcomes than Septuagenarians. Furthermore, female Octogenarians have higher mortality rates than their male counterparts and are more likely to face postoperative complications such as infection, bleeding, and respiratory issues[12]. This trend is unsurprising and rather intuitive considering that several stacked risk factors would logically interact and have an additive or multiplicative effect upon potential for unfavorable operative and post-operative outcomes.

1.2 Modifiable Risk Factors

While the above risk factors are unmodifiable, there are also several modifiable preoperative risk factors that affect morbidity and mortality rates after cardiac surgery. There are several common comorbidities including anemia, frailty, obesity, obstructive sleep apnea (OSA), smoking, alcohol consumption, mental health disorders, nutritional deficiency, renal insufficiency, liver disease, pulmonary disease, and neurological dysfunction[13]. These comorbidities and risk factors can often lead to unwanted operative and post-operative complications which harm patient health and increase healthcare burden at large. Though there are many possible risk factors, some of the most significant are explored further below.

1.2.1 Anemia

The World Health Organization defines anemia as a hemoglobin level less than 12 g/DL in women and 13g/dL in men[14]. It is a very common condition and 40% of cardiac surgery patients are anemic[15]. The diagnostic path is quite simple as hemoglobin, ferritin and/or transferrin saturation levels can be compared against well-established clinical benchmarks. Patients with any level of anemia have an increased (4.6%) risk of all-cause mortality after cardiac surgery, while patients with severe anemia have up to 12.7% operative mortality[16]. Furthermore, a meta-analysis of over 900,000 patients undergoing major surgery found that preoperative anemia is an independent risk factor for worse post-operative outcomes at large[17]. While it is important to recognize that this study was done in the context of only elective procedures, rather than emergency procedures, the results are still extremely significant and indicative of the detrimental impact of anemia.

Despite preoperative anemia being associated with longer intensive care unit stays, increased renal injury, more cardiac events, and higher transfusion rates, it is typically considered only a surrogate marker of physical status and as a result is often not adequately treated prior to surgery[18-20]. When treatment is pursued, too often the quick fix solution is a perioperative blood transfusion[21]. This is especially problematic considering that patients receiving a red blood cell transfusion are 3.4 times more likely to suffer from ischemic or infectious postoperative complications[22]. Cardiac surgical procedures also have higher rates of blood product usage than any other surgical specialty[23-24], indicating that it is uniquely key to appropriately address anemia amongst cardiac surgical candidates specifically. However, the sometimes urgent nature of cardiac surgery does not allow for enteral iron supplementation to be an effective course of action (can take up to 6 months to see clinical affect)[25] instead of transfusion. In these cases, intravenous iron

infusions are fast, cost effective, show clinical impact within 2 weeks[26], and thus are the better suited to treat perioperative anemia on a tight timeline. Supplementary B12 and folate prescriptions can be given alongside iron to further address the issue effectively[13]. Erythropoietin has also been successfully used preoperatively in cardiac surgical patients to treat anemia and improve outcomes[27]. Overall, anemia is a significant comorbidity that is too often resolved through dangerous intraoperative transfusions as it is somewhat difficult to address on a compressed timeline.

1.2.2 Diabetes Mellitus

A key diagnostic biomarker for diabetes is hemoglobin A1c (HbA1c) as glycated hemoglobin represents the hemoglobin's exposure to mean blood glucose levels within the last 3 months and is thus an indicator of long-term glycemic control[28]. HbA1c levels above 6.5% indicate diabetic status and above 5.7% is considered prediabetic[29]. This comorbidity is of great relevance in the context of cardiac surgery as up to 38% of candidates are diabetic[30]. Patients undergoing CABG with HbA1c levels above 7% have longer hospital stays, greater in-hospital mortality rates, increased risk of renal failure and wound infection; those with levels above 8.5% had 4 times the overall mortality rate of their nondiabetic counterparts[31]. As a result of the profound differences in outcome based on level, the Society for Thoracic Surgeons recommends a level less than 7% ideally or at least less than 9% in the context of all comorbidities[32].

Though glycemic control is a difficult and complex process, there are several steps that can be taken in order to decrease the overall level. Nutrition counseling should be utilized to educate patients regarding glycemic index at large, as well as the specific development of a lower glycemic index diet for use during the months or weeks leading up to surgery. Eating such a diet in

preparation for elective cardiac surgery has been associated with better clinical outcomes and decreased length of stay in hospital[33]. There are also several classes of non-insulin based injectable and oral drug options that should be considered[34-35] as these drugs have shown decreased mortality and adverse event occurrence in both short- and long-term settings compared to insulin-based methods[36]. Furthermore, a consultation with an endocrinologist may be required for patients with poorly controlled diabetes.

1.2.3 Obstructive Sleep Apnea

The initial clinical screener for obstructive sleep apnea (OSA) is the STOP-BANG questionnaire, which is then followed up with sleep testing through polysomnography (preferred) or a home sleep study to confirm and diagnose officially based off Apnea-Hypoxia index (AHI) score. The screening questions inquire about snoring, fatigue, breathing obstruction while asleep, hypertension, BMI > 35, age > 50, neck circumference > 40 cm and male gender. If patients answer yes to at least 5 questions, they are high risk and further steps are pursued. AHI is calculated during the sleep testing and scores between 5-14 indicate mild apnea, 15-29 indicate moderate apnea, and 30 or more indicate severe apnea[37]. Roughly 74% of cardiac surgical patients meet AHI guidelines for at least mild apnea, while 48% meet guidelines for at least moderate apnea and 27% meet guidelines for severe apnea[38]. After cardiac surgery, patients with OSA have 33.3% higher odds of developing a major cardiac or cerebrovascular event (death, myocardial infarction, stroke, congestive heart failure, etc.) and 18.1% higher odds of developing postoperative atrial fibrillation (POAF) according to a recent meta-analysis accounting for over 1800 patients[39].

The preferred treatment methods are continuous positive airway pressure (CPAP) therapy and weight loss, as the condition is very prevalent amongst obese patients[40]. In fact, just a 10%

decrease in overall weight predicts a 26% reduction in AHI score from baseline[41]. Preoperative CPAP treatment is also associated with a 41% decrease in risk of developing POAF after major cardiac surgery amongst patients with OSA[42]. It is important to note that both treatment methods require weeks if not months to be effective. Furthermore, OSA is typically underdiagnosed by surgeons (58% of patients incorrectly undiagnosed) and anesthesiologists (15% of patients incorrectly undiagnosed) during preoperative evaluation[43]. Thus, even more patients are not referred to needed treatment, at large and prior to surgery, and unknowingly suffer from the increased risk of complications.

1.2.4 Smoking Cessation

Smoking has long been associated with worse health outcomes at large and while overall prevalence of smoking is certainly decreasing with time, prevalence amongst surgical candidates remains high (22.3%)[44]. Patients who identify as current smokers prior to cardiac surgery have roughly twice the length of ICU stay, 14.6% higher chance of ICU readmission, almost doubled risk of in-patient mortality, and significantly higher risk of infection and complications[45]. Smoking cessation therapy can begin with a simple "Ask, Advise, Connect" approach that is practical for perioperative physicians to pursue[46]. Alongside behavioral counseling and referral to cessation programs, pharmacotherapy options such as nicotine replacement therapy should also be considered as they have been proven effective in general clinical settings (though no evidence specific to cardiac surgery is available)[47].

1.2.5 Risky Alcohol Consumption

Risky alcohol consumption is delineated by the consumption of more than 3 alcoholic units (AU) per day or 21 AU per week (with 1 AU consisting of 12 g of ethanol). Prevalence of AUD is significantly underestimated by anesthesiologists during preoperative assessment (6.9% estimate vs 18.1% true prevalence) and more intentional efforts should be made to address the issue[48]. This is necessary because the postoperative complication likelihood increases by roughly 50% if 3-4 AU are consumed per day, rather than 0-2 AU per day, and increases by up to 400% if consuming more than 5 AU per day[49]. Behavioral therapy, counseling programs and pharmacotherapies such as vitamin B, disulfiram or chlordiazepoxide should all be considered as possible treatment options, especially in the weeks and months leading up to the surgical date[50].

1.2.6 Pulmonary Diseases

Several different conditions fall under the umbrella of pulmonary disease including asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, pneumonia, and lung cancer. COPD is the third leading cause of death worldwide and the most prevalent pulmonary disease amongst cardiac surgical candidates[51]; a recent meta-analysis of more than 13,000 patients undergoing CABG found that over 20% had at least mild COPD, while almost 13% had moderate to severe COPD[52]. Perioperative evaluation requires risk assessment through history and clinical examination along with imaging studies and lung function evaluation. Depending on the age and presenting symptoms of the patient, a chest x ray may not suffice and additional imaging such as computer tomography (CT) may need to be pursued[53]. Additionally, pulmonary function tests

(PFT) can be utilized to address underdiagnosis as a study of almost 1,200 cardiac surgery patients showed that PFT results helped to reclassify COPD status of 31% of patients[54].

Once appropriately diagnosed, patients can be linked to pulmonary rehabilitation, pursue inspiratory muscle training (IMT) and utilize incentive spirometry (IS) before and after surgery. In a recent randomized clinical trial, it was found that amongst CABG patients those who utilized preoperative IS had significantly shorter length of in-hospital stay and duration of ventilation, as well as increased oxygen saturation and arterial blood oxygen[55]. A meta-analysis of 12 clinical trials found that preoperative IMT is associated with reduced length of in-hospital stay and decreased atelectasis (partial or complete lung collapse)[56]. Additionally, bronchodilators, inhaled steroids and/or home oxygen can be prescribed to further optimize pulmonary status. If needed, patients can also be linked to a pulmonologist or respiratory therapist.

1.3 Surgical Prehabilitation

Postoperative morbidity and mortality outcomes are primarily determined by three key factors: 1) quality of surgical care, 2) degree of surgical stress elicited, and finally 3) the preoperative condition of the surgical candidate[57]. Prehabilitation deals with the third and generally consists of a set of personalized interventions designed and implemented with the intention of improving future physiologic, psychologic, and metabolic response to an expected stressor. In the context of surgical prehabilitation specifically, the expected major stressor is of course surgery. Though there is no single static definition of surgical prehabilitation, typically interventions are related to exercise, nutrition, and/or psychocognitive training.

Amongst growing patient and clinician interest in the field, a recent (2022) umbrella review of 55 systemic reviews regarding prehabilitation before elective surgery determined that there is evidence that prehabilitation prior to cardiac surgery reduces the risk of complications and length of stay. However, they also identified that the certainty of this evidence was low to very low and thus the authors recommend further high-quality research be done to strengthen and clarify the empirical evidence regarding success. The umbrella review also identified that the great majority of studies (56%) were solely exercise based prehabilitation (EBPrehab), while another 20% were solely nutrition intervention based[58]. Clearly, there is a lack of knowledge, regardless of quality, surrounding multi-modal and integrated forms of surgical prehabilitation.

Furthermore, there is very limited data regarding prehabilitation in the context of cardiac surgery. While still not robust, most research regarding cardiac surgery prehabilitation is in the context of single-component programs specifically consisting of EBPrehab or pulmonary optimization (through IMT) exclusively and thus the value or impact of multimodal interventions are not well known[59]. Though there are two international (Spain[60], Netherlands[61]) preliminary or exploratory multi-modal intervention studies that have recently been published, there is almost no information regarding multimodal intervention within the US. The only US (and Canada) specific information available is the "NEW" approach consisting of nutritional status (N), exercise capacity (E), and worry reduction (W). An implementation guide was published in 2018, but it is unknown if the model has yet been adopted or evaluated[63].

1.4 Gaps In Knowledge

This study would be filling a unique niche within the literature by exploring differences in outcome between patients who experience multi-modal prehabilitation specifically prior to major cardiac surgery within the US. This study would offer preliminary evidence and data that could then be utilized to determine if randomized clinical trials or further studies should be pursued. Moreover, novel prehabilitative interventions will be explored for the first time amongst cardiac surgical patients as anemia, OSA, substance abuse, and other key risk factors were targeted preoperatively as potential areas for personalized intervention.

1.5 Public Health Significance

As the number of patients undergoing major cardiac surgery increases every year, it is essential to utilize all possible interventions to reduce postoperative morbidity and mortality. Despite current protocols such as Enhanced Recovery After Surgery and advancements in surgical techniques, there is still much room for improvement, especially in the preoperative phase. This is especially important because a study of almost 2000 professional, patient and caregiver stakeholders identified that the possibility of prehabilitation improving outcomes is a top 10 priority within the field of anesthesia and perioperative care research[63]. While this study was conducted in the UK, similar trends in interest likely exist within the US among perioperative care givers. Furthermore, surgical pathway re-design to expand and prioritize the preoperative pathway will allow for benefits and value to accrue from that period due to opportunities for collaborative decision making and behavioral change[64].

Benefits will be seen through improved patient outcomes and decreased overall healthcare costs and burden. At large, heart disease costs over $200 billion annually when healthcare services, medications, and productivity loss due to mortality are taken into consideration[4]. More specifically, amongst CABG patients over the past decade, there has been an almost $80 million dollar increase in healthcare costs due to additional hospitalization time and therapies resulting from comorbidity related post-operative complications[65]. One of the previously discussed modifiable risk factors, perioperative anemia, increases the likelihood of intraoperative red blood cell transfusion if left untreated. Amongst patients undergoing CABG, those who received an intraoperative red blood cell transfusion not only had worse outcomes, but also had 1.4 times the nonoperative costs of their counterparts who did not receive a transfusion[66]. Through effective cardiac surgical prehabilitation, additional services and costs such as transfusion can be avoided, while also improving patient care and outcomes. By taking steps to optimize these comorbidities prior to surgery, the financial and resource burden currently placed on the healthcare system through major cardiac surgeries can be minimized.

