EXAMINING THE PROGNOSTIC VALUE OF FRAILTY DETERMINED BY A MULTIDIMENSIONAL QUESTIONNAIRE, THE FRAILTY ASSESSMENT IN CARE-PLANNING TOOL (FACT), IN CARDIAC SURGERY

by

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DEDICATION

It is with deepest gratitude and warmest affection that I dedicate this thesis to my grandfather, William Smith, and to my aunt, Mary Wilson, both of whom first inspired my love of reading and learning.

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ABSTRACT

We assessed whether the Frailty in Care-Planning Tool (FACT) added discriminatory power to a standard cardiac surgery risk prediction model for mortality and major adverse cardiac events (MACE). To date, risk prediction models employed in cardiac surgery do not include frailty. We assessed whether the FACT, and each of its domains, were predictive of MACE, and MACE and/or mortality, after adjustment for the EuroSCORE II, a prominent risk prediction index. Likelihood ratio tests, sensitivity, specificity, and area under the ROC curve were used to compare models. For mortality and/or MACE, as well as MACE alone, certain domains of the FACT (Social, Daily Tasks, and Memory) provide improved fit over the EuroSCORE II alone; however, this was not the case for mobility or the overall FACT score. Traditional risk assessment scores such as the EuroSCORE II may benefit from having a measure of frailty included as a risk factor.

LIST OF ABBREVIATIONS USED

PATH	Palliative and Therapeutic Harmonization
CABG	Coronary Artery Bypass Graft
MVR	Mitral Valve Replacement
AVR	Atrial Valve Replacement
TEE	Transesophageal Echocardiography
FACT	Frailty Assessment in Care-planning Tool
CFS	Clinical Frailty Scale
QOL	Quality of Life
TAVI	Transcatheter Aortic Valve Implantation
TAVR	Transcatheter Aortic Valve Replacement
IABP	Intra-Aortic Balloon Pump
STS	Society of Thoracic Surgeons
EuroSCORE	European System for Cardiac Operative Risk Evaluation
NYHA	New York Heart Association
CCS	Canadian Cardiovascular Society
CAD	Coronary Artery Disease
COPD	Chronic Obstructive Pulmonary Disease
PAD	Peripheral Artery Disease
CGA	Comprehensive Geriatric Assessment
FI	Frailty Index
GFE	Groningen Frailty Evaluation
ADL	Activities of Daily Living

MACE	Major Adverse Cardiac Events
PHIA	Personal Health Information Agreement

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CHAPTER 1 INTRODUCTION

1. Background and Rationale

1.1 Preoperative risk stratification in clinical settings & standard clinical practice

Standard clinical practice indicates that preoperative risk stratification is essential in order to determine patient suitability for cardiac surgery in Canada. Cardiac surgery guidelines provided by the American Heart Association (AHA) and the Canadian Cardiovascular Society (CCS) provide cardiac surgeons with a set of recommendations to follow, based on the amount and quality of evidence available to support a given procedure.

Risk scoring systems have been developed to predict mortality after cardiac surgery, and are now routinely used to inform decisions on whether surgery is the best option, and if so, to guide triage (1). Risk stratification models can detect and quantify changes and differences in risk for a variety of patient profiles presenting for cardiac surgery (2). Each risk model predicts the risk of operative mortality and morbidity after adult cardiac surgery on the basis of patient demographic and clinical variables (2–4). Risk prediction allows for more objective assessment of surgical intervention in unique patients by facilitating accurate weighing of potential benefits and risks, leading to better decision-making. It can be an important component of shared decision-making, where the patient and the surgeon collaborate to make a choice regarding surgery.

While there are multiple, different scoring systems in existence, the most common are the European System for Cardiac Operative Risk Evaluation (EuroSCORE II), and the Society for Thoracic Surgery score (STS score). These scoring systems both have calculators which can be accessed online (5,6). Current clinical practice indicates that these two risk assessment scoring systems, EuroSCORE and STS, are used in the majority of hospitals in North America and Europe (2). For example, at the Halifax Infirmary, a score is determined for each patient using the EuroSCORE II, which is the

dominant scoring system for risk stratification internationally. Countless studies have examined this measure and determined that it is both internally and externally valid and reliable (1–4,7).

The EuroSCORE II scoring system contains risk variables essential to consider before surgery. These include patient, cardiac, and operative factors in the scoring process. Age, gender, renal impairment, extracardiac arteriopathy, previous cardiac surgery, poor mobility, chronic lung disease, active endocarditis, critical preoperative state, and diabetes on insulin are all patient-related factors. Cardiac (or disease) related factors include New York Heart Association (NYHA) score, Canadian Cardiovascular Society (CCS) class 4 angina score, left ventricle (LV) function, recent myocardial infarction (MI), and pulmonary hypertension. Finally, operative factors include urgency, weight of the intervention (the type of surgery performed – i.e. coronary artery bypass graft), and if surgery on thoracic aorta was performed. However, there are some limitations to the EuroSCORE II, including less optimal performance in adults over the age of 65 in which the predicted risks overestimate mortality and do not correlate well with postoperative morbidity (8,9). In addition, this scoring system only includes physiological factors (10–12). Neither STS nor EuroSCORE II use measures of frailty in their risk prediction models.

1.2 Age and frailty are key preoperative risk factors for cardiac surgery

Age and frailty are also regarded as preoperative risk factors for cardiac surgery, although they are not routinely used in risk scoring. In general, frailty is defined as a biological syndrome that reflects a state of decreased physiological reserve and vulnerability to stressors (13). Epidemiological analysis revealed that the prevalence of frailty increases with age (14). One quarter to one half of individuals aged 65 and over are expected to be frail, and in the most recent Canadian analysis, the percentage of frail community-dwelling seniors rose with age (13–15). One in four Canadians is expected to be 65 or over by 2051 (16). Trends from Statistics Canada's most recent census demonstrate the

same pattern. Seniors make up the fastest-growing age group (16). Accordingly, the number of seniors aged 65 and over increased 14.1% from 2006 to 2011. In 2011, the proportion of seniors was the highest in the Atlantic provinces, Quebec, and British Columbia (17). Nova Scotia had the highest population of seniors, 16.5%, in 2011 (16). NS also has the second highest median age (43.8 years) out of all the provinces and this is projected to increase into the coming years (48.8 years). The current proportion of seniors was 17.7% in NS in 2013, and this is expected to increase drastically up to and beyond 2038, with predicted growth scenarios ranging from low (31.4%) to high (32.2%; (18)). In a recent case-mix analysis published by our research team, Halifax has seen an increase in older people (aged 80 and older) being referred for cardiac surgery from 3.8% to 4.4% from 2001-2010 (19).

Older patients are more likely to have comorbid conditions and experience a variety of adverse outcomes after surgery (compared to younger patients). There is increasing prevalence of comorbidity with age in both men and women in European and American studies, including the Canadian population (20). Comorbidity becomes progressively more common with age, and is associated with high mortality, reduced functional status, and increased use of inpatient and ambulatory health care (21). Outcome studies have demonstrated that morbidity and mortality are increased following surgery in the elderly as compared with a younger population (22). In addition, perioperative complications are directly related to poor outcomes in the elderly (23). Fatal and major complications increase with age, and perioperative complications in the elderly are associated with greater mortality (24). For example, Hamel et al. showed that patients aged 80 years and older with complications have a 25% greater 30-day mortality than patients without complications (25). Compared with younger participants, older patients receiving coronary artery bypass grafts (CABG) are more likely to experience a host of negative outcomes, including severe coronary artery disease (CAD), left ventricular systolic dysfunction, and concomitant valvular dysfunction. In addition, older patients often have comorbid conditions, such as diabetes mellitus, chronic obstructive pulmonary disease (COPD), hypertension, azotemia, and peripheral artery disease (PAD).

One of the most prominent and controversial risk variables in these scoring systems is age. Chronological age, however, can function poorly as a marker for older patients' health status, as chronological age is not always correlated with biological age. Comprehending the impact of age is not as straightforward as writing down a single number. A number of terms exist to measure age, including biological, chronological, subjective, and physiological age, among others (26–31). Each of these definitions describe and measure a different aspect of age, and are calculated in unique ways, rendering such a process far more complicated than previously anticipated. As such, it follows that individuals with the same chronological age vary widely in health and function, despite the fact that prevalence of both illness and functional decline rise with age (32). Personal biological age is a stronger correlate of mortality than chronological age (28). Not all older individuals exhibit cognitive difficulties, and an observed lack of uniform aging has focused interest on the aging process (29). The rapidly accumulating number of terms to measure aging likely originated due to confusion around what age is really attempting to capture – frailty. This realization, that age is not synonymous with vulnerability to adverse health outcomes, has led to the development of the concept of frailty.

Frailty is a biological syndrome that reflects a state of decreased physiological reserve and vulnerability to stressors. It is defined as a decrease in the physiologic reserves as well as multi-system impairments, which are separate from the normal process of aging. Such changes lead to increased vulnerability, placing the patient at greater risk of morbidity and mortality (13,32,33). While the biological components of frailty are essential for assessing frailty, and are accounted for in most if not all frailty assessments, there are numerous other dimensions that can affect a patient's frailty. Assessments measure numerous variables associated with frailty, such as cognition, social vulnerability, amount of home care, activities of daily living, falls, and mobility, among others (13,28,33–37).

By adding frailty to a standard preoperative risk assessment model, it is likely that outcomes will be predicted with more accuracy and discriminatory power. Since age-

related deficits accumulate in relation to frailty, and frailty is a better measure of age-related deficits, it is logical that frailty may improve prediction of adverse outcomes following surgery.