2.0 Objective

The objective of this study was to examine if patients who underwent the prehabilitation process significantly differed in their operative and postoperative outcomes compared to those who did not after major cardiac surgery. We hypothesize that patients who undergo the prehabilitation process will have significantly improved outcomes as a result of preoptimization of their comorbidities as opposed to their counterparts who undergo a typical surgical timeline and approach. Although the outcomes we hope to investigate have several different factors and variables which impact them, we will account for as many of these variables as possible whilst analyzing the data and still expect the prehabilitation status to explain at least a portion of the variances in outcomes.

3.0 Methods

3.1 Study Design and Population

A retrospective cohort study design was used for this project. Study subjects were retrieved from the University of Pittsburgh Medical Center (UPMC) electronic health records (EHRs) and the Society for Thoracic Surgeons (STS) Adult Cardiac Surgery Database (ACSD). Specifically, all patients who had major elective cardiac surgery at either UPMC Presbyterian or UPMC Shadyside from 5/1/2021 to 12/31/22 were initially pulled for analysis from the STS ACSD. We only included patients who underwent urgent or elective cardiac surgical procedures. Patients who underwent emergency procedures, transcatheter aortic valve [TAVR] or other valve replacement, ventricular assist device [VAD], heart transplant, and other mechanical support devices were excluded from the study. The study cohort included mainly major invasive cardiac surgeries such as CABG, valve, combined CABG/valve procedures, multivalve procedures and aortic procedures. Patients with incomplete follow up data were excluded in the final analysis. Then, patients who underwent prehabilitation were identified through the UPMC EHR using an interactive dashboard which provided a list of those who had been seen by the Center for Perioperative Care (CPC) either in person or through telemedicine prior to their surgical date at least once. Control patients included any patients who met all inclusion/exclusion criteria discussed above during the same time period but were not identified on the list from the UPMC CPC EHR dashboard and thus underwent traditional perioperative care for major cardiac surgery. The detailed steps of this process are shown in Figure 2 at the end of the methods.

3.2 Prehabilitation Implementation

This study was approved by the University of Pittsburgh Institutional Review Board (STUDY#20070119). In 2021, the UPMC initiated the optional, surgeon referred prehabilitation program through the Center for Perioperative Care (CPC) across 2 academic hospitals in the city of Pittsburgh for patients undergoing major cardiac surgeries. The program design and implementation were heralded by one core multidisciplinary team of clinical experts (anesthesiologists, surgeons, and nurses). Several other clinical practitioners (physician assistants and nurse practitioners), information technology personnel, pharmacists and physical/respiratory therapists were involved in the downstream treatments and interventions pursed as a result of CPC evaluation and coordinated optimization.

The standardized core prehabilitation protocol consists of utilization of key clinical pathways and guidelines during preoperative visits by physicians in order to evaluate and optimize modifiable risk factors prior to surgery. Each risk factor has a specific provider facing flow diagram that allows clinical practitioners to not only assess the current status of the patient, but also determine or prescribe the appropriate next steps to attempt to address the issue in question. Flow diagrams exist for several key risk factors and were integrated into the care of those seen by the CPC. The preoperative anemia evaluation tool below (Figure 1) shows the high level of detail and use of clinically relevant benchmarks for care provider clarity. The evaluation flow diagrams for all other relevant risk factors are included in Appendix A.

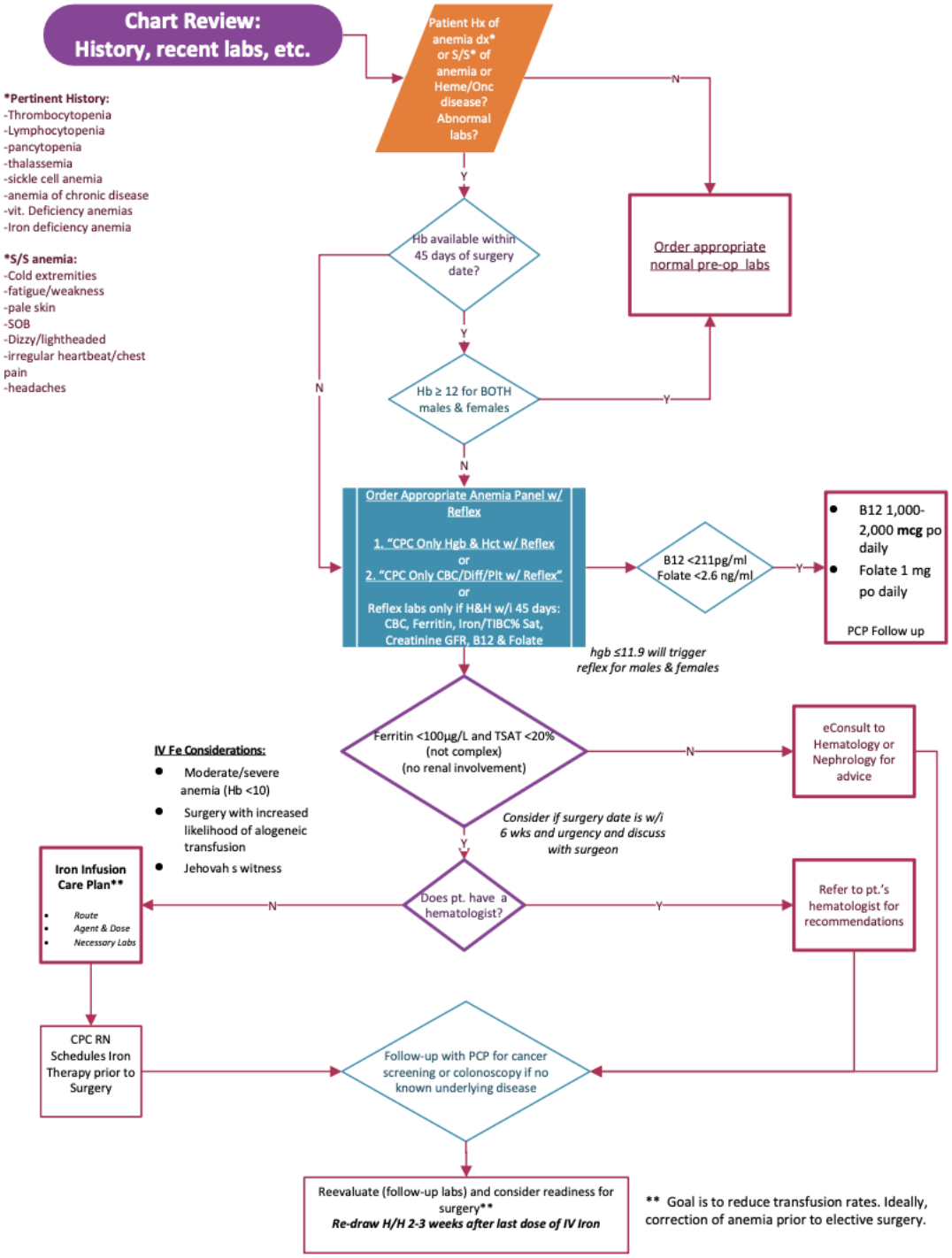

Figure 1. Anemia Clinical Evaluation and Optimization Pathway

While being seen by the CPC is optional and at the surgeon's discretion, guidelines were distributed regarding the prehabilitation program to all surgical team members. Patients were seen by an anesthesia team member at the cardiac surgery clinic once the candidacy for surgery was determined. Risk prediction and evaluation was done through several tools and an appropriate prehabilitation plan was formulated after discussion with the surgical team regarding both timing of surgery and severity of disease. While it is ideal to have 4-6 weeks of prehabilitation, the duration was discussed with surgical team and a case specific consensus was developed. Additional laboratory testing and consultations were ordered as needed as well. Appropriate follow up of interventions was done by the center for presurgical care. Finally, readiness for surgery was discussed with the surgical team after a period of prehabilitation measures.

3.3 Outcome Measures

All variables were abstracted from the STS ACSD and reflect the collection protocols and procedures outlined by the database with no involvement or interference from the study team. Per the STS, all-cause mortality data was verified by the U.S. Social Security National Death Index Database as well.

The primary outcome measures were death within 30 days and death at large as reported by the database. Secondary outcome measures examined postoperative complication rates between groups including incidence of stroke, sepsis, deep sternal infection, pneumonia, renal failure, transient ischemic attack (TIA), pulmonary thromboembolism, deep vein thrombosis, cardiac arrest, atrial fibrillation, left ventricular ejection fraction (LVEF), prolonged mechanical

ventilation beyond 24 hours, total mechanical ventilation duration, and readmission within 30 days.

3.4 Statistical Analysis

First, baseline and operative characteristics of prehabilitated patients and traditional patients in the full cohort sample were compared. Regarding missing values, if less than 15% of total values were missing for the variable then the group median was used instead. Furthermore, if final follow up time points were missing or had not yet occurred for a patient, they were censored on the date of data extraction. For continuous measures student t-tests or nonparametric Mann-Whitney U tests were utilized and for categorical measures chi-square or fisher exact tests were utilized. Normality was assessed by the Kolmogorov-Smirnov Test. All categorical variables were presented by count and percentage; continuous variables were presented by median (with a range of quartile one through quartile three) as they were not normally distributed.

Propensity score matching was utilized to overcome the baseline covariate imbalances often prevalent in retrospective observational cohort studies[67] and in order to develop truly causal estimates on the prehabilitation outcome relationships. Logistic regression was used to calculate the propensity score based on all the baseline characteristics (saturated) to reduce selection bias. Propensity scores were calculated with several different baseline and operative characteristics (detailed in Table 1). Several factors were evaluated while deciding on which variables to match on, including their relationship with the various outcomes of interest and the intervention of prehabilitation as well as general clinical relevance. All variables with significant differences amongst baseline groups (p value <.05) were matched on including gender, COPD,

immunocompromised status, peripheral artery disease (PVD), previous myocardial infarction (MI), prior heart failure, New York Heart Association (NYHA) classification, number of preoperative days admitted in hospital, preoperative left ventricular ejection fraction (LVEF), hematocrit, total albumin, HbA1c level, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) within 48 hours prior to surgery, IV inotropic agents within 48 hours prior to surgery, use of cardiopulmonary bypass (CBP), cross clamp time, CBP time (minutes), lowest temperature recorded in operating room, and surgical type. However, the matching algorithm does not utilize cases with missing values and the variables cross clamp time and CBP time are both only available in on-pump CBP surgical cases. Thus, only on-pump surgical cases were utilized when matching. We also matched on preoperative dialysis requirement and lipid lowering medications due to the proximity of the p-value to significance (P=0.07 & P=0.08 respectively).

A 1 to 1 Greedy Matching algorithm (nearest neighbor matching without replacement) was selected in order to create balanced groups[68] and a caliper width of 0.2 was employed. The algorithm was unable to match 12 prehabilitated patients with controls due to extreme propensity scores. After propensity score matching, McNemar's test was used to assess the statistical significance of the risk difference for categorical variables, and t-test or Wilcoxon signed rank test was utilized for continuous variables. Regarding outcomes, all analysis after matching accounts for the matched pairs specifically rather than the original sample cohort.

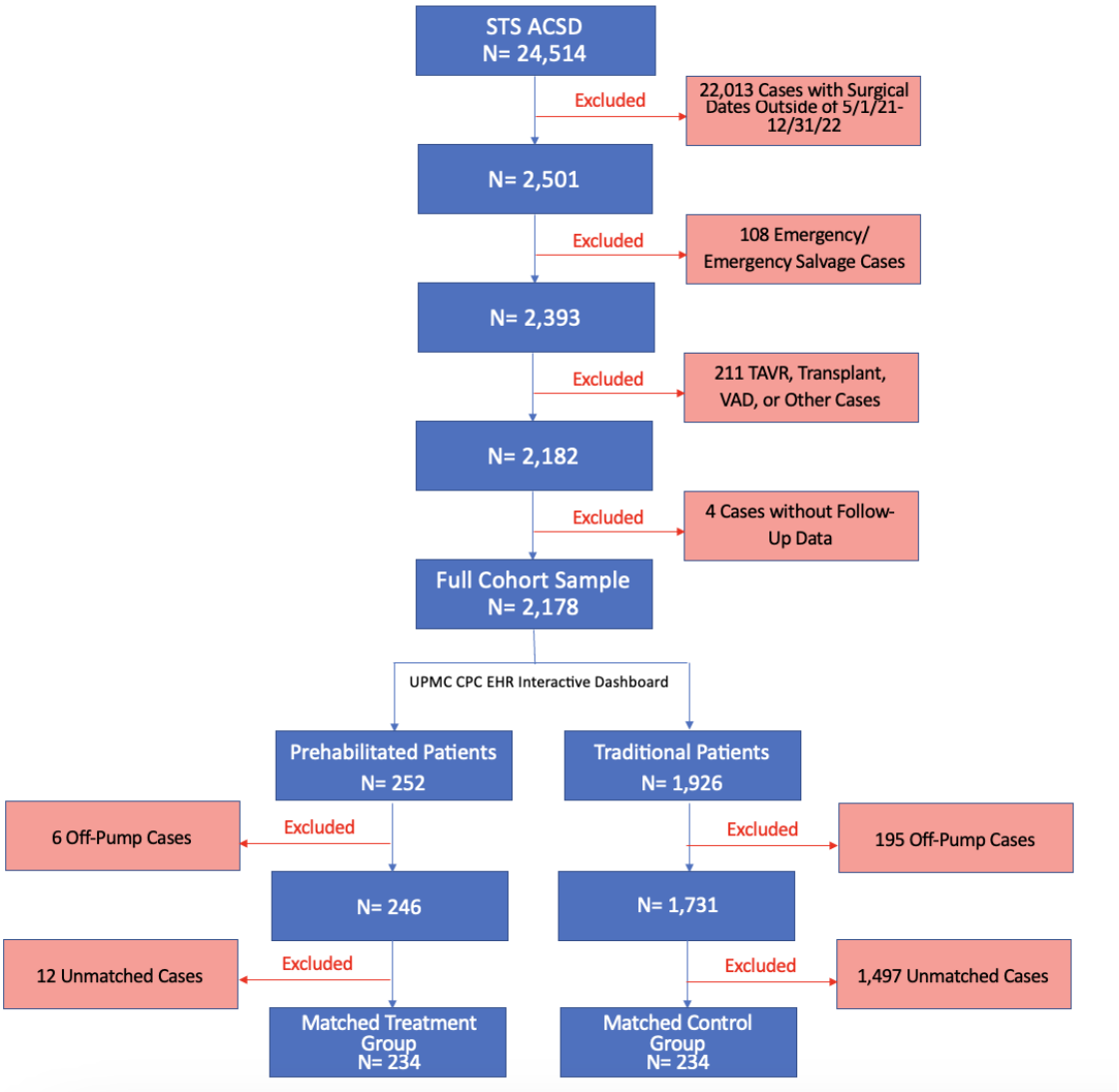

Figure 2. Diagram of Study Sample Selection and Matching

4.0 Results

4.1 Preoperative and Procedural Characteristics of Full Cohort Sample

The full cohort sample (N=2,178) selection process is shown above in Figure 2 and details the exclusion criteria and number of cases excluded at each point. The treatment (N=252) and control (N=1,926) groups of the sample at this stage had many significant differences in both preoperative and procedural characteristics. While both groups had no significant difference in mean age, BMI, diabetes, dialysis, hypertension, cerebrovascular disease (CVD), cigarette smoking, creatinine, bilirubin, beta blockers within 2 weeks, lipid lowering medication within 24 hours prior to surgery, and duration of CBP (all $p>0.05$) (Table 1), there were several other variables which were not similar between the groups. Gender ($p<0.001$), COPD ($p=0.002$), immunocompromised status ($p<0.001$), PVD ($p=0.005$), previous MI ($p<0.001$), prior heart failure ($p<0.001$), NYHA classification ($p=0.016$), number of preoperative days admitted in hospital ($p<0.001$), preoperative LVEF ($p=0.015$), hematocrit ($p=0.025$), total albumin ($p<0.001$), HbA1c level ($p<0.001$), ACE inhibitors or ARB within 48 hours prior to surgery ($p=0.002$), IV inotropic agents within 48 hours prior to surgery ($p<0.001$), lipid lowering medication within 24 hours prior to surgery ($p=0.076$), use of CBP ($p<0.001$), cross clamp time ($p<0.001$), lowest temperature recorded in operating room ($p<0.001$), and surgical type ($p<0.001$) (Table 1) were all significantly different between the prehabilitation and control groups of the full cohort sample.

Table 1. Preoperative and Procedural Characteristics of Full Cohort Sample Prior to Propensity Matching

	Prehabilitated (N=252) Mean[25th,75th percentile]or n (%)	**Control (N=1926) Mean[25th,75th percentile] or n (%)**	**P- Value**
Patient Characteristics			
Age (yrs)	66.0 [59.0-71.0]	67.0 [59.0-72.0]	0.575
Female	93 (36.9)	492 (25.6)	<.001
Body Mass Index (kg/m^2)	30.1 [25.4-34.1]	28.9 [25.6-33.3]	0.148
Diabetes	90 (35.7)	767 (39.8)	0.209
Dialysis	12 (4.8)	52 (2.7)	0.068
Hypertension	215 (85.3)	1659 (86.1)	0.724
Chronic Obstructive Pulmonary Disease	91 (36.1)	516 (26.8)	0.002
Immunocompromised	26 (10.3)	85 (4.4)	<.001
Peripheral Artery Disease	42 (16.7)	205 (10.6)	0.005
Cerebrovascular Disease	57 (22.6)	421 (21.9)	0.784
Previous Myocardial Infarction	43 (17.1)	766 (39.8)	<.001
Prior Heart Failure	198 (78.6)	626 (32.5)	<.001
Current Cigarette Smoker	57 (22.6)	431 (22.4)	0.931
Preoperative Hospitalization (days)	0.0 [0.0- 1.0]	0.0 [0.0- 4.0]	<.001
Preoperative Laboratory Parameters			
Hematocrit (%)	39.6 [37.2-43.5]	39.6 [35.8-42.7]	0.025
Creatinine (mg dl^{-1})	1.0 [0.8- 1.2]	1.0 [0.8- 1.1]	0.775
Total Albumin (g dl^{-1})	4.0 [3.8- 4.3]	3.8 [3.5- 4.1]	<.001
Total Bilirubin (mg dl^{-1})	0.6 [0.4- 0.8]	0.6 [0.5- 0.8]	0.735
Last Hemoglobin A1C (%)	5.7 [5.4- 6.5]	5.8 [5.5- 6.6]	<.001

Preoperative Medications			
ACE/ARB* within 48 h	13 (5.2)	247 (12.8)	0.002
Beta Blockers within 2 weeks	146 (57.9)	1137 (59.0)	0.480
Inotropes within 48 h	28 (11.1)	50 (2.6)	<.001
Lipid-lowering drugs within 24 h	149 (59.1)	1236 (64.2)	0.076
Preoperative Cardiac Condition			
New York Heart Association Class			0.016
1&2:	197 (78.2)	1621 (84.1)	
3&4:	55 (21.8)	305 (15.8)	
Left Ventricular Ejection Fraction (%)	58.0 [53.0-63.0]	58.0 [48.0-63.0]	0.015
Procedural Characteristics			
Surgical Type			<.001
Multi Valve	14 (5.6)	49 (2.5)	
Isolated CABG**	48 (19.0)	1173 (60.9)	
Isolated Valve	78 (31.0)	389 (20.2)	
CABG + Valve**	45 (17.9)	184 (9.6)	
Aortic	67 (26.6)	131 (6.8)	
Cardiopulmonary Bypass Utilized	246 (97.6)	1731 (89.9)	<.001
Cross Clamp Time (min)	67.0 [54.0-82.5]	79.0 [60.0-99.0]	<.001
Duration of Cardiopulmonary Bypass (min)	94.0 [79.0-126.0]	103.0 [82.0-128.0]	0.082
Lowest Temperature in Operating Room (°C)	31.8 (29.1-33.5]	34.0 [32.4-35.0]	<.001

*Angiotensin Converting Enzyme (ACE)/Angiotensin Receptor Blockers (ARB)

**Coronary artery bypass grafting (CABG)

4.2 Postoperative Outcomes of Full Cohort Sample

Table 2 shows the differences in postoperative outcomes and complications between the two groups in the full cohort sample prior to matching. Statistically significant differences were found in both the primary outcome measures of death within 30 days ($p<0.001$) and death ($p=0.002$). Statistically significant differences in incidence were also found in several secondary outcome measures including renal failure ($p=0.001$), cardiac arrest ($p<0.001$), prolonged mechanical ventilation ($p<.001$), and total mechanical ventilation duration ($p<0.001$). Transient ischemic attack (TIA) and pulmonary thromboembolism complications were not seen in either group.

Table 2. Postoperative Outcomes of Full Cohort Sample Prior to Propensity Matching

	Prehabilitated (N=252)	**Control (N=1926)**	**P- Value**
Stroke	5 (2.0%)	17 (0.9%)	0.100
Sepsis	0 (0%)	13 (0.7%)	0.191
Deep Sternal Infection	0 (0%)	3 (0.2%)	0.531
Pneumonia	10 (4.0%)	51 (2.7%)	0.232
Renal Failure	12 (4.8%)	32 (1.7%)	0.001
Transient Ischemic Attack	0 (0%)	0 (0.0%)	.
Pulmonary Thromboembolism	0 (0%)	0 (0.0%)	.
Deep Vein Thrombosis	0 (0%)	6 (0.3%)	0.375

Cardiac Arrest	18 (7.0%)	27 (1.4%)	<.001
Atrial Fibrillation	69 (27.4%)	487 (25.3%)	0.473
Left Ventricular Ejection Fraction (%)	48.0 [30.5-53.0]	53.0 [38.0-58.0]	0.055
Prolonged Mechanical Ventilation (>24 h)	54 (21.4%)	147 (7.6%)	<.001
Total Mechanical Ventilation Duration (h)	5.8 [3.7-20.6]	4.15 [2.8-7.0]	<.001
Readmission within 30 days	63 (25.0%)	408 (21.2%)	0.166
Death within 30 days	13 (5.2%)	35 (1.8%)	<.001
Death	21 (8.3%)	77 (4.0%)	0.002

4.3 Preoperative and Procedural Characteristics of Propensity Matched Sample

After propensity score matching (234 match pairs, N=468), there were no statistically significant differences in the distribution of any preoperative or procedural variables examined between the prehabilitated (N=234) and control groups (N=234).

Table 3. Preoperative and Procedural Characteristics of Sample Matched by Propensity Score

	Prehabilitated (N=234) Mean[25th,75th percentile] or n (%)	**Control (N=234) Mean[25^{th},75^{th} percentile] or n (%)**	**P- Value**
Patient Characteristics			
Average Age (yrs)	66.0 [60.0-72.0]	67.0 [59.00-72.0]	0.528
Female	82 (35.0)	77 (32.9)	0.626
Body Mass Index (kg/m^2)	30.4 [25.4-34.6]	29.1 [25.3-34.0]	0.326
Diabetes	85 (36.3)	66 (28.2)	0.060
Dialysis	11 (4.7)	9 (3.9)	0.648
Hypertension	200 (85.5)	201 (85.9)	0.900
Chronic Obstructive Pulmonary Disease	88 (37.6)	87 (37.2)	0.924
Immunocompromised	21 (9.0)	20 (8.6)	0.870
Peripheral Artery Disease	40 (17.1)	42 (18.0)	0.808
Cerebrovascular Disease	54 (23.1)	43 (18.4)	0.210
Previous Myocardial Infarction	40 (17.1)	38 (16.2)	0.804
Prior Heart Failure	183 (78.2)	189 (80.8)	0.492
Current Cigarette Smoker	53 (22.7)	39 (16.7)	0.103
Preoperative Hospitalization (days)	0.0 [0.0- 1.0]	0.0 [0.0- 1.0]	0.917
Preoperative Laboratory Parameters			

Hematocrit (%)	39.5 [37.1-43.2]	40.2 [37.2-43.1]	0.424
Creatinine (mg dl^{-1})	1.0 [0.8- 1.2]	1.0 [0.8- 1.1]	0.671
Total Albumin (g dl^{-1})	4.0 [3.8- 4.2]	4.0 [3.8- 4.3]	0.872
Total Bilirubin (mg dl^{-1})	0.6 [0.4- 0.8]	0.6 [0.5- 0.8]	0.118
Last Hemoglobin A1C (%)	5.7 [5.4- 6.5]	5.7 [5.4- 6.1]	0.855
Preoperative Medications			
ACE/ARB* within 48 h	11 (4.7)	9 (3.9)	0.539
Beta Blockers within 2 weeks	134 (57.3)	140 (59.8)	0.532
Inotropes within 48 h	24 (10.3)	18 (7.7)	0.332
Lipid-lowering drugs within 24 h	141 (60.3)	131 (56.0)	0.547
Preoperative Cardiac Condition			
New York Heart Association Class			0.819
1&2:	185 (79.1)	187 (79.9)	
3&4:	49 (20.9)	47 (20.1)	
Left Ventricular Ejection Fraction (%)	58.0 [53.0-63.0]	58.0 [55.0-63.0]	0.117
Procedural Characteristics			
Surgical Type			0.821
Multi Valve	14 (6.0)	10 (4.3)	
Isolated CABG**	40 (17.1)	39 (16.7)	
Isolated Valve	73 (31.2)	78 (33.3)	

CABG + Valve**	43 (18.4)	49 (20.9)	
Aortic	64 (27.4)	58 (24.8)	
Cross Clamp Time (min)	67.0 [54.0-83.0]	64.0 [51.0-89.0]	0.580
Duration of Cardiopulmonary Bypass (min)	95.0 [80.0-126.0]	96.0 [73.0-126.0]	0.410
Lowest Temperature in Operating Room (°C)	31.7 [29.1-33.3]	31.8 [29.2-33.4]	0.490

*Angiotensin Converting Enzyme (ACE)/ Angiotensin Receptor Blockers (ARB)

**Coronary artery bypass grafting (CABG)

4.4 Postoperative Outcomes of Propensity Matched Sample

All analysis below refers to the 234 matched pairs only. No significant differences were seen regarding the primary outcome measures of death or death within 30 days. A statistically significant difference in incidence of cardiac arrest ($p<0.005$) was seen between the two groups, with a 5.6% greater incidence in the prehabilitated patients. There was a significant difference in prolonged mechanical ventilation ($p=0.023$) as well; while 33 patients in the control group experienced more than 24 hours of ventilation, 52 patients in the treatment group experienced the same (8.1% difference). Finally, there was a significant difference between groups regarding the total hours of mechanical ventilation ($p=0.008$). The median length in the control group was 4.8 hours compared to 5.8 hours in the treatment group. Furthermore, the variability of length (spread) was far greater in the treatment group as shown by the comparatively wide interquartile range.