1.3 Frailty as a risk factor in cardiac surgery patient assessment and care

Although little research exists in this field, the studies demonstrate that patients classified as frail are more likely to experience mortality, morbidity, functional decline, and major adverse outcomes after surgery. Increasing frailty is associated with higher mortality and more utilization of healthcare services (38). Logically, frail patients will likely not cope well with a major stressor, such as surgery (39). Many studies have demonstrated mortality is an operative outcome associated with frailty, with significant odds ratios ranging from 1.10 to 31.84 (11,40–46). Other studies have demonstrated the association between frailty and the development of postoperative complications, with the odds ratios for 30-day postoperative complications between 1.05 in older adult abdominal surgical patients to 11.70 in patients undergoing emergency general surgery (10,38,47–52). The most frequent complications post-surgery associated with frailty are those caused by infection, such as surgical site infections, pneumonia, urinary tract infections, and septicemia (38,48,49,53,54). Additionally, prolonged ventilation and reintubation were two outcomes demonstrating increased incidence in the frail population (at 39% and 22.2% respectively)(48). Institutionalization was another adverse outcome associated with frailty, in both cardiac surgery patients and general surgery patients (10,41). Even with a multitude of frailty assessments used and variation in surgical populations, these studies appear to have reached a consensus that patients deemed to be frail have a higher likelihood of experiencing mortality, morbidity, complications, and discharge to a non-home institution (10,11,39,41–47,50–52,55).

Our previous research, using a relatively crude measure of frailty, the Katz index, allowed us to demonstrate for the first time in the literature that frail patients undergoing cardiac surgery were at increased risk for morbidity, prolonged institutional care, and mortality. The Katz Index determines frailty by evaluating an individual's ability to

complete activities of daily life by assessing dementia and ambulation. This measure is relatively insensitive and reveals only patients with a high degree of frailty (56). Using this frailty measure, results showed that frail cardiac patients were at increased risk for in-hospital mortality (OR = 1.8; 95% CI 1.1-3.0), prolonged dependence on institutional care (lack of independent living; OR = 6.3; 95% CI 4.2-9.4) and additionally have a shorter midterm (2-6 month) survival rate (HR 1.5; 95% CI 1.1-2.2) (57).

Sundermann et al. (2012) found frailty was a risk factor for mortality in patients undergoing cardiac surgery (11). They developed a new tool to assess frailty and risk of mortality one year after cardiac surgery. Their test was successful in showing a significant difference between frail and non-frail patients' mortality rates after undergoing cardiac surgery (OR = 1.1; 95% CI 1.04-1.16). In this case, cardiac surgery would be the critical frailty-provoking stressor, dividing frail from non-frail patients (11). Very similar results were found by Green in 2012, which support these findings; instead of in a general cardiac surgery population, they focused on transcatheter aortic valve replacement (TAVR) only (HR = 3.16; 95% CI 1.33-7.51) (58).

Afilalo et al. (using the 6-minute walk test) found frailty was a risk factor for mortality or major morbidity in patients undergoing cardiac surgery. After measuring frailty with this technique, they discovered that frailty was associated with mortality or major morbidity after CABG and/or valve surgery (OR = 2.63; 95% CI 1.17-5.90). Slow gait speed was an independent predictor of negative outcomes (i.e. mortality, morbidity) after adjustment (55).

Stortecky and Schoenenberger found frailty was a risk factor for mortality, major morbidity, and functional decline in transcatheter aortic valve implantation (TAVI) (59,60). These two studies focused on adverse outcomes associated with TAVI. Stortecky et al. (2012) looked at all-cause mortality and major adverse cardiac events (MACE) one year post TAVI, and found an association between these outcomes and frailty (OR = 3.68; 95% CI 1.21-11.19; OR = 4.89, 95% CI 1.64-14.60 respectively) (59). Similarly, Schoenenberger (2013) found that, after TAVI, frailty was associated with functional

decline (OR = 3.31; 95% CI 1.21-9.03), or functional decline and death (OR = 4.46; 95% CI 1.85-10.75) (60).

De Arenaza et al. found that frailty was a risk factor for a composite outcome of mortality, myocardial infarction (MI), or stroke in aortic valve replacement (AVR) patients (61). Using the 6-minute walk test (6MWT), they demonstrated that patients who failed the test were more likely to experience the composite outcome (13%) compared with those who were able to complete the test in 6 minutes (4%). In a regression analysis, the 6MWT distance was the only predictor of the composite outcome of death, MI, or stroke at 12 months (15.9% in frail patients vs. 5.5% in non-frail patients) (61,62).

Results of these studies have clearly shown that patients classified as frail were more likely to experience functional decline, major adverse outcomes, morbidity, and even mortality (11,60,63–66). These studies have demonstrated that preoperative frailty is correlated with adverse outcomes in elderly persons undergoing cardiac surgery.

1.4 Limitations of existing frailty measures

While most frailty measures manage to identify and categorize an element or domain of frailty, there are considerable limitations to all of these measures that make them unsuitable for routine risk assessment of cardiac surgery outcomes. A large number of frailty measures exist in the literature, some of the most prominent being the Fried Frailty Phenotype, 6-minute walk test (6MWT), Comprehensive Geriatric Assessment, Frailty Index, and the Edmonton Frailty Scale. Only the most well-validated and commonly used measures will have their limitations addressed below.

Most frailty measures only examine one or two domains of frailty. This category includes frailty tools such as the 6MWT, Barthel Scale, Comprehensive Assessment of Frailty (CAF), Katz Index, and Fried Frailty Phenotype. The CAF, 6MWT, and Fried Frailty Phenotype only measure mobility issues, such as shrinking, weakness, poor endurance and energy, slowness, low physical activity, and slow gait speed. In contrast, the Barthel

Scale and Katz Index only measure activities of daily living (i.e. feeding, bathing, dressing, toileting, and mobility).

Three prominent measures of frailty (the Comprehensive Geriatric Assessment (CGA), Comprehensive Assessment of Frailty (CAF), and the Frailty Index (FI)) are too long to use in a clinical setting. These three tests encompass one or more domains of frailty, for example, physical mobility, comorbidities, disabilities, and activities of daily living. They require a geriatric assessment and contain over 70 questions encompassing numerous domains. A critical meta-analysis of these measures notes that these measures are overly complicated, have many questions, and are difficult to routinely use in clinical settings (62).

The Katz index is dichotomous and has low sensitivity (57). It was lauded as a key player in frailty assessment after its use in the study determining the association between frailty and adverse outcomes after cardiac surgery (19,57). The Katz Index determines frailty by evaluating an individual's ability to complete activities of daily life, and by assessing dementia and ambulation. This type of measure is relatively insensitive and unidimensional, and reveals only patients with a high degree of frailty (56).

One measure of frailty, the Frailty Assessment in Care-planning Tool (FACT), has not been assessed as a risk factor for cardiac surgical outcomes, and appears to circumvent all limitations mentioned above. An advanced questionnaire originally targeted at geriatric patients, the FACT was developed by Moorhouse and Mallory to assess geriatric patient frailty. It is rendered a more sensitive tool by virtue of its numerous levels to assess frailty, using a detailed scale (67).

The FACT assesses four domains of frailty, representing a wide variety of possible contributors to frailty. Categories include usual mobility, socialization, daily tasks, and memory (67–69). Each of these four domains are measured on seven levels of severity, demonstrating its sensitivity. Participants are ranked on a scale of 1 to 8, where 1 is

thriving and 8 is very severely frail. See Appendix A for an example of the participant FACT (67,69).

By using this more sensitive measure, observations on the effect of frailty on cardiac surgery outcomes can be extended to patients with lesser degrees of frailty (13,32,67,70). Whereas, for example, the Katz index measures mobility and activities of daily living (ADLs) in a dichotomous fashion, the FACT measures an additional two domains (socialization and memory), and it measures each of the four domains on seven levels of severity.

1.5 The predictive ability of FACT, in addition to standard preoperative risk assessment tools, on adverse outcomes following cardiac surgery

To date, the FACT has not been used as a way to measure frailty as a risk factor for cardiac surgical outcomes. This tool circumvents the limitations of other frailty measures that we have identified above. As mentioned above, the FACT is a more sensitive tool that measures the impact of varying levels of frailty across four distinct domains (usual mobility, daily tasks, social function, and cognition) using a more detailed scale (67,69). By using this measure, observations on the effect of frailty on cardiac surgery outcomes can be extended to a broader range of patients (13,32,70). It is a one-page questionnaire using self-report from the participant as well as an objective cognitive assessment which is factored into the patient's final scores in each domain. A flow chart provides direction for the researcher in assessing the participant's overall frailty score, as well as each domain alone.

Previous research found that the addition of frailty increased predictive power of conventional risk scores (11,40,55,58). However, these four studies used alternative measures of frailty and different measures of risk assessment. In addition, comprehensive reviews of these studies noted that further validation is required to clarify this relationship (62,71).

However, no previous research has investigated frailty using the FACT to predict these adverse outcomes: mortality, MACE, and discharge to an institution. Using the Katz index demonstrated that even one frailty deficit led to increased likelihood of adverse outcomes for patients (57). Targeting preoperative frailty as a risk factor for cardiac surgery may have significant clinical utility by providing patients information about their personal risk as they enter into the surgery process.

The benefits of the FACT provide a unique advantage with the added improvement of increased sensitivity and multidimensionality. The FACT is fast and easy to administer, in addition to measuring a broad spectrum of domains (mobility, social, daily tasks and memory) across seven levels (from thriving to severely frail). This makes the tool ideal for use in a fast-paced clinical setting, while still measuring frailty with greater sensitivity (using ordinal categories) over four domains (72).

1.6 Objectives

This research attempted to improve risk assessment for cardiac surgery. The aim of this study was to examine whether the FACT frailty measure provides prognostic value above and beyond that of usual practice (i.e. assessment using the EuroSCORE II).