Deep sternal infection, TIA, pulmonary thromboembolism, and deep vein thrombosis complications were not seen whatsoever in either group.

Table 4. Postoperative Outcomes of Sample Matched by Propensity Score

	Prehabilitated (N=234)	**Control (N=234)**	**P- Value**
Stroke	5 (2.1)	5 (2.1)	1
Sepsis	0 (0.0)	3 (1.3)	0.082
Deep Sternal Infection	0 (0.0)	0 (0.0)	.
Pneumonia	9 (3.9)	9 (3.9)	1
Renal Failure	11 (4.7)	7 (3.0)	0.336
Transient Ischemic Attack	0 (0.0)	0 (0.0)	.
Pulmonary Thromboembolism	0 (0.0)	0 (0.0)	.
Deep Vein Thrombosis	0 (0.0)	0 (0.0)	.
Cardiac Arrest	18 (7.7)	5 (2.1)	0.005
Atrial Fibrillation	64 (27.4)	73 (31.2)	0.361
Left Ventricular Ejection Fraction (%)	48.0 [29.0-53.0]	52.0 [35.0-58.0]	0.052
Prolonged Mechanical Ventilation (>24 h)	52 (22.2)	33 (14.1)	0.023

Total Mechanical Ventilation Duration (h)	5.8 [3.6-22.1]	4.8 [3.2- 9.8]	0.008
Readmission within 30 days	58 (24.8)	44 (18.8)	0.117
Death within 30 days	13 (5.6)	7 (3.0)	0.170
Death	20 (8.6)	12 (5.1)	0.143

5.0 Discussion

We investigated the association between prehabilitation prior to major cardiac surgery and postoperative outcomes with a retrospective cohort design among 234 propensity matched pairs. While no significant differences were seen in the primary mortality-based outcomes, the secondary outcomes involving non-fatal complications were better in patients undergoing the traditional surgical process specifically for cardiac arrest, prolonged mechanical ventilation, and total mechanical ventilation duration. Unexpectedly, our findings did not align with the initial hypothesis as patients in the prehabilitated group had statistically significant higher incidences of complications compared to their control counterparts.

To date, and to our knowledge, there has been no other published study that has explored a multimodal form of prehabilitation amongst major cardiac surgical patients in the US. Thus, the study results are unique and not directly comparable to any of the existing literature. However, two studies have explored multimodal intervention in cardiac surgery internationally.

The pilot Heart-ROCQ program was implemented in a university medical center in the Netherlands and consisted of 3 weekly prehabilitation visits for at least 3 weeks prior to surgery. The intervention consisted of aerobic cycling, strength training, IMT, psychological guidance, dietary advice and a non-smoking consultancy. However, the program also included a clinical inpatient rehabilitation phase following discharge which may affect the outcomes as well. The retrospective study utilized propensity score matching and examined 91 prehabilitated patients with 3 matched control cases per patient. The self-described explorative study examined several postoperative complications, but only found a significant difference in incidence of atrial fibrillation between the two groups (14.3% control vs 25.3% treatment)[61]. Our study results

differed as atrial fibrillation incidence was not significantly different between groups. This difference in results can be explained by the variance in prehabilitation (3 week minimum, lack of optimization of comorbidities such as diabetes, anemia, etc.), the post operative in-patient rehabilitation element of the intervention, and general medical protocol differences between the US and the Netherlands. Furthermore, the rather small sample size of the study as well as the fact that patients in each group were referred from different hospitals may affect the validity of the results.

The second multimodal study based in Spain self-described as a pilot interventional study and consisted of a 45-day intervention period during which patients underwent a supervised exercise training program, breathing incentive exercises, nutritional support and mindfulness training. This study utilized functional capacity measures (six-minute walking test, and chair test) as well as the Yale physical activity questionnaire in order to evaluate the program. While the study saw significant improvements in the 45-day period prior to surgery in the treatment group[60], the outcome measures are very distinct from the postsurgical outcome measures pursued by our study and thus are not comparable. Furthermore, once again this study does not include the optimization of certain key comorbidities prior to surgery and may reflect procedural medical differences between different countries.

It is important to note that our study has a few key limitations. First, the study only examines patients from a single center in a retrospective manner. The study also suffers from having only roughly 34% female patients and just 5% of all procedures are multivalve procedures indicating that the results may not be generalizable. Race was also not examined or matched on and may be an additional confounding factor. One key confounder that was not accounted for is the length of optimization underwent by each patient. While the CPC recommends 3-6 weeks of

preoptimization, there was huge variation amongst patients regarding when optimization began, ranging anywhere from the day prior to surgery to even 9 months prior. Another key confounder that was not explored is the exact surgeon who performed the procedures. As the program is optional and surgeon referred, there is a significant amount of variability that can be introduced as a result of surgeon preference in the preoperative phase as well as in the operation itself depending on provider specific historical success rates for different procedures. Finally, the specific anesthesiologist or preoperative care provider for CPC appointments could be another important confounder that the analysis did not account for. Though the intervention utilizes clear and clinically relevant benchmarks for optimization, there is still a substantial amount of room for provider preference, judgement, and modification of the intervention during each visit. Though the matched analysis accounts for several possible confounders, several other unmeasured confounding factors could exist beyond even those explicitly discussed above. Furthermore, it is possible that sick patients are more often referred for prehabilitation and the degree of sickness is not measured adequately by statistical means.

However, there are several notable strengths to our study. First, the unique intervention expands the scope of prehabilitation beyond any previous studies by including perioperative optimization of risk factors other than solely nutritional status, exercise, pulmonary capacity, and mental health. Outcome measures are not self-reported and were pulled directly from an established and trustworthy database (STS ACSD). Finally, the retrospective cohort study utilized a large population size (compared to other similar studies) with appropriate exclusions, and propensity matching ensured no significant baseline differences existed amongst the two groups for the preoperative and operative variables examined in the study.

In conclusion, our study shows that multimodal prehabilitation prior to major cardiac surgery is not associated with improvement in post-surgical mortality and complications. Our findings, though not comparable to current literature, dissent from the consensus that prehabilitation results in equivalent or better outcomes after surgery[69]. However, the impact of multimodal interventions amongst cardiac candidates is not yet known due to a paucity of studies[69] and this study begins to fill that gap in the literature. By utilizing the first ever cardiac prehabilitation intervention to optimize novel and unique comorbidities this study also expands the scope of prehabilitation at large. Future steps to further improve this study include controlling for historical surgical success rates of each surgeon, matching on perioperative care provider, stratifying by length of optimization, and including race in the baseline characteristic analysis. For future studies, prehabilitation protocols should be clarified and standardized further in order to limit confounders and eventually randomized clinical trials should be pursued in order to truly understand the impact of multimodal prehabilitation interventions on major cardiac surgical patients. The use of prehabilitation, and especially multimodal prehabilitation, is a somewhat novel intervention whose public health impact is not yet thoroughly known; this study offers further clarity regarding its potential value and impact on patient outcomes and health.