The specific objective was to determine, in patients aged 65 and older undergoing elective cardiac surgery, whether frailty, as measured by the FACT, provided added prognostic value over the EuroSCORE II for three outcomes (discharge to a care institution, mortality, and MACE, within a 5-7 month period post-surgery. As well as assessing the predictive value of the overall score, the predictive value of each domain of

the FACT (mobility, social, daily tasks, and memory) was investigated separately.

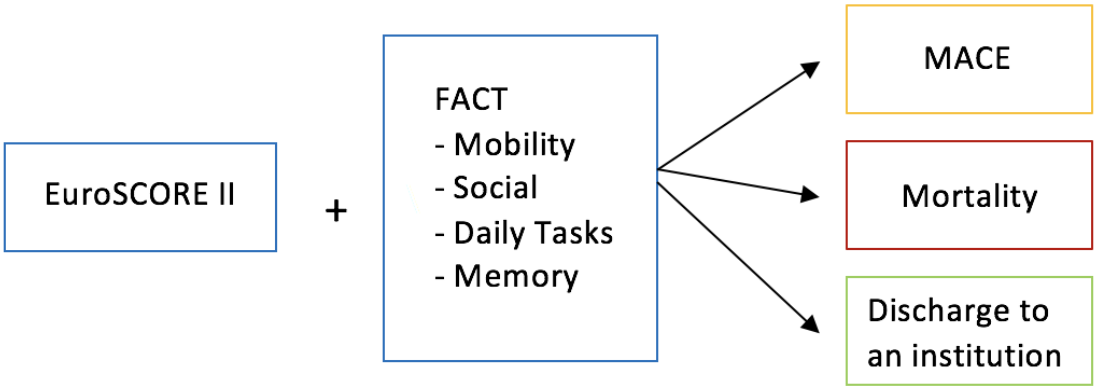

Figure 1.1 Flow diagram model of the EuroSCORE II plus each domain of frailty measured by the FACT for each of the three adverse outcomes.

CHAPTER 2 METHODS

2.1 Overview

A prospective cohort design was used to evaluate the predictive power of risk variables (frailty, as measured by the FACT, and EuroSCORE II) on adverse outcomes (mortality, MACE, discharge to a care institution, and mortality and/or MACE) at both the Halifax Infirmary and the Saint John Regional Hospital. We obtained NSHA Research Ethics Board and Horizon Health Research Ethics Board approval to approach study participants who fit all inclusion criteria and recruited participants from October 2015-September 2017.

Study participants who fit all inclusion criteria and none of the exclusion criteria were approached in various hospital locations for interest in participating in the study. Once enrolled, participants answered a questionnaire, the FACT, preoperatively. The three primary outcomes, mortality, discharge to a care institution, and MACE were measured at follow-up, post-surgery, using chart abstraction from the clinical database.

The predictiveness of FACT on outcomes was measure through comparing the predictive power of three models: (1) a standard model using only the EuroSCORE II as a risk predictor; (2) the standard model plus frailty by domain (overall, mobility, social, daily tasks, and memory); (3) the standard model with the addition of the cumulative score, with all four domains combined together. This analysis process will be further explained in Section 2.4.1.

2.2 Research design

2.2.1 Populations of interest

The target population included all elderly individuals who were candidates for cardiac surgery. The study population comprised all individuals 65 years of age or older at the time of recruitment, receiving a Coronary Artery Bypass Graft (CABG), Aortic Valve

Replacement (AVR), or a CABG & AVR at the Halifax Infirmary or the New Brunswick Heart Centre from October 2015- September 2017. Additionally, exclusion criteria for this study were: emergent or urgent cases, preoperative intra-aortic balloon pumps (IABP), inotropes, cardiac shock, endocarditis, previous cardiac surgery, or a recorded ejection fraction of less than 35%.

2.2.2 Informed consent procedures and research ethics application

The study gained ethics approval from the Nova Scotia Health Authority Research Ethics Board (REB #1011856) and the Horizon Health Ethics Board to proceed in September 2015. The informed consent form educated patients about their rights and ensured that potential participants were completely aware their participation was voluntary, what the study entailed, that their privacy and confidentiality was respected, and that they could withdraw from the study at any time. Any questions were answered before consent signatures were obtained.

2.2.3 Data collection procedures

The research team searched for patients who fit the inclusion and exclusion criteria as described above at two locations (the Halifax Infirmary and the Saint John Regional Hospital). Potential participants were targeted at four locations in the hospital: inpatient wards, same-day admittance clinic, cardiovascular surgery clinic, and the cardiac catheterization clinic. Inpatients were approached on wards following a specific method. Once the researcher arrived on the floor, the patients were identified on the ward chart to confirm their room and bed number. Patients were only approached if they had a Personal Health Information Agreement (PHIA) waiver in their chart or, if not, the patient's nurse was asked for permission to discuss the study with the patient. Following this step, the patient was approached, and the researcher introduced the study and asked for informed consent. If consent was given, the study proceeded to the interview portion, where the participant filled out the FACT. Participants filled out a number of questionnaires in the

interview, only one of which was used in this study (the FACT). The others provide data for future analyses.

Outpatients were approached in a similar fashion. The same-day admission (SDA) clinic clerk was approached and the research team requested that the clerk (who had permission from REB to approach patients about this research study) approached the patient to see if the patient would consent to talk to a member of the research team. If the patient was delayed or not available, the research team member gave their phone number and was called by the SDA clinic clerk to arrange a meeting if they were interested. If informed consent was given, the study interview materials were administered, where the participant filled out the FACT. In the cardiovascular surgery clinic, the patient was approached by their doctor, who performed the informed consent discussion. Following this, if consent was given, a member of the research team administered the study interview. Participant information was assembled into a file and stored confidentially. See Appendix A for a full interview package, which is filled out at the first interview with the patient.

Data were recorded and categorized in several Excel sheets detailing participant information and participant scores for the appropriate questionnaires. See Sections 2.3.1 and 2.3.2 for more detailed information on how and when these variables are collected. Both EuroSCORE II data and outcome variables were abstracted from patient charts according to standardized definitions listed below, in the 5-7 month period post-surgery. Participant information was de-identified and recorded to assist with tracking and follow-up post-interview. This information was shared between NB and NS sites in a completely confidential manner, with study researchers performing password protection and anonymizing data before sharing.

2.3 Measures

2.3.1 Risk stratification variables

2.3.1.1 EuroSCORE II

The EuroSCORE II is a well-calibrated, powerful discriminator, providing a risk assessment score from various patient, cardiac, and operative factors. Age, sex, renal impairment, extracardiac arteriopathy, previous cardiac surgery, poor mobility, chronic lung disease, active endocarditis, critical preoperative state, and insulin treated diabetes are all patient factors included in the score. Cardiac related factors include New York Heart Association (NYHA) score, Canadian Cardiovascular Society (CCS) class 4 angina score, left ventricle (LV) function, recent myocardial infarction (MI), and pulmonary hypertension. Finally, operative factors include urgency, weight of the intervention (i.e. CABG), and surgery on thoracic aorta. Scores are given as a percentage, grouped into low (<2%), moderate (2-5%), and high (>5%) categories for interpretation. In this study, EuroSCORE II was treated as a continuous variable.

These variables are captured at both centres by data abstractors; in Nova Scotia, this data is abstracted and uploaded to a database. However, since the data for these files was not yet entered in the database, the author of this thesis abstracted this information from patient files. In New Brunswick, this information is collected in patient files, which were abstracted by the author of this thesis.

2.3.1.2 FACT

The FACT is a valid, reliable tool, originally derived from the CFS, providing a detailed score across four domains and seven levels of frailty (67,69). Typically used in geriatrics research, it is being used for the first time in cardiac surgery in this research study. It is administered in questionnaire form to the participant (Appendix A). The FACT assesses four domains of frailty, representing a wide variety of possible contributors to frailty. Categories include usual mobility, socialization, daily tasks, and memory (67–69).

Memory, or cognition, is measured in two ways: through a cognitive screening test for the participant, and through self-report via the participant. The cognitive screening test asks patients two questions to determine a baseline level of cognition. The first question is a memory recall task asking patients to remember three words (e.g. “apple”, “penny”,

and “watch”). The second task is a clock drawing task, where patients must draw a clock with the arms of the clock pointing to “ten minutes after eleven”. Following the second question, participants are asked to recall the three words mentioned earlier. Depending on how many they remember and how the clock is drawn (abnormal versus normal), they are given a score based on a flowchart mapping a variety of options. If cognition is below a certain level, subsequent questions are asked to the participant in order to determine a more severe (vulnerable or higher) frailty rating.

Each of these four domains are measured on seven levels of severity, demonstrating its sensitivity. Participants are ranked on a scale of 1 to 8, where 1 is thriving and 8 is very severely frail. See Appendix A for an example of the participant FACT (67,69). During scoring, participants are given a score in each domain from 1-8. Following convention in the use of FACT, participants were stratified into two groups: frail (4 and above) and non-frail (3 and below) (72,73). Originally, this analysis had planned to split the FACT into three groups: frail (5 and above), vulnerable (4), and non-frail (3 and below), however, with such a limited sample size, using two categories was necessary.

A variety of FACT scores were calculated for analysis. In geriatrics, the overall score is reported, which is the highest score in any one domain. For analysis, a cumulative score is also reported, which combines scores from each domain together in one model. For clarity, scoring methods are defined with examples in Table 2.1. (67,69).

Table 2.1. Method of tabulating different FACT scores for participants

Score Name	**Calculation**	**Example**
Domain score	Examine highest score in one domain, i.e. Social	A participant has marked a 5 in the Social domain. They receive a score of 5 for Social frailty.
Overall score	Highest score from any of the four domains	A participant has marked a 6 in the Mobility domain, a 1 in Social, 1 in Daily Tasks, and 1

		in Memory. They receive a score of 6 for Overall frailty.
Cumulative score	Not calculated manually, but all four domains added to multivariable models	Each domain, Mobility, Social, Daily Tasks, and Memory, added to the model together.