Appendix A Risk Factor Optimization Clinical Pathways

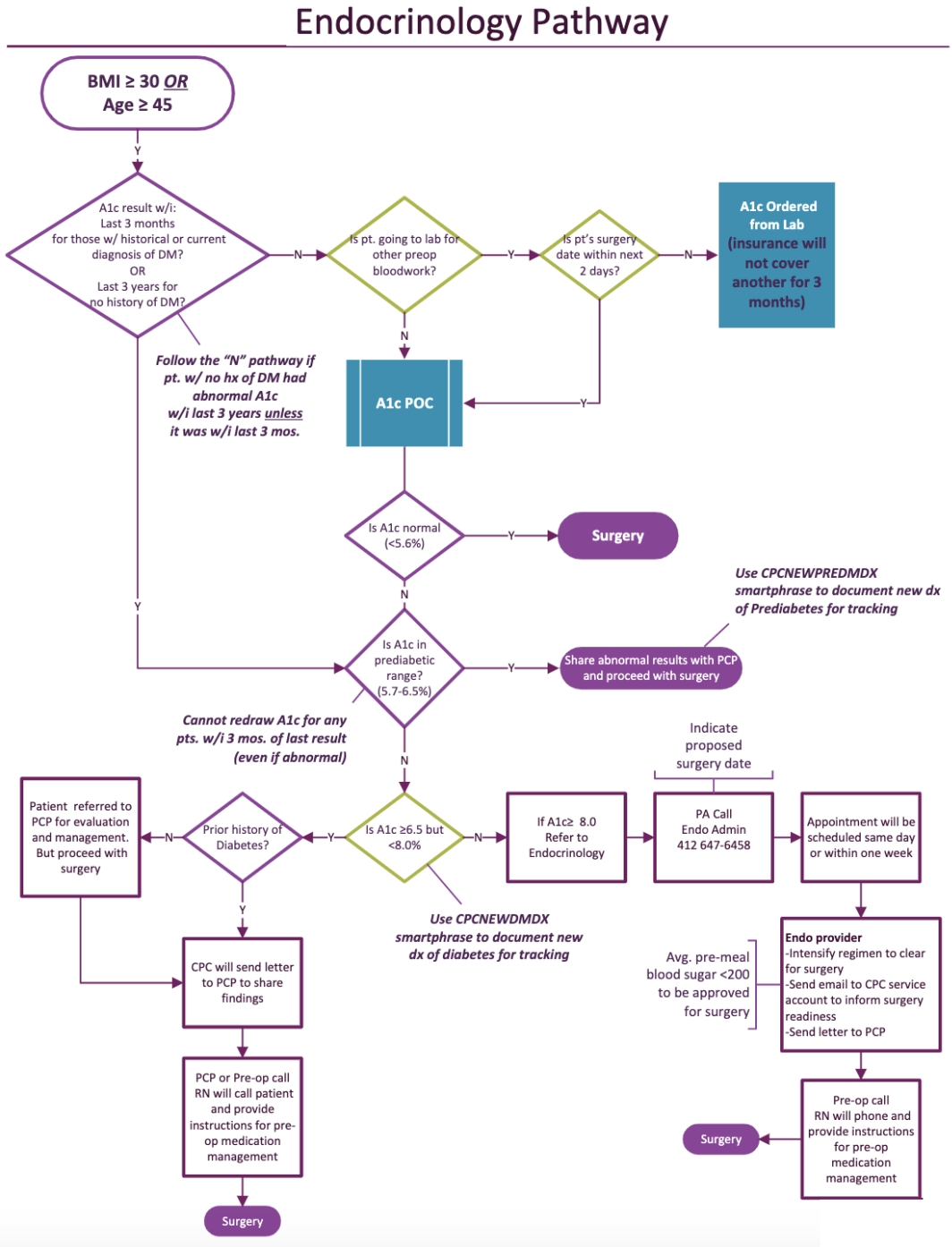

Figure 3. Endocrinology Clinical Evaluation and Optimization Pathway

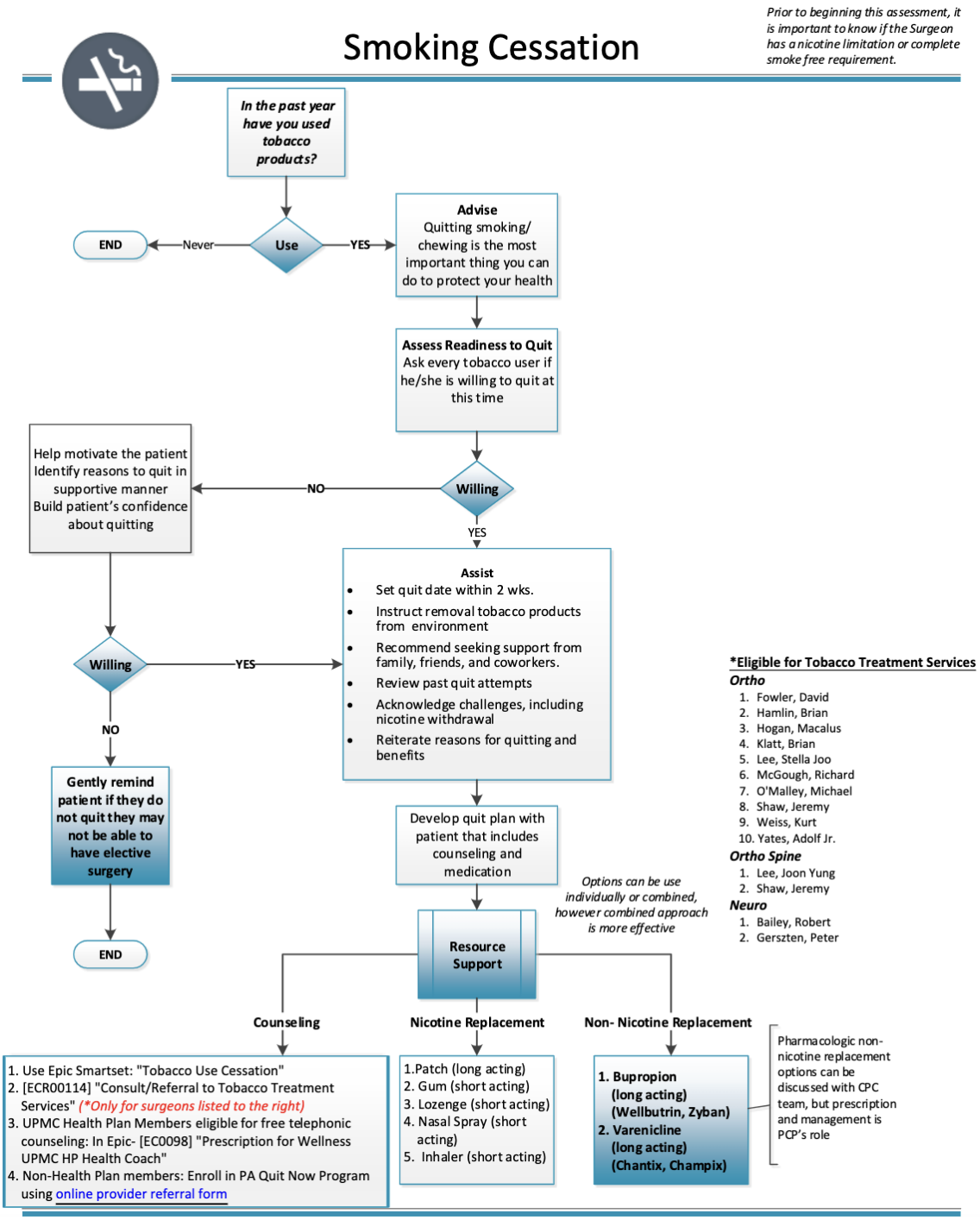

Figure 4. Smoking Cessation Clinical Evaluation and Optimization Pathway

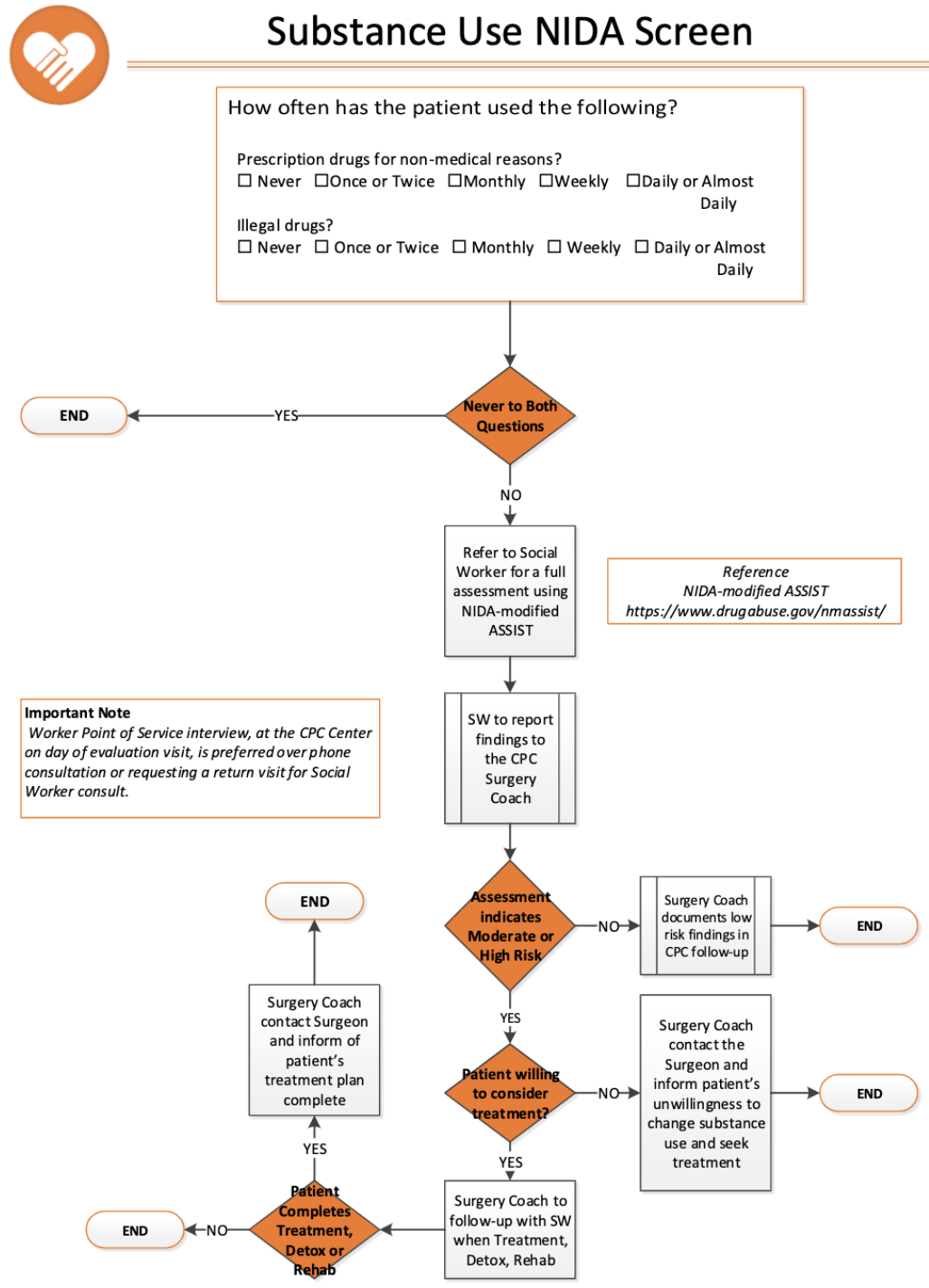

Figure 5. Substance Use Clinical Evaluation and Optimization Pathway

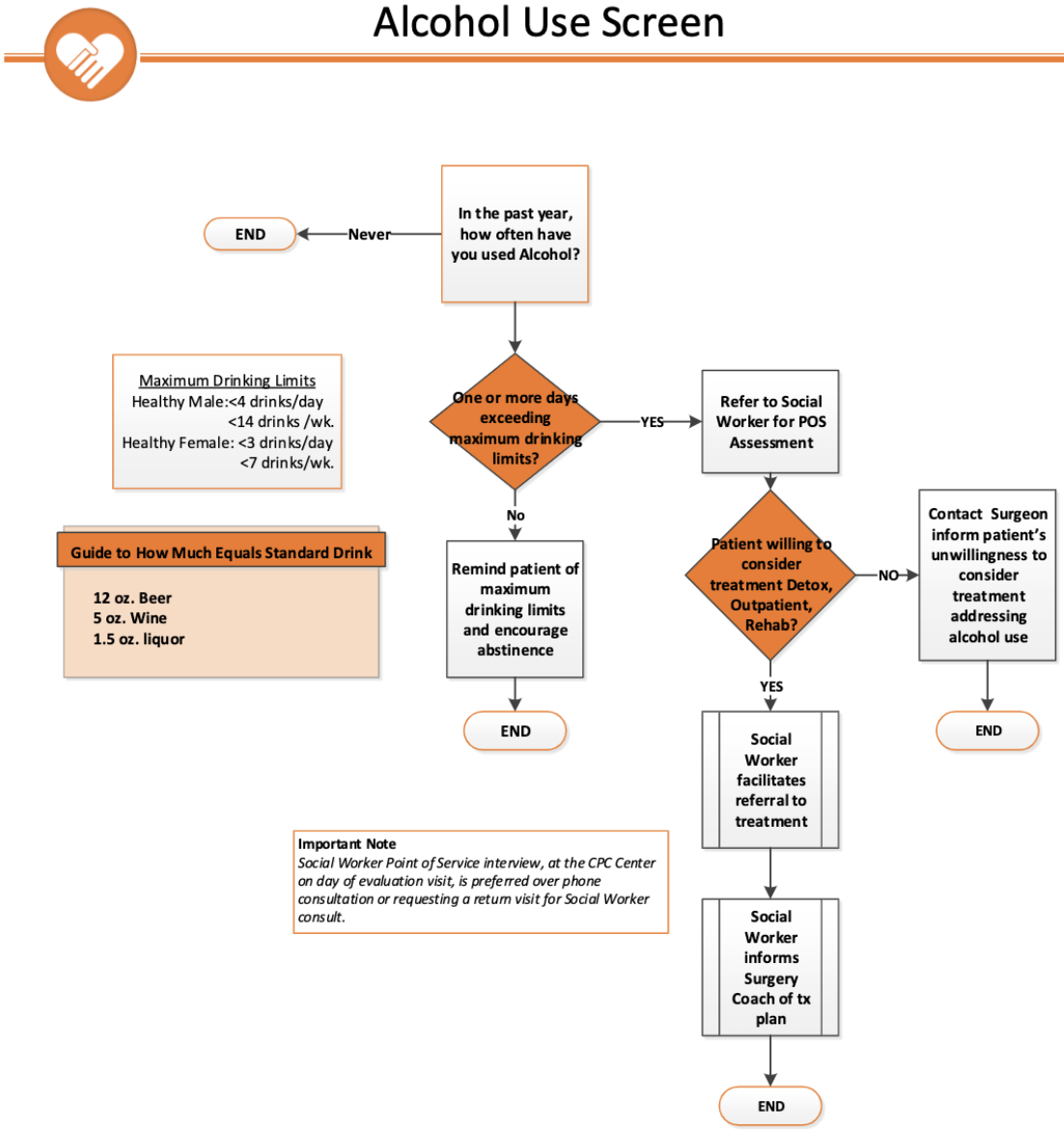

Figure 6. Alcohol Use Clinical Evaluation and Optimization Pathway

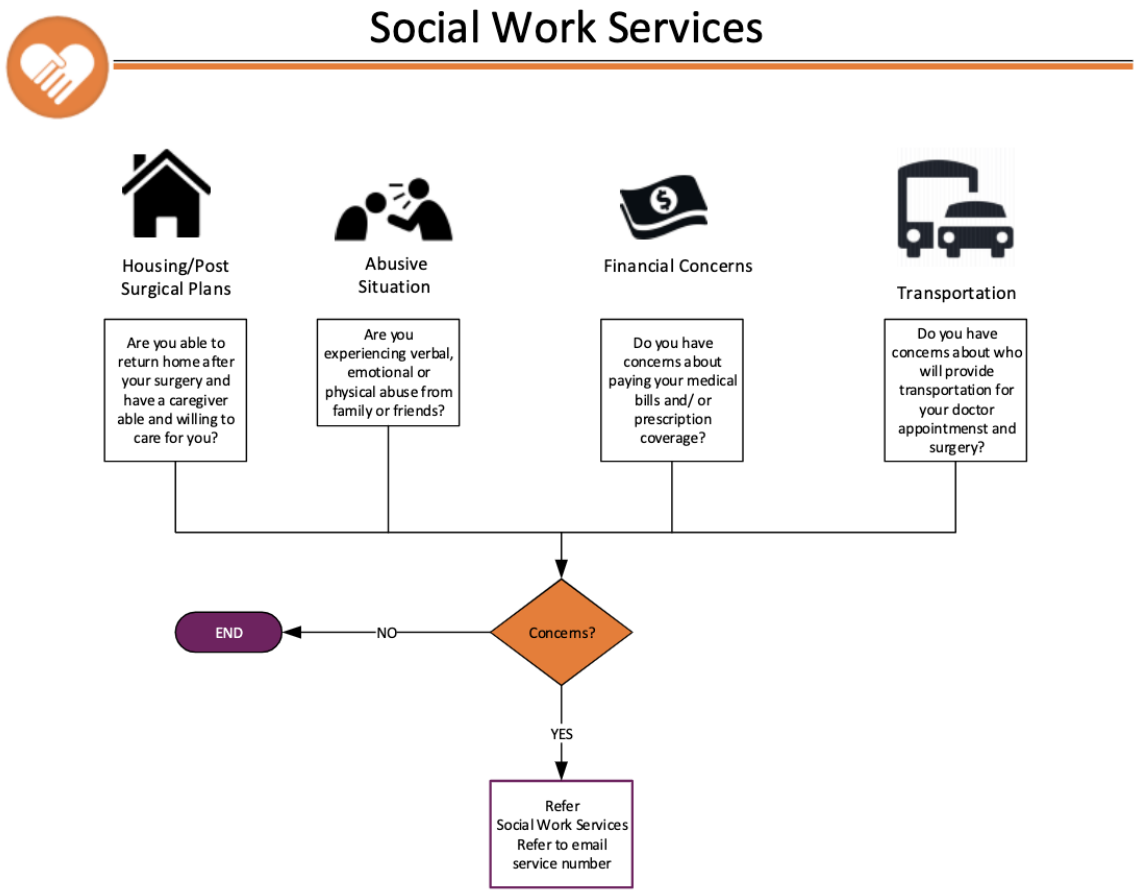

Figure 7. Social Work Needs Evaluation and Optimization Pathway

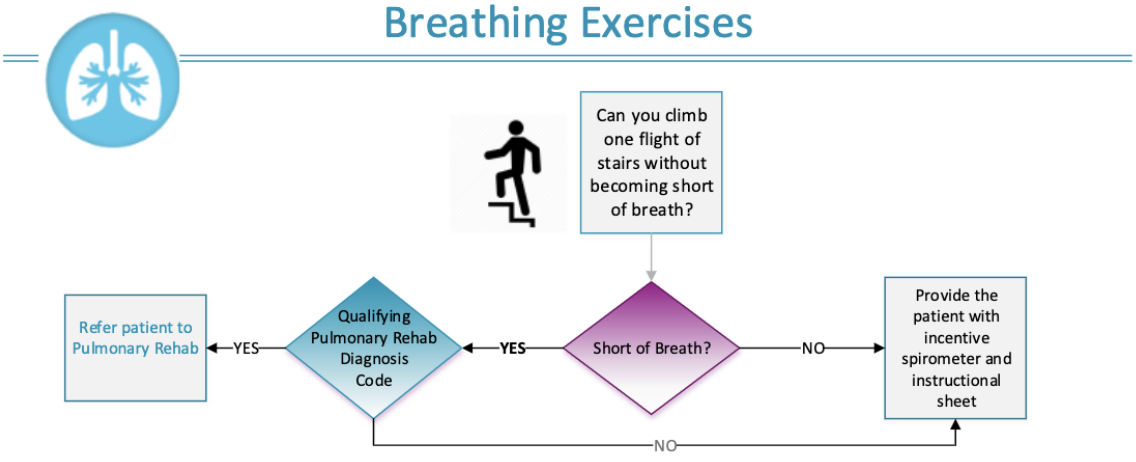

Figure 8. Pulmonary Clinical Evaluation and Optimization Pathway

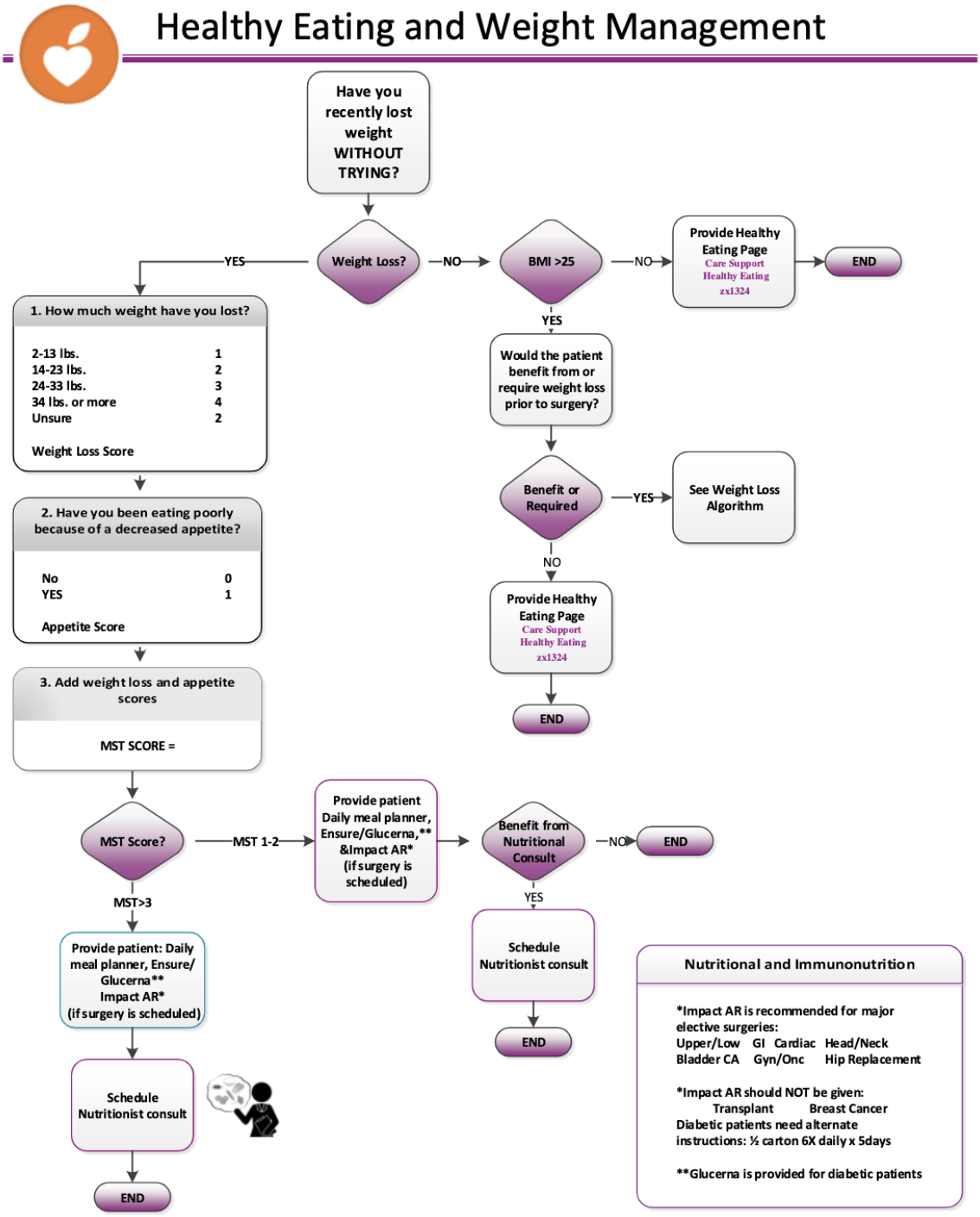

Figure 9. Nutrition Evaluation and Optimization Pathway

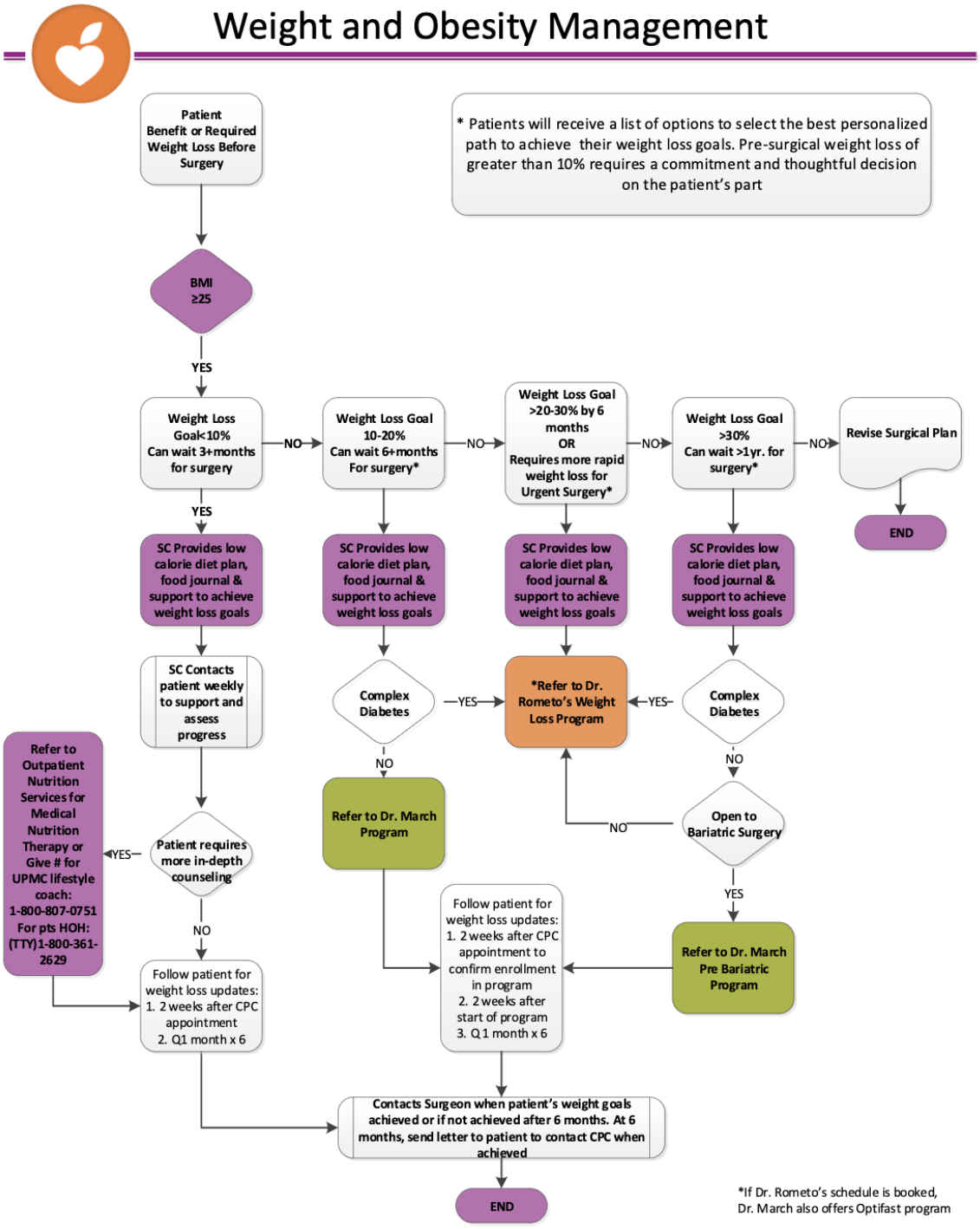

Figure 10. Obesity Clinical Evaluation and Optimization Pathway

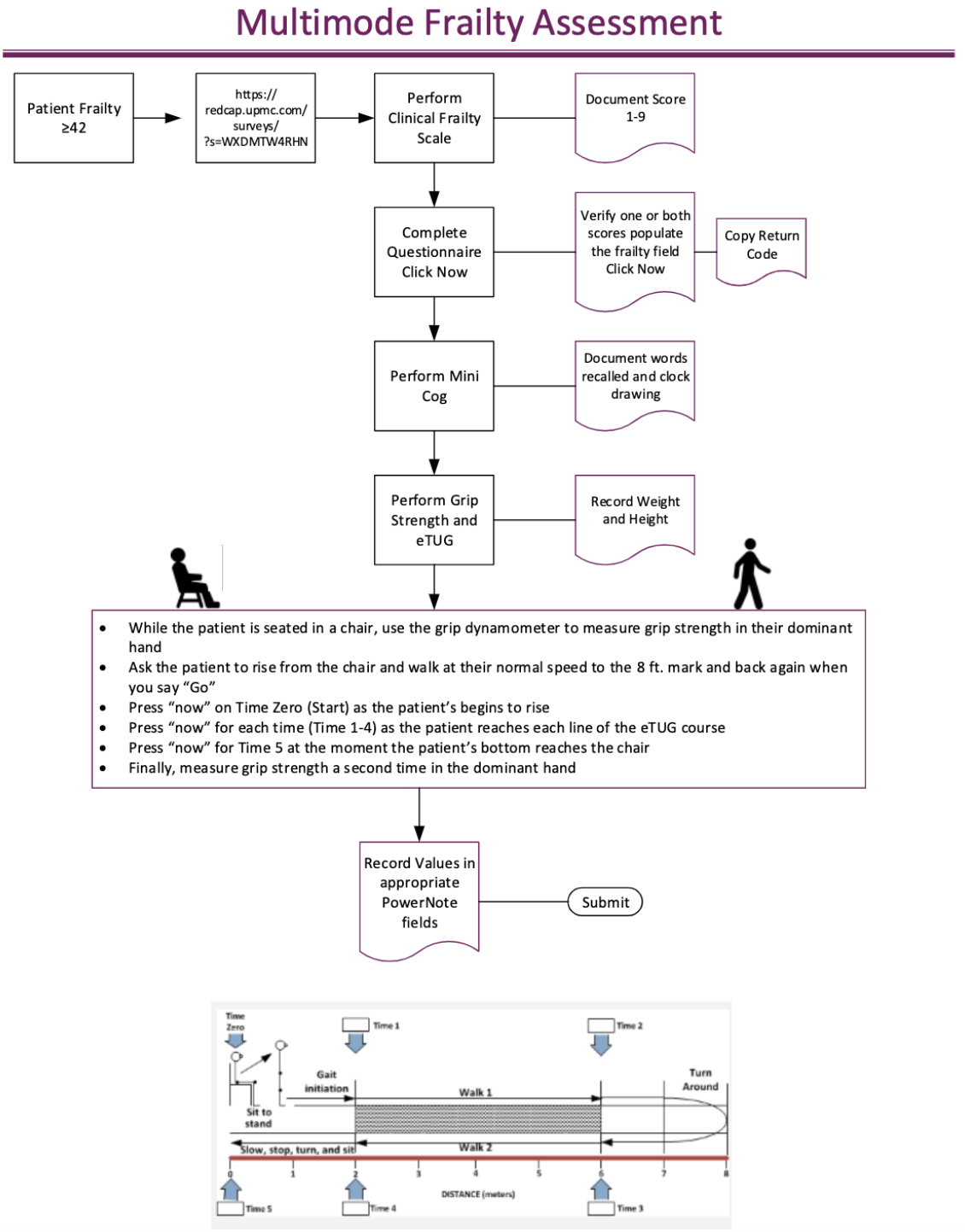

Figure 11. Frailty Clinical Evaluation and Optimization Pathway

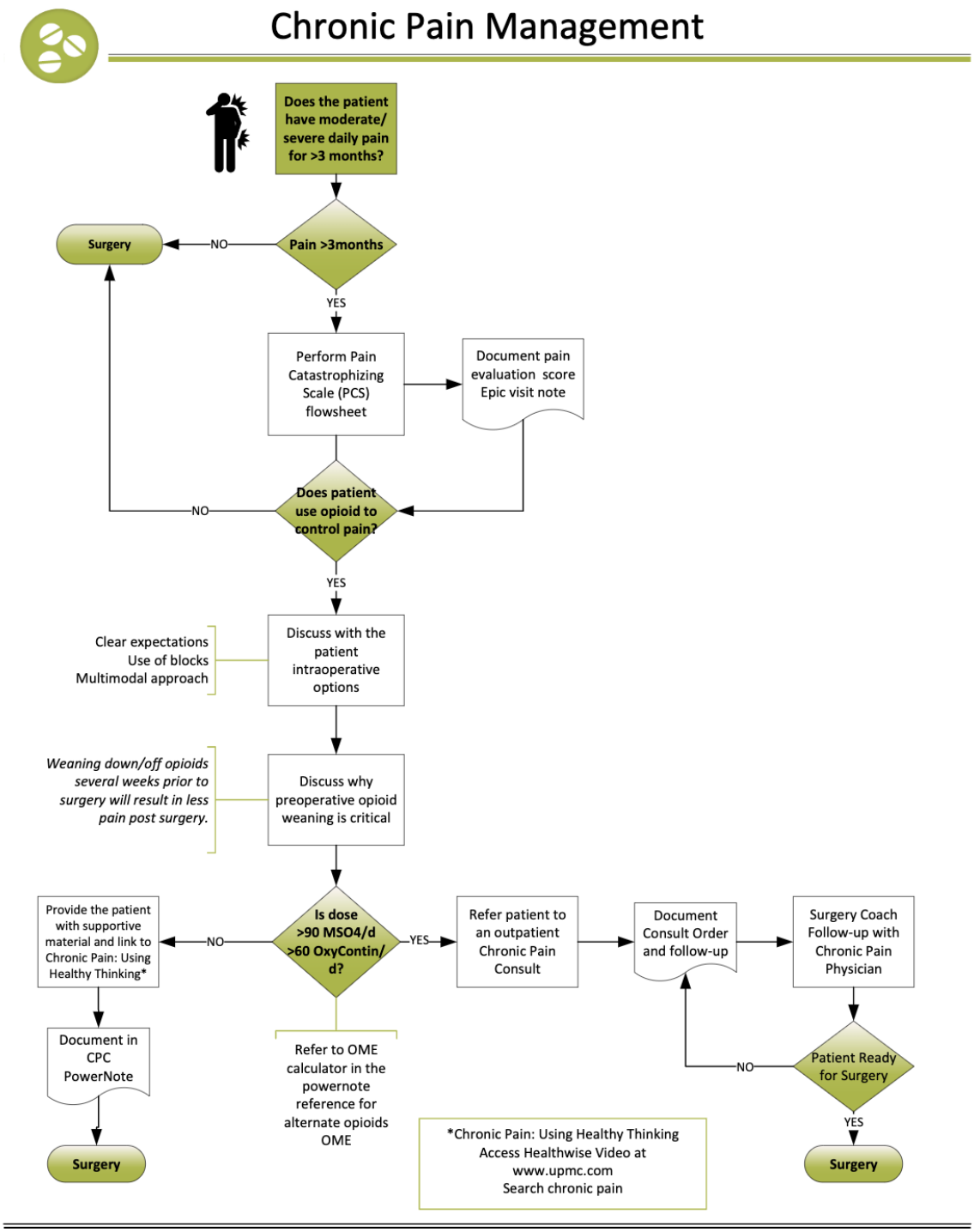

Figure 12. Chronic Pain Clinical Evaluation and Optimization Pathway

Bibliography

1. ElBardissi, A. W., Aranki, S. F., Sheng, S., O'Brien, S. M., Greenberg, C. C., & Gammie, J. S. (2012). Trends in isolated coronary artery bypass grafting: An analysis of the society of thoracic surgeons adult cardiac surgery database. *The Journal of Thoracic and Cardiovascular Surgery*, *143*(2), 273-281.https://doi.org/10.1016/j.jtcvs.2011.10.029

2. Kim, K. M., Arghami, A., Habib, R., Daneshmand, M. A., Parsons, N., Elhalabi, Z., Krohn, C., Thourani, V., & Bowdish, M. E. (2023). The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2022 update on outcomes and research. *The Annals of Thoracic Surgery*, *115*(3), 566–574. https://doi.org/10.1016/j.athoracsur.2022.12.033

3. Tsao, C. W., Aday, A. W., Almarzooq, Z. I., Alonso, A., Beaton, A. Z., Bittencourt, M. S., Boehme, A. K., Buxton, A. E., Carson, A. P., Commodore-Mensah, Y., Elkind, M. S. V., Evenson, K. R., Eze-Nliam, C., Ferguson, J. F., Generoso, G., Ho, J. E., Kalani, R., Khan, S. S., Kissela, B. M., … Martin, S. S. (2022). Heart disease and stroke statistics—2022 update: A report from the American Heart Association. *Circulation*, *145*(8). https://doi.org/10.1161/cir.0000000000001052

4. Centers for Disease Control and Prevention. (2022, October 14). *Heart disease facts*. Centers for Disease Control and Prevention. Retrieved April 18, 2023, from https://www.cdc.gov/heartdisease/facts.htm

5. Enumah, Z. O., Canner, J. K., Alejo, D., Warren, D. S., Zhou, X., Yenokyan, G., Matthew, T., Lawton, J. S., & Higgins, R. S. (2020). Persistent racial and sex disparities in outcomes after coronary artery bypass surgery. *Annals of Surgery*, *272*(4), 660–667. https://doi.org/10.1097/sla.0000000000004335

6. Rangrass, G., Ghaferi, A. A., & Dimick, J. B. (2014). Explaining racial disparities in outcomes after cardiac surgery. *JAMA Surgery*, *149*(3), 223. https://doi.org/10.1001/jamasurg.2013.4041
7. Bechtel, A. J., & Huffmyer, J. L. (2020). Gender differences in postoperative outcomes after cardiac surgery. *Anesthesiology Clinics*, *38*(2), 403–415. https://doi.org/10.1016/j.anclin.2020.01.007