2.3.2 Outcome variables

2.3.2.1 Primary outcomes

The clinical database at the Halifax Infirmary contains outcome information on all patients' health status, including the three primary outcomes of interest: in-hospital mortality, discharge to a care institution, and MACE. These variables were measured through chart abstraction from patient records at the Cardiac Surgery Maritime Heart Centre database. The Maritime Heart Centre Cardiac Surgery Registry database is a detailed clinical registry that has prospectively collected pre-, intra-, and postoperative data on all adult patients undergoing cardiac surgery at this centre since 1995.

Patient records were examined by chart abstractors and pertinent details are uploaded to the database for future analyses. Since the data during these years was not uploaded to the database at the time, the author of this thesis abstracted relevant details from the database for all Halifax Infirmary participants to streamline the data collection process. The same process was used at the Saint John Regional Hospital, except the chart information was in paper format; these data were abstracted from charts and into an Excel file for analysis by the author of this thesis. The final spreadsheet with all 230 participants was abstracted by the author of this thesis, with 20% of the Halifax charts double-checked by members of the chart abstraction team at the Halifax Infirmary to ensure correctness.

This study used a composite outcome measure of non-fatal outcome, major adverse cardiac events (MACE), which included deep sternal wound infection, permanent stroke, acute renal failure, septicemia, and prolonged postoperative stay (Table 2.2). Composite

outcomes are routinely used in cardiac surgery research to capture a variety of serious adverse outcomes as one endpoint. Many cardiovascular studies examine the effects of frailty on composite outcomes (11,40,55,59,60,71,74). Some term these outcomes major adverse cardiac and cerebrovascular events (MACCE), or MACE. A few of these studies investigating frailty examine MACCE and MACE (11,60,71,74). The MACE used in the present study has been used in previous studies by our group and has considerable internal validity, while external validity is limited (19,57). However, external validity for MACE/MACCE in general has been demonstrated (74).

Table 2.2 Clinical outcome variables, as defined by the Maritime Heart Centre database

Outcome variable to be measured	Method and measurement issues
1. All-cause mortality • Death from any cause occurring during or post-surgery until 5-7 months post-surgery	Dichotomous; abstracted from hospital records at the 5-7-month follow-up period.
2. MACE • Deep sternal wound infection o Involving muscle, mediastinum, bone, or a combination • Permanent stroke o Neurologic deficit, persistent or resolved at hospital discharge • Acute renal failure o Postoperative serum creatinine level > 176 mmol/L and > 50% higher than preoperative serum creatinine levels • Prolonged postoperative stay	A standard definition for MACE was defined at the outset of the study by the two centres, to ensure both centres were using the same criteria. Dichotomous; abstracted from hospital records at the 5-7 month follow-up period.

○ Length of stay ≥ 10 days • Septicemia ○ Positive blood culture result	
3. Discharge to a care institution • Discharge to a community hospital, restorative or rehabilitation care facility, or skilled nursing facility, among patients discharged alive	This may be difficult to define depending on the level of care. Also dichotomous; abstracted from hospital records at the 5-7 month follow-up period.

2.3.2.2 Changes to primary outcomes after data collection

Out of necessity, two of the outcomes of interest were eliminated from the final data analysis, due to small sample size, close association to the outcomes. However, a new outcome was also created, in order to incorporate mortality, since it was not able to be assessed alone. This left the two final outcomes as MACE, as well as mortality and/or MACE, which were both examined in multivariable logistic regression models (Figure 2.1).

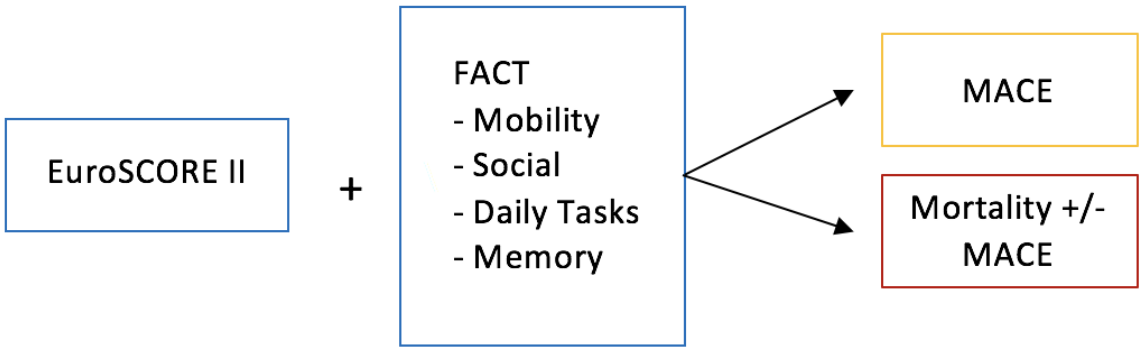

Figure 2.1 Modified flow diagram model of the EuroSCORE II plus each domain of frailty measured by the FACT for the two adverse outcomes

2.4 Overview of statistical analysis

For each of the clinical outcomes of interest, analyses determined whether the variation in outcomes explained by the standard clinical model, using the EuroSCORE II alone, was improved by the addition of FACT. This was done for each outcome of clinical interest (MACE and mortality and/or MACE) using seven models. The first, and most basic model, used the EuroSCORE II alone as a predictor. Second, the overall FACT score was added into the first model, to form Model 2. FACT individual scores by domain were factored into the first model separately, to form Models 3-6. Model 7 was comprised of all domains combined into one model. To compare goodness of fit and predictive power of these models, parametric analysis of ROC curves using a maximum likelihood model was performed. As well, relative model fit was assessed using likelihood ratio (LR) tests.

2.4.1 Analytical approach

2.4.1.1 Descriptive analysis of preliminary demographics

Initial descriptive analysis examined the distribution of all variables of interest, stratifying by frailty status. Since sample size was small, this descriptive analysis did not examine each of the eight levels of the FACT separately; participants were stratified into two groups, frail (4 and above) and non-frail (3 and below). While the FACT was dichotomized in accord with the few studies which have attempted to dichotomize the FACT, we also conducted sensitivity analyses to assess how different dichotomizations based on different cutoffs affected results (72,73). Categorical variables were reported as frequencies and proportions, while continuous variables were reported as means (with 95% confidence intervals). This descriptive analysis examined the study population to detect any significant differences in preoperative variables.

As such, to first determine if there were significant differences in preoperative demographic variables (such as age and sex) and medical characteristics (such as type of medication, history of previous heart conditions) between these two frailty groups, we used statistical tests appropriate to the type of variable and the distribution of data. For

categorical variables, chi-squared tests were used to determine if there were differences between proportions. Fisher's exact test was used when cell sizes were less than 5.

Continuous variables were tested for normality using the Shapiro-Wilk test. Following this, either a Mann-Whitney test (normal, parametric) or a Wilcoxon rank sum test (non-normal, nonparametric) test was used to determine differences in central tendency. Summary scores across domains were derived and reported as median and interquartile range (IQR) for variables which required this information. Post-hoc tests were not used to examine the differences between groups in more detail, as no significant differences were found.

2.4.1.2 Analytic approach using the standard clinical model as a predictor of adverse outcomes after cardiac surgery

Seven models were composed for each of the two adverse outcome variables, for a total of 14 models. The first, and most basic model, looked at the EuroSCORE II alone as a predictor of outcomes. Second, the overall FACT score was added into the first model, to form Model 2. FACT individual scores by domain were factored into the first model separately, to form Models 3-6. Model 7 was comprised of all domains combined into one model.

We added FACT to these models to determine if it significantly improved predictive power over and above that of the previously established models. As mentioned above, FACT scores were divided into frail (levels 4-8: vulnerable and frail) and non-frail (levels 1-3: thriving and well) categories, and this dichotomization was used for the overall score and for all four domain scores. Frailty, as measured by the FACT, was added to two separate models, first as an overall score (Model 2), and then by domains (Models 3-6). Model 7 added all of the domains together in one model, to determine the additive predictive ability of the four domains.

In summary, these models assessed the added value of frailty in predicting adverse outcomes after adjusting for clinical characteristics such as age, sex, comorbidities, severity of cardiac disease, and urgency of surgery.

Table 2.3. Models used in statistical analysis

Model 1	EuroSCORE II
Model 2	EuroSCORE II + Overall FACT score
Model 3	EuroSCORE II + Mobility FACT score
Model 4	EuroSCORE II + Social FACT score
Model 5	EuroSCORE II + Daily Tasks FACT score
Model 6	EuroSCORE II + Memory FACT score
Model 7	EuroSCORE II + Mobility FACT + Social FACT + Daily Tasks FACT + Memory FACT

2.4.1.3 Comparison and evaluation of models

We assessed relative and absolute fit of each model. To assess relative improvement of fit for nested models, likelihood ratio (LR) tests were used, along with the Bayesian and Akaike Information criteria. To assess absolute fit, the area under the ROC curve was calculated for model. The area under the ROC curve is a measure of the discriminating ability of a model, with higher areas indicating better predictive performance. Area under the curve is a measure of test accuracy, with the area measuring discrimination – the ability of the test to correctly classify those experiencing and not experiencing the outcome. For example, with mortality as the chosen outcome, an area of 0.50 indicates the model predicts mortality no better than by chance alone whereas an area of 1.00 predicts mortality perfectly.

Aikaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), both penalized-likelihood criteria, will also be used to determine predictive performance by assessing parsimony of the models. A lower AIC means the model is closer to the truth, since this means there is a smaller relative distance between the unknown true likelihood

function of the data and the fitted likelihood function of the model. Since BIC penalizes model complexity more heavily, a model with more predictors such as the Cumulative frailty model for both outcomes may become less optimal.