8. Matyal R, Qureshi NQ, Mufarrih SH, Sharkey A, Bose R, Chu LM, Liu DC, Senthilnathan V, Mahmood F, Khabbaz KR. Update: Gender differences in CABG outcomes-Have we bridged the gap? PLoS One. 2021 Sep 15;16(9):e0255170. doi: 10.1371/journal.pone.0255170.

9. Alexander, K. P., Anstrom, K. J., Muhlbaier, L. H., Grosswald, R. D., Smith, P. K., Jones, R. H., & Peterson, E. D. (2000). Outcomes of cardiac surgery in patients age ≥80 years:

Results from the National Cardiovascular Network. *Journal of the American College of Cardiology*, *35*(3), 731–738. https://doi.org/10.1016/s0735-1097(99)00606-3

10. Raja, S. G., Shah, J., Navaratnarajah, M., Amin, F., & Amrani, M. (2013). Outcomes and predictors of mortality and stroke after on-pump and off-pump coronary artery bypass surgery in Octogenarians. *Innovations: Technology and Techniques in Cardiothoracic and Vascular Surgery*, *8*(4), 269–275. https://doi.org/10.1097/imi.0000000000000000

11. Nicolini, F., Fortuna, D., Contini, G. A., Pacini, D., Gabbieri, D., Zussa, C., De Palma, R., Vezzani, A., & Gherli, T. (2017). The impact of age on clinical outcomes of coronary artery bypass grafting: Long-term results of a real-world registry. *BioMed Research International*, *2017*, 1–11. https://doi.org/10.1155/2017/9829487

12. Lemaire, A., Soto, C., Salgueiro, L., Ikegami, H., Russo, M. J., & Lee, L. Y. (2020). The impact of age on outcomes of coronary artery bypass grafting. *Journal of Cardiothoracic Surgery*, *15*(1). https://doi.org/10.1186/s13019-020-01201-3

13. Knight, J. B., Subramanian, H., Sultan, I., Kaczorowski, D. J., & Subramaniam, K. (2022). Prehabilitation of cardiac surgical patients, part 1: Anemia, diabetes mellitus, obesity, sleep apnea, and cardiac rehabilitation. *Seminars in Cardiothoracic and Vascular Anesthesia*, *26*(4), 282–294. https://doi.org/10.1177/10892532221121118

14. World Health Organization. (n.d.). *Anaemia*. World Health Organization. Retrieved April 18, 2023, from https://www.who.int/data/nutrition/nlis/info/anaemia

15. Muñoz, M., Laso-Morales, M. J., Gómez-Ramírez, S., Cadellas, M., Núñez-Matas, M. J., & García-Erce, J. A. (2017). Pre-operative haemoglobin levels and iron status in a large multicentre cohort of patients undergoing major elective surgery. *Anaesthesia*, *72*(7), 826–834. https://doi.org/10.1111/anae.13840

16. Miceli, A., Romeo, F., Glauber, M., de Siena, P. M., Caputo, M., & Angelini, G. D. (2014). Preoperative anemia increases mortality and postoperative morbidity after cardiac surgery. *Journal of Cardiothoracic Surgery*, *9*(1). https://doi.org/10.1186/1749-8090-9 137

17. Fowler, A. J., Ahmad, T., Phull, M. K., Allard, S., Gillies, M. A., & Pearse, R. M. (2015). Meta-analysis of the association between preoperative anaemia and mortality after surgery. *British Journal of Surgery*, *102*(11), 1314–1324. https://doi.org/10.1002/bjs.9861

18. Gómez-Ramirez, S., Jericó, C., & Muñoz, M. (2019). Perioperative anemia: Prevalence, consequences and pathophysiology. *Transfusion and Apheresis Science*, *58*(4), 369–374. https://doi.org/10.1016/j.transci.2019.06.011