2.4.1.4 Other considerations: Software, missing data, power, and sample size

All of our analyses were conducted using Stata version 15 (75). Significance levels were set at 0.05. Missing data from item non-response was addressed by removing all participants with missing variables from the analysis. Previous work by our group in this field has also employed the practice of removing participants with missing data from analyses (19,57). Sensitivity analysis in these studies demonstrates that excluding people with missing data makes no difference to the overall analysis (19,57).

Post-study power calculations indicated power levels below acceptable: for overall frailty, 61.97% power for MACE, and 65.91% power for mortality and/or MACE. Using the most balanced domain in terms of sample size (daily tasks), a 77.82% power for MACE and 84.80% power for mortality and/or MACE was found, which meet the desired minimum percentage. With a given significance level, the power of the test is increased by having a larger sample size. The minimum acceptable level is considered to be 80%, which means having an eight in ten chance of detecting a difference of the specified effect size.

CHAPTER 3 RESULTS

3.1 Baseline patient characteristics and frailty distribution among participants

In total, 276 participants were recruited for the study between October 2015 and September 2017, and 230 participants were included in the final data analysis. The majority of participants were excluded due to ultimately deciding on a different procedure (n = 33) or receiving a different procedure (n = 4), rendering them ineligible to participate in the study. See Appendix C, Supplementary Figure 1 for details.

Using the standard cutpoint for the FACT (split between levels 4 and 5), the distribution of frailty varied considerably by domain. The proportion of participants by frailty level varied by domain, with different distributions across the four domains (Table 1). Overall and mobility scores had highest proportion in the vulnerable category (level 4), while social had the greatest proportion being well (level two and three). Daily tasks was more evenly distributed, and memory had the greatest number of participants rate themselves as thriving (level 1) . Categories 2 & 3 were grouped together in the FACT questionnaire in order to correspond with the Clinical Frailty Scale (CFS), and Table 3.1 reflects that grouping.

Table 3.1. Frequencies of participants' frailty score by level and domain, as measured by the FACT

Frailty level	Overall	Mobility	Social	Daily Tasks	Memory
1	3 (1.30%)	9 (3.91%)	18 (7.83%)	30 (13.21%)	100 (43.86%)
2 & 3	23 (10.0%)	34 (14.78%)	165 (71.74%)	77 (33.77%)	70 (30.70%)
4	132 (56.52%)	146 (63.47%)	17 (7.39%)	95 (41.85%)	49 (21.49%)
5	52 (22.60%)	31 (13.48%)	17 (7.39%)	24 (10.43%)	8 (3.51%)
6	18 (7.83%)	8 (3.47%)	12 (5.23%)	1 (0.44%)	1 (0.44%)
7	2 (0.87%)	2 (0.87%)	1 (0.43%)	1 (0.44%)	0 (0.00%)
8	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	230 (100.0%)	230 (100.0%)	230 (100.0%)	228 (100.0%)	228 (100.0%)

*Overall frailty score was calculated using the highest frailty score from across the four domains; frailty level: 1 = Very fit, 2 & 3 = Well, 4 = Vulnerable, 5 = Mildly frail, 6 = Moderately frail, 7 = Severely frail, 8 = Very severely frail. These categories were dichotomized due to small sample size, into categories: 1-3 Not frail, 4-8 Frail. Standard cutpoint occurs between categories 2 & 3 and 4.

The overall FACT score, used to judge a patient's level of frailty in clinical geriatric assessments, is calculated using the highest score overall from any of the four domains (Mobility, Social, Daily Tasks, and Memory). In this patient population, mobility is the key driver of overall frailty status, while the other domains are less likely to determine the overall score (Table 3.1). Interestingly, most participants were not frail (either 1 - very fit or 2 & 3 - well) in the social and memory domains, and this trend was reversed for the mobility domain, as well as the daily tasks domain, although this effect was less pronounced for daily tasks.

None of the preoperative characteristics of the study participants were significantly associated with frailty status, as measured by Pearson's chi-squared test or Fisher's exact test if cell sizes were less than 5, or by Wilcoxon rank sum tests if the distribution was not normally distributed (Table 3.2). However, the data are underpowered to detect differences between frail and non-frail participant groups. Of the 230 patients, 88.70% demonstrated frailty in one or more domains of the FACT, and just 11.30% were not frail in any domain of the FACT.

Table 3.2. Preoperative participant characteristics of interest, stratified by overall frailty status

	Non-frail (n = 26)	**Frail (n = 204)**	***p***
Median age, y (IQR)	70.5 (67-76)	72 (69-77)	0.147
Age range	65-81	65-85	
Median weight, kg (IQR)	85.5	84.1	0.791
Female sex	5 (19.23%)	45 (22.05%)	0.742
Diabetes	11 (42.31%)	79 (38.73%)	0.440
COPD	3 (11.54%)	29 (14.22%)	0.495

	Non-frail (n = 26)	Frail (n = 204)	*p*
Recent MI (in last 90 days)	6 (23.08%)	58 (28.43%)	0.376
Renal failure	1 (3.85%)	4 (1.96%)	0.454
Renal insufficiency	5 (19.23%)	37 (18.14%)	0.535
Extracardiac arteriopathy	3 (11.54%)	38 (18.63%)	0.279
Final EuroSCORE II (%)	3.22	3.92	0.771

*Overall frailty score was calculated using the highest frailty score from across the four domains, and dichotomized into two groups for analysis due to small sample size, into the following categories: 1-3 Not frail, 4-8 Frail.

Baseline clinical and procedural characteristics of the study population revealed no significant differences between participants across case-mix and procedure type. Surgical case-mix included AVR (18.10%), CABG (14.66%), and AVR + CABG (67.24%) patients. When case mix was stratified by surgeon, distribution among surgeons was similar. Surgeries were performed by 13 different cardiac surgeons, and case by surgeon was fairly evenly distributed, with a range from 1.29%-15.52% of total cases completed by one surgeon alone.

3.2 Unadjusted and adjusted in-hospital adverse outcomes stratified by frailty status

The overall FACT is not significantly predictive of surgical outcomes, before or after adjustment for EuroSCORE II. However, when included in the model as single predictors, domains of FACT other than mobility are significantly associated with outcomes. These results provided a basis for further investigation of these results, which were then adjusted for potential confounders (in this case, the EuroSCORE II).

For both adverse outcomes, certain frailty domains proved significantly different in frail versus non-frail patients after adjustment for EuroSCORE II. Odds ratios demonstrated that Social, Daily Tasks, and Memory domains of frailty were associated with higher risk of mortality and/or MACE, while Social and Daily Tasks domains were predictive of

higher risk of MACE alone ($P < 0.05$, Table 3). For example, participants who were socially frail had 2.67 times the odds of experiencing mortality and/or MACE than those who were not socially frail; those who were frail in the daily tasks domain were 3.38 times the odds of experiencing mortality and/or MACE, compared to non-frail patients.

Similar results were found for the MACE outcome; participants who were socially frail had 2.43 times the odds of experiencing MACE compared to those who were not socially frail, and those who were frail in the daily tasks domain had 3.58 times the odds of experiencing MACE compared to those who are not frail in the daily tasks domain. EuroSCORE II remained significant in all adjusted models, even after addition of various FACT scores (Supplementary Table 1).

Table 3.3 Logistic regression models of FACT on primary adverse outcomes, adjusted and unadjusted for EuroSCORE II, stratified by frailty status

	Unadjusted		*Adjusted*	
	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*
Mortality and/or MACE				
EuroSCORE II	1.09 (1.02-1.16)	0.009	--	--
+ Overall	3.02 (0.69-13.29)	0.097	2.89 (0.65-12.82)	0.163
+ Mobility	1.23 (0.50-2.98)	0.418	1.16 (0.47-2.85)	0.746
+ Social	**2.98 (1.44-6.18)**	**0.004**	**2.67 (1.25-5.69)**	**0.011**
+ Daily Tasks	**3.48 (1.62-7.47)**	**0.000**	**3.38 (1.56-7.33)**	**0.002**
+ Memory	**2.56 (1.28-5.15)**	**0.007**	**2.45 (1.20-5.00)**	**0.014**
MACE				
EuroSCORE II	1.12 (1.05-1.20)	0.001	--	--
+ Overall	3.11 (0.70-13.69)	0.088	2.95 (0.66-13.21)	0.157
+ Mobility	1.27 (0.52-3.08)	0.388	1.18 (0.48-2.90)	0.751
+ Social	**2.86 (1.38-5.90)**	**0.005**	**2.43 (1.13-5.24)**	**0.023**
+ Daily Tasks	**3.63 (1.69-7.77)**	**0.000**	**3.58 (1.64-7.84)**	**0.001**
+ Memory	**2.16 (1.07-4.34)**	**0.023**	2.05 (0.99-4.24)	0.052

*P-values derived by regression analysis; FACT overall score calculated by taking the highest overall score from the four domains; FACT dichotomized into two groups for analysis due to small sample size, into the following categories: 1-3 Not frail, 4-8 Frail; N = 230

Changing cutpoint values did not alter our basic conclusions regarding which domains were significant. To examine results from different cutpoints (4 vs. 5) and using three frailty levels (instead of dichotomizing), sensitivity analyses were performed. Although results were slightly different, this did not unduly alter results (Table 3.4).

Table 3.4. Sensitivity analysis on logistic regression models of FACT on primary adverse outcomes, adjusted for EuroSCORE II

	Adjusted – 3 Frailty Levels		*Adjusted – Cutpoint at 5*	
	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*
Mortality and/or MACE				
EuroSCORE II	--	--	--	--
+ Overall	**V**: 2.46 (0.54-11.20)	0.246	--	--
	F: 3.63 (0.77-17.12)	0.103	1.65 (0.82-3.32)	0.159
+ Mobility	**V**: 1.15 (0.46-2.89)	0.762	--	--
	F: 1.11 (0.35-3.49)	0.859	0.99 (0.41-2.40)	0.986
+ Social	**V**: 1.30 (0.35-4.87)	0.692	--	--
	F: 3.64 (1.53-8.67)	**0.004***	**3.56 (1.50-8.41)**	**0.004***
+ Daily Tasks	**V: 3.44 (1.55-7.65)**	**0.002***	--	--
	F: 3.19 (1.05-9.71)	**0.041***	1.56 (0.59-4.12)	0.370
+ Memory	**V: 2.26 (1.05-4.84)**	**0.036***	--	--
	F: 3.94 (0.93-16.63)	0.062	3.15 (0.76-13.04)	0.113
MACE				
EuroSCORE II	--	--	--	--
+ Overall	**V**: 2.45 (0.53-11.28)	0.076	--	--
	F: 3.85 (0.81-18.26)	0.090	1.76 (0.87-3.55)	0.117
+ Mobility	**V**: 1.13 (0.45-2.85)	0.795	--	--
	F: 1.26 (0.40-3.92)	0.694	1.14 (0.48-2.73)	0.766

	Adjusted – 3 Frailty Levels		*Adjusted – Cutpoint at 5*	
+ Social	**V**: 1.30 (0.35-4.86)	0.701	--	--
	F: **3.19 (1.31-7.72)**	**0.010***	**3.12 (1.30-7.49)**	**0.011***
+ Daily Tasks	**V**: **3.72 (1.65-8.35)**	**0.001***	--	--
	F: **3.13 (1.00-9.79)**	**0.050***	1.46 (0.54-3.96)	0.453
+ Memory	**V**: 1.87 (0.86-4.07)	0.116	--	--
	F: 3.49 (0.80-15.27)	0.097	2.97 (0.69-12.75)	0.143

*P-values derived by regression analysis; FACT overall score calculated by taking the highest overall score from the four domains; V = Vulnerable, F = Frail; N = 230

3.3 Model fit, discrimination, calibration, and comparison for in-hospital outcomes by frailty status

Certain domains of frailty significantly improve the predictive value of the EuroSCORE II in predicting mortality and/or MACE as well as MACE alone. For the mortality and/or MACE outcome, frailty domains which improve the predictive value of the EuroSCORE II includes Social, Daily Tasks, Memory, and Cumulative models. All of these models, with the exception of Cumulative frailty, provide a lower AIC and BIC, as well as a higher AUC. For MACE alone, Social, Daily Tasks, and Cumulative models have a higher AUC value, as well as a lower AIC and BIC (Table 3.4).

Using the AIC, BIC, and AUC, the most parsimonious model with the best fit is the Daily Tasks model for both outcomes (Mortality +/- MACE, MACE; Table 3.4). This model provides improved model fit over and above that of the EuroSCORE II while still remaining as parsimonious as possible.

There is reasonable evidence that social, daily tasks, and memory domains improve model fit, when included singly in the models. A multivariable model including all domains of FACT maintains AUC, while slightly improving AIC and moderately improving BIC.

Table 3.5. Multivariable model fit statistics for each adverse outcome event, relative to a baseline model with EuroSCORE II

	AUC (95% CI)	AIC	BIC	LR
Mortality and/or MACE				
EuroSCORE II	0.62 (0.52-0.71)	218.09	224.95	--
+ Overall	0.64 (0.55-0.73)	217.58	227.87	0.11
+ Mobility	0.62 (0.52-0.71)	219.98	230.27	0.74
+ Social	**0.65 (0.55-0.74)**	**213.95**	**224.24**	**0.01**
+ Daily Tasks	**0.69 (0.61-0.77)**	**209.29**	**219.58**	**0.00**
+ Memory	**0.63 (0.54-0.73)**	**214.22**	**224.51**	**0.00**
+ Cumulative	**0.71 (0.63-0.80)**	**208.24**	**228.82**	**0.00**
MACE				
EuroSCORE II	0.64 (0.54-0.73)	215.26	222.12	--
+ Overall	0.66 (0.56-0.75)	214.67	224.96	0.11
+ Mobility	0.64 (0.54-0.73)	217.13	227.42	0.72
+ Social	**0.67 (0.57-0.76)**	**212.39**	**222.68**	**0.03**
+ Daily Tasks	**0.71 (0.62-0.79)**	**205.64**	**215.93**	**0.00**
+ Memory	0.64 (0.55-0.74)	213.62	223.91	0.06
+ Cumulative	**0.72 (0.64-0.80)**	**206.99**	**227.57**	**0.00**

*Each model included the base model (EuroSCORE II) with the addition of each domain (overall, mobility, social, daily tasks, and memory) alone. The cumulative model included all four domains, not including overall frailty, in one model together. AUC indicates area under the receiver operating curve; CI, 95% confidence interval; AIC, Aikaike Information Criterion; BIC, Bayesian Information Criterion, LR, likelihood ratio test (each model compared to EuroSCORE II model alone); outcomes based on event rates at discharge; FACT overall score calculated by taking the highest overall score from the four domains; FACT dichotomized into two groups for analysis due to small sample size, into the following categories: 1-3 Not frail, 4-8 Frail; N = 230

Removing mobility from the cumulative model, and retaining social, daily tasks, and memory, results in a more parsimonious model with the best AUC (Mortality and/or MACE, AUC = 0.71; MACE, AUC = 0.72; Table 3.6).

Table 3.6 Multivariable model fit statistics for each adverse outcome event occurring post-discharge, relative to a baseline model with EuroSCORE II, examining additional models involving the most predictive domains (Social, Daily Tasks, and Memory)

	AUC (95% CI)	**AIC**	**BIC**	**LR**
Mortality and/or MACE				
EuroSCORE II	0.62 (0.52-0.71)	218.09	224.95	--
+ S, DT, M	**0.71 (0.62-0.80)**	**207.83**	**225.02**	**0.00***
+ S, DT	**0.71 (0.62-0.80)**	**208.29**	**222.04**	**0.00***
MACE				
EuroSCORE II	0.64 (0.54-0.73)	215.26	222.12	--
+ S, DT, M	**0.72 (0.64-0.81)**	**206.56**	**223.75**	**0.00***
+ S, DT	**0.73 (0.64-0.81)**	**205.75**	**219.50**	**0.00***

*Each model included the base model (EuroSCORE II) with the addition of each domain (overall, mobility, social, daily tasks, and memory) alone. The cumulative model included all four domains, not including overall frailty, in one model together. AUC indicates area under the receiver operating curve; CI, 95% confidence interval; AIC, Aikaike Information Criterion; BIC, Bayesian Information Criterion, LR, likelihood ratio test (each model compared to EuroSCORE II model alone); outcomes based on event rates at discharge; FACT overall score calculated by taking the highest overall score from the four domains; FACT dichotomized into two groups for analysis due to small sample size, into the following categories: 1-3 Not frail, 4-8 Frail; N = 230

CHAPTER 4 DISCUSSION

4.1 Introduction

The predominant aim of this study was to assess if risk assessment for cardiac surgery in older patients could be improved by the use of a simple measure of frailty, the FACT, in addition to a widely used risk assessment score, the EuroSCORE II. This is the first study to use the FACT and assess its usefulness in prediction of MACE and MACE and/or mortality in cardiac surgery. Frailty is a popular topic in the medical literature, however, using frailty as a cardiac surgery risk prediction tool, and moreover using the FACT in combination with the EuroSCORE II has not been conducted previously. Ironically, much literature has sought to assess independent effects of risk prediction of different medical outcomes, yet this does not reflect practical clinical outcomes that are highly applicable to clinical practice. This is likely due to primary data collection and labour-intensive data gathering specific to this type of research, and difficulty implementing these studies in busy cardiac surgical settings.

4.2 Frailty assessment in evaluating risk for cardiac surgery patients

Frail patients are at increased risk for adverse outcomes. All-cause mortality and MACE, as well as MACE alone, was more prevalent among frail than non-frail patients ($p < 0.05$), as measured by the FACT. This finding is supported by several studies; patients classified as frail were more likely to experience major cardiac or cerebrovascular events, postoperative delirium, increased hospital length of stay, functional decline, morbidity, and mortality (11,40,55,71,76). This is logical given that cardiac surgery represents a major physiologic stressor and is likely to impact frail patients with more severity than non-frail patients (11,19,59–61). Even after a minor health stressor, such as a urinary tract infection, frail patients undergo a larger deterioration and may never return to baseline homeostasis (13). Although frailty tends to increase with age, its assessment is independent of age or any specific medical condition (11,39,59,60,71).

Certain frailty domains may be better than others at predicting outcomes. Overall and mobility frailty were both domains that were not associated with adverse outcomes. Overall frailty was highly driven by mobility, since the overall score is determined by choosing the highest score from each of the four domains (usual mobility, social, daily tasks, and memory). Mobility was often the highest score, since this was highly likely to be disease-driven frailty (i.e. driven by the participant's heart condition). This aspect of frailty is reversible with surgery and is not the true aspect of frailty we attempted to capture.

Frailty, as measured by the FACT, predicts certain adverse outcomes even after controlling for typical cardiac surgery variables (i.e. type of procedure, low ejection fraction, recent MI), as captured by the EuroSCORE II (77). Despite this, the overall FACT score was not predictive. In this research, the EuroSCORE II, which is used widely to assess patient suitability for cardiac surgery, was used to predict two adverse outcomes. Odds ratios demonstrated that Social, Daily Tasks, and Memory domains of frailty were associated with higher odds of mortality and/or MACE, while Social and Daily Tasks domains were predictive of higher odds of MACE alone ($P < 0.05$), after controlling for EuroSCORE II. The current study's results are confirmed by the literature on adverse outcomes, specifically major adverse cardiac events: mortality, morbidity, long length of stay, sepsis, and acute renal failure, among others, are often a result of cardiac surgery in frail patients (11,57,59–61). These studies control for common characteristics associated with cardiac surgery, such as diabetes, COPD, and peripheral vascular disease (PVD), among others (11,57,59–61).