19. Loor, G., Rajeswaran, J., Li, L., Sabik, J. F., Blackstone, E. H., McCrae, K. R., & Koch, C. G. (2013). The least of 3 evils: Exposure to red blood cell transfusion, anemia, or both? *The*

Journal of Thoracic and Cardiovascular Surgery, *146*(6). https://doi.org/10.1016/j.jtcvs.2013.06.033

20. von Heymann, C., Kaufner, L., Sander, M., Spies, C., Schmidt, K., Gombotz, H., Wernecke, K.-D., & Balzer, F. (2016). Does the severity of preoperative anemia or blood transfusion have a stronger impact on long-term survival after cardiac surgery? *The Journal of Thoracic and Cardiovascular Surgery*, *152*(5), 1412–1420. https://doi.org/10.1016/j.jtcvs.2016.06.010

21. Muñoz, M., Gómez-Ramírez, S., Kozek-Langeneker, S., Shander, A., Richards, T., Pavía, J., Kehlet, H., Acheson, A. G., Evans, C., Raobaikady, R., Javidroozi, M., & Auerbach, M. (2015). 'fit to fly': Overcoming barriers to preoperative haemoglobin optimization in surgical patients. *British Journal of Anaesthesia*, *115*(1), 15–24. https://doi.org/10.1093/bja/aev165

22. Murphy, G. J., Reeves, B. C., Rogers, C. A., Rizvi, S. I. A., Culliford, L., & Angelini, G. D. (2007). Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation*, *116*(22), 2544–2552. https://doi.org/10.1161/circulationaha.107.698977

23. Tinegate, H., Pendry, K., Murphy, M., Babra, P., Grant-Casey, J., Hopkinson, C., Hyare, J., Rowley, M., Seeney, F., Watson, D., & Wallis, J. (2015). Where do all the red blood cells (rbcs) go? results of a survey of RBC use in England and North Wales in 2014. *Transfusion*, *56*(1), 139–145. https://doi.org/10.1111/trf.13342

24. Robich, M. P., Koch, C. G., Johnston, D. R., Schiltz, N., Chandran Pillai, A., Hussain, S. T., & Soltesz, E. G. (2014). Trends in blood utilization in United States Cardiac Surgical Patients. *Transfusion*, *55*(4), 805–814. https://doi.org/10.1111/trf.12903

25. Meybohm, P., Westphal, S., Ravn, H. B., Ranucci, M., Agarwal, S., Choorapoikayil, S., Spahn, D. R., Ahmed, A. B., Froessler, B., & Zacharowski, K. (2020). Perioperative anemia management as part of PBM in cardiac surgery – A narrative updated review. *Journal of Cardiothoracic and Vascular Anesthesia*, *34*(4), 1060–1073. https://doi.org/10.1053/j.jvca.2019.06.047

26. Klein, A. A., Chau, M., Yeates, J. A., Collier, T., Evans, C., Agarwal, S., & Richards, T. (2020). Preoperative intravenous iron before cardiac surgery: A prospective multicentre feasibility study. *British Journal of Anaesthesia*, *124*(3), 243–250. https://doi.org/10.1016/j.bja.2019.11.023

27. Shin, H. J., Ko, E., Jun, I., Kim, H. J., & Lim, C. H. (2022). Effects of perioperative erythropoietin administration on acute kidney injury and red blood cell transfusion in patients undergoing cardiac surgery. *Medicine*, *101*(9). https://doi.org/10.1097/md.0000000000028920

28. Sherwani, S. I., Khan, H. A., Ekhzaimy, A., Masood, A., & Sakharkar, M. K. (2016). Significance of hba1c test in diagnosis and prognosis of diabetic patients. *Biomarker Insights*, *11*. https://doi.org/10.4137/bmi.s38440

29. American Diabetes Association; 2. Classification and Diagnosis of Diabetes. *Diabetes Care*1 January 2015; 38 (Supplement_1): S8–S16. https://doi.org/10.2337/dc15-S005