The clinical utility of these risk prediction tools varies, and the EuroSCORE II plus frailty as assessed by the FACT would be easy and quick to assess and calculate. Risk prediction tools most suited for application at the clinic or at the bedside need to be user-friendly and easily accessible. The FACT only takes 10 minutes to administer and can be easily administered by any health professional providing care to the patient (78). The supplemental information provided could mean a better risk prediction model for the

patient and ideally, a more informed decision making process could occur, informed by the FACT and EuroSCORE II data.

Improved predictive power of the EuroSCORE II with the addition of the FACT could lead to better care planning. Optimally, this would occur through a shared decision-making process, in order for both patients and providers to have access to the best risk prediction models in making a decision for or against cardiac surgery. Making a decision for or against surgery is important, and must be done in an objective manner, based on the best available evidence and data. This should result in an improved comprehension on both sides, and the clinician and the patient can feel they have reached a positive and confirmed decision to proceed with a certain treatment path. In cases relevant to the present study, patients are likely to be complex cases, influenced by various aspects of frailty, and surgeon recommendations may not be clearly guided by evidence in the literature (78). This is when prediction of risk becomes particularly crucial during the shared decision-making process between patient and surgeon. Shared decision-making processes include being involved in the process of knowledge transfer, active engagement, and reaching a collaborative consensus (79).

In these high-risk cases, improved prediction is crucial for making informed decisions (78). State of the art risk communication involves using frequencies and graphical displays which demonstrate numbers of patients who will and will not be affected by the outcome (79). Individualized risk estimation expressed using Montori plots, a pictograph dot plot expressing an individual's risk out of 100 others like them, has been shown to be the most effective way for patients to comprehend risk (79–81). This research can provide more specific, individualized risk with better predictive ability; this risk of adverse outcomes can be easily assessed and computed, which can then be entered into a decision aid and presented to the patient and their families at the patient's bedside. This will result in increased satisfaction with surgery decision and greater comprehension of risks in the population this research aims to target: older, more frail patients who have been shown to experience unprecedented levels of equipoise between the options of cardiac surgery and continued medical treatment (19,57,79,81).

4.3 Frailty domains in model prediction of adverse outcomes with varying degrees of ability, and the clinical utility of the FACT in routine practice

In the present study, we demonstrated that improved prediction over and above that of the EuroSCORE II is possible by adding information on some domains of frailty to this risk prediction tool. The most parsimonious model with the best improved model fit is the Daily Tasks frailty model added to the base model (EuroSCORE II) for both adverse outcomes (Mortality +/- MACE, MACE). Certain domains of frailty, as measured by the FACT, provide added prognostic value when combined with the EuroSCORE II for two outcomes (MACE and MACE +/- mortality) within a 5-7 month period post-surgery, even after controlling for adjustment for the EuroSCORE II. For MACE, both social and daily tasks domains provide additional prognostic value to the EuroSCORE II. For MACE +/- mortality, social, daily tasks, and memory categories provide added prognostic value to the EuroSCORE II (Tables 4 & 5). These findings demonstrate not only an association between frailty and adverse outcomes, but also of specific frailty domains from the FACT over and above that of the EuroSCORE II alone.

Few studies exist to confirm or deny these results in such a specific population, using a similar tool (82–84,73). In addition, the studies that currently exist provide mixed conclusions on these findings. Certain studies have compared the validity of different risk prediction scores on adverse outcomes, and found positive results (82,85). Lytwyn et al. (2017) examined the addition of frailty scores to the EuroSCORE II; results demonstrated a non-statistically significant improvement in the risk prediction of poor 1-year functional survival (being alive with a good health-related quality of life) when compared with the EuroSCORE II alone (73). This study used three different frailty scales to evaluate the impact of frailty when added to the EuroSCORE II in identifying patients at risk of poor 1-year functional survival. They found that adding frailty to the EuroSCORE II provided incremental value in identifying patients at risk of poor functional survival 1 year after cardiac surgery (73). Although these results were not significant, they provide a trend which agrees with the pattern of results found in this study.

Kovacs et al. (2017) examined a variety of prominent frailty scales, as well as risk prediction tools, in predicting adverse outcomes such as long length of stay, postoperative complications, and mortality. However, this study did not add frailty to the EuroSCORE II model, merely looked at each scale alone. As such, they found that the EuroSCORE II was still the best predictor when compared to various frailty scoring scales (86). This adds support to the study's hypothesis, however leaves an obvious gap for this study to fill: to combine both the EuroSCORE II and a frailty measure together in order to improve risk prediction.

In summary, there is a dearth of literature around the topic of risk prediction using the EuroSCORE II in elderly, frail patients undergoing cardiac surgery; however, existing literature provides support for this study's results. The EuroSCORE II is widely recognized as the prominent measure of risk prediction for cardiac surgery (85). Despite this, evidence indicates traditional risk scores such as the EuroSCORE II have low ability to predict postoperative adverse outcome risks in elderly patients experiencing frailty (73,87,88). By adding specific domains of frailty from the FACT frailty score, such as Daily Tasks and Social, patient risks can be assessed with better predictive ability. We found that by adding frailty to, for example, MACE, the predictive ability significantly improved from an AUC of 0.62 to an AUC of 0.72. This may be useful to both clinicians and patients in preoperative assessment and counselling in determining patient suitability for cardiac surgery and in shared decision-making processes.

The FACT is useful clinically in a busy cardiac surgery setting. This research has successfully demonstrated that it is very feasible to incorporate the FACT as a preoperative assessment for patients choosing to undergo cardiac surgery. The assessment itself takes 10-15 minutes to complete, and it does not require a trained geriatrician or physician to complete the assessment. The patient can fill out the FACT at their own pace, by themselves, as this is a self-directed questionnaire.

4.4 Finding the correct cutoff point useful in clinical use of the FACT, specifically in cardiac surgery

Using a cutpoint of 4 or higher on the FACT to dichotomize frailty, while less useful in the current study due to a high proportion of vulnerable patients, may be clinically useful in cardiac surgery frailty assessments. The FACT produces continous scores, but because of small sample size and the distribution of scores in our sample, the overall score and domain specific scores had to be dichotomized. This explains why the present study had a population with a high proportion of participants experiencing frailty (88.70%), while most studies present with a study population of up to 50% frail (40,76,73). Among elderly patients undergoing cardiac surgery, the rate of frail patients was much higher when compared with other such studies (57,87,89,90).

This effect is likely due to the study's use of the overall level of frailty in the preliminary demographic analysis to determine differences between groups. As mentioned above, the current study utilized a cutpoint of 4 (vulnerable) or higher on the FACT to dichotomize frailty (73). While using different cutpoints to dichotomize the groups (such as using levels 1-4 and 5-8) might have divided participants more evenly, meaning there would be more power in each group, using a cutpoint of 5 was not significant and had less clinical utility. This might have affected the generalizability of results, and the assessment of the predictve value of the FACT. Future research needs to examine the clinical utility of the FACT for cardiac surgery outcomes in larger samples which have greater diversity in terms of all the FACT domains.

The use of mobility as a domain in the FACT may be problematic for purposes of assessing cardiac surgery risk. As a result of this domain, most of the sample ends up being classified as frail, as noted above. However, during analysis, it was noted that there were significant limitations with using the overall frailty level to categorize participants, as it was skewed heavily by the influence of the mobility domain. Low mobility is a direct result of the cardiac condition leading to the need for surgery, and thus may not be representative of frailty.

4.5 Study strengths

The major strength of this study is its clinical relevance and patient-oriented focus. The results of this study could be used to improve clinical practice on a daily basis by better educating future heart surgery patients about their possible risks. This ties into shared decision making (SDM), which is an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options in order to achieve informed preferences (79). Knowledge transfer, deliberation, and forming a decision consensus are all important stages of the SDM process. Information from this study could provide invaluable information to a patient's risk profile to assist the patient and surgeon in making their surgery decision.

Another strength of this project is its uniqueness. This study is the first of its kind in the Maritime Provinces of Canada. The investigation of frailty and cardiac surgery outcomes in this study spans most of Atlantic Canada's provinces, with the exception of Newfoundland and Labrador. It is a multi-centre study which recruited participants in NB and NS, however, has patients from all over Atlantic Canada, including Nova Scotia, New Brunswick, PEI, and Newfoundland and Labrador. This study will act as a solid basis for which future research can rely on and will promote research and deeper inquiry into this important topic.

Additionally, this project has uniquely strong collaborators in geriatrics who have shown leadership in frailty by pioneering the CFS (Dr. Rockwood), followed by Drs. Mallory and Moorhouse devising the FACT for clinical use. This questionnaire is unique, and its specificity gives us the ability to evaluate frailty in a completely novel way.

Primary data collection has several advantages, primarily that administration of questionnaires is easy and relatively inexpensive, tabulation and data entry of responses is easy, fast, and straightforward, and reduces the chance of interviewer bias.

4.6 Study limitations

The principal limitation of the study was that sample size was limited, due to time constraints, which in turn led to a small incidence of in-hospital mortality, and to an extent, other adverse outcomes (Appendix B). Low rates of mortality can be explained by the inclusion criteria, as patients receiving elective surgery are unlikely to be as serious as other cases (i.e. urgent, emergent, or salvage), which is why mortality alone was eliminated as an outcome during the analysis stage. Analysis was not feasible with so few participants experiencing that particular outcome.