30. Whang, W., & Bigger, J. T. (2000). Diabetes and outcomes of coronary artery bypass graft surgery in patients with severe left ventricular dysfunction: Results from the CABG Patch Trial Database. *Journal of the American College of Cardiology*, *36*(4), 1166–1172. https://doi.org/10.1016/s0735-1097(00)00823-8

31. Halkos, M. E., Puskas, J. D., Lattouf, O. M., Kilgo, P., Kerendi, F., Song, H. K., Guyton, R. A., & Thourani, V. H. (2008). Elevated preoperative hemoglobin A1C level is predictive of adverse events after coronary artery bypass surgery. *The Journal of Thoracic and Cardiovascular Surgery*, *136*(3), 631–640. https://doi.org/10.1016/j.jtcvs.2008.02.091

32. Fihn, S. D., Gardin, J. M., Abrams, J., Berra, K., Blankenship, J. C., Dallas, A. P., Douglas, P. S., Foody, J. A. M., Gerber, T. C., Hinderliter, A. L., King, S. B., Kligfield, P. D., Krumholz, H. M., Kwong, R. Y. K., Lim, M. J., Linderbaum, J. A., Mack, M. J., Munger, M. A., Prager, R. L., … Williams, S. V. (2012). 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. *Journal of the American College of Cardiology*, *60*(24). https://doi.org/10.1016/j.jacc.2012.07.013

33. Patel, V. C., Aldridge, R. D., Leeds, A., Dornhorst, A., & Frost, G. S. (2004). Retrospective analysis of the impact of a low glycaemic index diet on hospital stay following coronary artery bypass grafting: A hypothesis. *Journal of Human Nutrition and Dietetics*, *17*(3), 241–247. https://doi.org/10.1111/j.1365-277x.2004.00519.x
34. Preiser, J.-C., Provenzano, B., Mongkolpun, W., Halenarova, K., & Cnop, M. (2020). Perioperative management of oral glucose-lowering drugs in the patient with type 2 diabetes. *Anesthesiology*, *133*(2), 430–438. https://doi.org/10.1097/aln.0000000000003237

35. Sudhakaran, S., & Surani, S. R. (2015). Guidelines for perioperative management of the Diabetic patient. *Surgery Research and Practice*, *2015*, 1–8. https://doi.org/10.1155/2015/284063

36. Munnee, K., Bundhun, P. K., Quan, H., & Tang, Z. (2016). Comparing the clinical outcomes between insulin-treated and non-insulin-treated patients with type 2 diabetes mellitus after coronary artery bypass surgery. *Medicine*, *95*(10). https://doi.org/10.1097/md.0000000000003006

37. Nagappa, M., Liao, P., Wong, J., Auckley, D., Ramachandran, S. K., Memtsoudis, S., Mokhlesi, B., & Chung, F. (2015). Validation of the stop-bang questionnaire as a screening

tool for obstructive sleep apnea among different populations: A systematic review and meta-analysis. *PLOS ONE*, *10*(12). https://doi.org/10.1371/journal.pone.0143697

38. Foldvary-Schaefer, N., Kaw, R., Collop, N., Andrews, N. D., Bena, J., Wang, L., Stierer, T., Gillinov, M., Tarler, M., & Kayyali, H. (2015). Prevalence of undetected sleep apnea in patients undergoing cardiovascular surgery and impact on postoperative outcomes. *Journal of Clinical Sleep Medicine*, *11*(10), 1083–1089. https://doi.org/10.5664/jcsm.5076

39. Nagappa, M., Ho, G., Patra, J., Wong, J., Singh, M., Kaw, R., Cheng, D., & Chung, F. (2017). Postoperative outcomes in obstructive sleep apnea patients undergoing cardiac surgery. *Anesthesia & Analgesia*, *125*(6), 2030–2037. https://doi.org/10.1213/ane.0000000000002558

40. Gottlieb, D. J., & Punjabi, N. M. (2020). Diagnosis and management of obstructive sleep apnea. *JAMA*, *323*(14), 1389. https://doi.org/10.1001/jama.2020.3514

41. Peppard, P. E. (2000). Longitudinal Study of moderate weight change and sleep disordered breathing. *JAMA*, *284*(23), 3015. https://doi.org/10.1001/jama.284.23.3015

42. Wong, J. K., Mariano, E. R., Doufas, A. G., Olejniczak, M. J., & Kushida, C. A. (2017). Preoperative treatment of obstructive sleep apnea with positive airway pressure is associated with decreased incidence of atrial fibrillation after cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia*, *31*(4), 1250–1256. https://doi.org/10.1053/j.jvca.2016.11.016

43. Singh, M., Liao, P., Kobah, S., Wijeysundera, D. N., Shapiro, C., & Chung, F. (2013). Proportion of surgical patients with undiagnosed obstructive sleep apnoea. *British Journal of Anaesthesia*, *110*(4), 629–636. https://doi.org/10.1093/bja/aes465

44. Howard, R., Singh, K., & Englesbe, M. (2021). Prevalence and trends in smoking among surgical patients in Michigan, 2012-2019. *JAMA Network Open*, *4*(3). https://doi.org/10.1001/jamanetworkopen.2021.0553

45. Jones, R., Nyawo, B., Jamieson, S., & Clark, S. (2011). Current smoking predicts increased operative mortality and morbidity after cardiac surgery in the elderly☆. *Interactive CardioVascular and Thoracic Surgery*, *12*(3), 449–453. https://doi.org/10.1510/icvts.2010.239863

46. Yousefzadeh, A., Chung, F., Wong, D. T., Warner, D. O., & Wong, J. (2016). Smoking cessation. *Anesthesia & Analgesia*, *122*(5), 1311–1320. https://doi.org/10.1213/ane.0000000000001170

47. Nolan, M. B., & Warner, D. O. (2015). Safety and efficacy of nicotine replacement therapy in the perioperative period: A narrative review. *Mayo Clinic Proceedings*, *90*(11), 1553–1561. https://doi.org/10.1016/j.mayocp.2015.08.003

48. Kip, M. J., Neumann, T., Jugel, C., Kleinwaechter, R., Weiss-Gerlach, E., Guill, M. M., & Spies, C. D. (2008). New strategies to detect alcohol use disorders in the preoperative assessment clinic of a German University Hospital. *Anesthesiology*, *109*(2), 171–179. https://doi.org/10.1097/aln.0b013e31817f5be3

49. Rubinsky, A. D., Bishop, M. J., Maynard, C., Henderson, W. G., Hawn, M. T., Harris, A. H. S., Beste, L. A., Tønnesen, H., & Bradley, K. A. (2013). Postoperative risks associated with alcohol screening depend on documented drinking at the time of surgery. *Drug and Alcohol Dependence*, *132*(3), 521–527. https://doi.org/10.1016/j.drugalcdep.2013.03.022

50. Egholm, J. W. M., Pedersen, B., Møller, A. M., Adami, J., Juhl, C. B., & Tønnesen, H. (2018). Perioperative alcohol cessation intervention for postoperative complications. *Cochrane Database of Systematic Reviews*, *2018*(11). https://doi.org/10.1002/14651858.cd008343.pub3

51. Zhao, H., Li, L., Yang, G., Gong, J., Ye, L., Zhi, S., Zhang, X., & Li, J. (2019). Postoperative outcomes of patients with chronic obstructive pulmonary disease undergoing coronary artery bypass grafting surgery. *Medicine*, *98*(6). https://doi.org/10.1097/md.0000000000014388

52. O'Boyle, F., Mediratta, N., Chalmers, J., Al-Rawi, O., Mohan, K., Shaw, M., & Poullis, M. (2012). Long-term survival of patients with pulmonary disease undergoing coronary artery bypass surgery. *European Journal of Cardio-Thoracic Surgery*, *43*(4), 697–703. https://doi.org/10.1093/ejcts/ezs454

53. den Harder, A. M., de Heer, L. M., de Jong, P. A., Suyker, W. J., Leiner, T., & Budde, R. P. J. (2018). Frequency of abnormal findings on routine chest radiography before cardiac surgery. *The Journal of Thoracic and Cardiovascular Surgery*, *155*(5), 2035–2040. https://doi.org/10.1016/j.jtcvs.2017.12.124

54. Adabag, A. S., Wassif, H. S., Rice, K., Mithani, S., Johnson, D., Bonawitz-Conlin, J., Ward, H. B., McFalls, E. O., Kuskowski, M. A., & Kelly, R. F. (2010). Preoperative pulmonary function and mortality after cardiac surgery. *American Heart Journal*, *159*(4), 691–697. https://doi.org/10.1016/j.ahj.2009.12.039

55. Sweity, E. M., Alkaissi, A. A., Othman, W., & Salahat, A. (2021). Preoperative incentive spirometry for preventing postoperative pulmonary complications in patients undergoing coronary artery bypass graft surgery: A prospective, randomized controlled trial. *Journal of Cardiothoracic Surgery*, *16*(1). https://doi.org/10.1186/s13019-021-01628-2

56. Katsura, M., Kuriyama, A., Takeshima, T., Fukuhara, S., & Furukawa, T. A. (2015). Preoperative inspiratory muscle training for postoperative pulmonary complications in adults undergoing cardiac and major abdominal surgery. *Cochrane Database of Systematic Reviews*, *2015*(10). https://doi.org/10.1002/14651858.cd010356.pub2

57. Gillis, C., Ljungqvist, O., & Carli, F. (2022). Prehabilitation, enhanced recovery after surgery, or both? A narrative review. *British Journal of Anaesthesia*, *128*(3), 434–448. https://doi.org/10.1016/j.bja.2021.12.007

58. McIsaac, D. I., Gill, M., Boland, L., Hutton, B., Branje, K., Shaw, J., Grudzinski, A. L., Barone, N., Gillis, C., Akhtar, S., Atkins, M., Aucoin, S., Auer, R., Basualdo-Hammond, C., Beaule, P., Brindle, M., Bittner, H., Bryson, G., Carli, F., … Wijeysundera, D. (2022). Prehabilitation in adult patients undergoing surgery: An Umbrella Review of Systematic Reviews. *British Journal of Anaesthesia*, *128*(2), 244–257. https://doi.org/10.1016/j.bja.2021.11.014

59. Zheng, Y.-T., & Zhang, J.-X. (2020). Preoperative exercise and recovery after cardiac surgery: A meta-analysis. *BMC Cardiovascular Disorders*, *20*(1). https://doi.org/10.1186/s12872-019-01308-z

60. López-Hernández, A., Arguis, M. J., Gimeno-Santos, E., Navarro, R., Coca-Martínez, M., & Martínez-Pallí, G. (2023). Feasibility and effects of prehabilitation in cardiac surgery. preliminary study. *Revista Española De Anestesiología y Reanimación (English Edition)*. https://doi.org/10.1016/j.redare.2022.01.009

61. Hartog, J., Mousavi, I., Dijkstra, S., Fleer, J., van der Woude, L. H., van der Harst, P., & Mariani, M. A. (2021). Prehabilitation to prevent complications after cardiac surgery - a retrospective study with propensity score analysis. *PLOS ONE*, *16*(7). https://doi.org/10.1371/journal.pone.0253459

62. Arora, R. C., Brown, C. H., Sanjanwala, R. M., & McKelvie, R. (2018). "New" prehabilitation: A 3-way approach to improve postoperative survival and health-related quality of life in cardiac surgery patients. *Canadian Journal of Cardiology*, *34*(7), 839 849. https://doi.org/10.1016/j.cjca.2018.03.020

63. Boney, O., Bell, M., Bell, N., Conquest, A., Cumbers, M., Drake, S., Galsworthy, M., Gath, J., Grocott, M. P., Harris, E., Howell, S., Ingold, A., Nathanson, M. H., Pinkney, T., & Metcalf, L. (2015). Identifying research priorities in anaesthesia and Perioperative Care: Final Report of the Joint National Institute of Academic Anaesthesia/James Lind Alliance Research Priority Setting Partnership. *BMJ Open*, *5*(12). https://doi.org/10.1136/bmjopen-2015-010006

64. Grocott, M. P., Plumb, J. O., Edwards, M., Fecher-Jones, I., & Levett, D. Z. (2017). Re-designing the pathway to surgery: Better Care and added value. *Perioperative Medicine*, *6*(1). https://doi.org/10.1186/s13741-017-0065-4

65. D'Agostino, R. S., Jacobs, J. P., Badhwar, V., Fernandez, F. G., Paone, G., Wormuth, D. W., & Shahian, D. M. (2018). The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2018 update on outcomes and quality. *The Annals of Thoracic Surgery*, *105*(1), 15–23. https://doi.org/10.1016/j.athoracsur.2017.10.035

66. Murphy, G. J., Reeves, B. C., Rogers, C. A., Rizvi, S. I. A., Culliford, L., & Angelini, G. D. (2007). Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation*, *116*(22), 2544–2552. https://doi.org/10.1161/circulationaha.107.698977

67. D'Agostino, R. B. (1998). Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Statistics in Medicine*, *17*(19), 2265–2281. https://doi.org/10.1002/(sici)1097-0258(19981015)17:19<2265::aid sim918>3.0.co;2-b

68. Stuart, E. A. (2010). Matching methods for causal inference: A review and a look forward. *Statistical Science*, *25*(1). https://doi.org/10.1214/09-sts313

69. West, M. A., Jack, S., & Grocott, M. P. W. (2021). Prehabilitation before surgery: Is it for all patients? *Best Practice & Research Clinical Anaesthesiology*, *35*(4), 507–516. https://doi.org/10.1016/j.bpa.2021.01.001