Second, this study only examines two outcomes, and many more outcomes may be potentially important to patients. Many outcomes which are relevant to patients, such as quality of life, were not included in the study. Thirty-day morbidity and mortality have been recognized as the gold standard for judging quality of care; however, this paradigm is under scrutiny due to the aging demographic of surgical patients. A limited lifespan makes patient-centred outcomes essential to measure quality of care (91). To ameliorate this limitation, quality of life questionnaires were administered to the same cohort of patients, and we intend to perform future analyses on this data to examine this very important and relevant patient-centred outcome.

Third, demonstrating that the FACT has potential predictive value is only a starting point. Ultimately, it is also important to understand how its measurement could be incorporated into clinical decision-making processes. Clinicians may use this integrative approach of combining risk scores with frailty to better characterize elderly patients referred for cardiac interventions and identify those who are vulnerable and at increased risk (40). Using a variety of health care disciplines (i.e. physiotherapy, geriatrics, cardiology, cardiac surgery, occupational therapy) to aid health and improved functioning, perhaps these diverse elements can be brought together to address contributors to postoperative risk. Once the FACT has demonstrated its predictive ability in different contexts and situations in Canada, perhaps this can be added to the EuroSCORE II calculator and be incorporated in routine care thereafter.

Additionally, this study represents the experience of two centres on patients undergoing CABG and/or AVR. While this is also a strength of the study, certain characteristics of our population (race, ethnic composition, and other characteristics) may limit generalizability to other populations. Due to the unique location of this research, we may have captured a more rural population with lower socioeconomic status (SES) presenting for cardiac surgery (93,94). Future studies should examine the effect of rurality, education, and other factors on these results.

Little psychometric analysis has been previously conducted on the FACT. A limited number of studies have used the FACT in clinical studies to predict outcomes (92). However, the FACT originated from, and is linked with, the CFS, a very well-validated measure of frailty, both internally and externally valid and reliable (32,33,67,73,92).

There are some biases, which may occur while participants fill out the questionnaires, primarily response bias and social desirability bias. Participants may forget to answer, not respond to certain questions, or answer questions in a manner they believe will be viewed favourably by others. If bias occurred, which would be unlikely, bias from these two sources would likely result in participants rating themselves lower on the FACT than they might actually be, since being frail is a less desirable quality. Research on response bias and desirability bias indicate that this type of questionnaire often results in an overestimation of participant health.

Estimates of satisfaction may be most inflated for the least healthy patients, which may threaten validity of the results (95). These biases could lead to fewer participants rating themselves as frail and might have led certain associations to become nonsignificant; however, this was not the case, as demonstrated by the results above. During the recruitment, team members took effective steps to combat these biases by allowing the participant to fill out the questionnaire on their own and only providing help to the participant when necessary and emphasizing that the research team would keep questionnaires private and confidential at all times; as well, being clear that responses would only be viewed by staff when preparing data for analysis.

CHAPTER 5 CONCLUSIONS

5.1 General conclusions

Not only is frailty predictive of mortality and/or MACE, as well as MACE alone, the FACT has been shown to be clinically useful in a busy cardiac surgery setting. This research has successfully demonstrated that it is very feasible to incorporate the FACT as a preoperative assessment for patients choosing to undergo cardiac surgery. These results provide a first look at a unique topic in cardiac surgery, with predictive models for various adverse outcomes.

5.2 Implications and future work

Frailty, while measured in heterogeneous ways in cardiac surgery research, is often accompanied by unfavourable sequelae that are commonly considered worse than death by patients (13,40). Focus groups previously performed by our research team illuminated the common misconception that while health care workers often think mortality the worse outcome, patients tend to have different priorities which may include avoiding various adverse postoperative outcomes such as discharge to a care institution and MACE.

Results of this study will help us better educate future heart surgery patients about their possible risks. Our hope is that frail patients who know more about their personal risks will be able to make a better decision about their surgical treatment, since they will be better informed regarding the potential risks and benefits of surgical intervention. In addition, these results should help develop a more robust evidence basis around recommendations for surgery.

These results give us the potential to mitigate these cardiovascular health risks by transforming certain processes of care. Forming strategies to address and reduce frailty could be useful to identify issues in individual patients which are potentially modifiable. Interventions could increase mobility, reduce nutritional deficiencies and improve

cognitive function (96). For example, a prospective intervention could be implemented through social work and home care to improve functional independence, social support, medication compliance, and nutrition. Such interventions have been shown to be effective in elderly patients with heart failure. Additionally, recent studies have demonstrated resistance training can improve cognitive performance in patients with subjective memory impairment (96,97).

Future research by our group will include studies that examine other aspects of frailty, and studies that build on the foundation that has been established with this research. Qualitative exit interviews were conducted with all participants, and these data will be analyzed to provide information about participants' progress following surgery. It will further examine how adverse outcomes impact patients and will examine long-term recovery from cardiac surgery in frail and non-frail patients. Hopefully, further research will be conducted in frailty and shared decision-making in cardiac surgery. Ultimately, this research will be disseminated in a variety of ways (as described above), leading to better patient satisfaction and decreasing decisional conflict.

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APPENDIX A Sample Interview Questionnaires

1. Consent Form

NSHA Consent Form Non-Interventional Study

STUDY TITLE:	**Impact of Frailty on Cardiac Surgery Outcomes**
PRINCIPAL INVESTIGATOR:	Dr. Gregory Hirsch 1796 Summer Street Halifax Nova, Scotia (902) 473-7890
STUDY SPONSOR:	*Dr. Greg Hirsch*
FUNDER:	Technical Evaluation in Elderly Care Network - TVN

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1. INTRODUCTION

You have been invited to take part in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood. Taking part in this study is voluntary. It is up to you to decide whether to be in the study or not. Before you decide, you need to understand what the study is for, what risks you might take and what benefits you might receive. This consent form explains the study.

The research team will tell you if there are any study timelines for making your decision.

Please ask the research team to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study.

The researchers will:

- Discuss the study with you
- Answer your questions
- Be available during the study to deal with problems and answer questions

You are being asked to consider participating in this study because of the type of heart surgery you are schedule to have (coronary artery bypass graft, valve, or coronary artery bypass graft plus valve) and your age.

If you decide not to take part or if you leave the study early, your usual health care will not be affected.

2. WHY IS THIS STUDY BEING CONDUCTED?

This study is being done because having a lower fitness level before having heart surgery has been linked to having bad results after surgery. Some of these bad results are longer in-hospital stay and being discharged to a care center. In this study, we will find out your fitness level before your surgery, to see how your fitness levels affects your recovery. What we find out from this study will help us better educate future heart surgery patients about their possible risks. Our hope is that patients who know more about their personal risks will be able to make a better decision about what treatment they want their doctors to do.

3. HOW LONG WILL I BE IN THE STUDY?

The length of this study for participants is approximately 15 minutes before your surgery, and a 15 minute phone conversation 5-7 months after your surgery. The entire study is expected to take about 2 years to complete and the results should be known in 3 years.

4. HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

It is anticipated that 450 people will participate in this study at the Halifax Infirmary hospital, Nova Scotia and the New Brunswick Heart Centre in Saint John, New Brunswick.

5. HOW IS THE STUDY BEING DONE?

Our study involves a meeting with you before surgery and a phone interview after surgery. Before surgery you will be asked questions so we can determine your fitness level. You will also be asked to fill out a quality of life questionnaire and a function questionnaire before your surgery. 5-7 months after surgery, you will again be asked to complete the same quality of life questionnaire and answer a few other questions by phone. Your commitment to this study will end after you finish this follow-up interview.

6. WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?

If you choose to take part in this study, you and your collateral will meet with us in separate rooms before your surgery and have another interview with us 6 to 9 months after your surgery.

Meeting Before Surgery

- 15-minute meeting with a member of our research team
- You will be asked questions specific to your mobility, activities of daily living, social and functional capacity to help us determine your level of fitness
- You will be asked to complete a quality of life and functional independence questionnaire

Interview After Surgery

- 15-minute phone interview with a member of our research team
- You will be asked to complete a quality of life questionnaire
- You will be asked questions about other aspects of your daily life (ex. living situation)

If you choose to take part in this study, you are free to choose not to participate in any of the study questionnaires at any time.

7. ARE THERE RISKS TO THE STUDY?

There are a few risks associated with participation in this study, just as there are with all studies. To give you the most complete information available, we have listed some *possible* risks. We want to make sure that if you decide to take part in the study, you have had a chance to think about all the risks carefully. Please be aware that there may be risks that we don't yet know about.

Interviews/Questionnaires

You may find the interviews and questionnaires you receive during the course of the study upsetting or distressing. You may not like all of the questions that you will be asked. You do not have to answer those questions you find too distressing.

8. ARE THERE BENEFITS OF PARTICIPATING IN THIS STUDY?

We cannot guarantee or promise that you will receive any benefits from this research.

9. WHAT HAPPENS AT THE END OF THE STUDY?

You will be thanked for your participation in this research study after your final interview. At this time, you will be given contact information for members of our research team in case you have any more questions about this study.

10. WHAT ARE MY RESPONSIBILITIES?

As a study participant you will be expected to:

- Follow the directions of the research team;
- Report all medications being taken or that you plan on taking;
- Report any changes in your health to the research team;
- Report any problems that you experience that you think might be related to participating in the study

11. CAN MY PARTICIPATION IN THIS STUDY END EARLY?

Yes. If you chose to participate and later change your mind, you can say no and stop the research at any time. If you wish to withdraw your consent please inform the research team. If you choose to withdraw from this study, your decision will have no effect on your current or future medical treatment and healthcare.

Also, the Nova Scotia Health Authority Research Ethics Board, the Horizon Health Network Research Ethics Board, and the principal investigator have the right to stop patient recruitment or cancel the study at any time.

Lastly, the principal investigator may decide to remove you from this study without your consent for any of the following reasons:

- You do not follow the directions of the research team;
- You are experiencing side effects that are harmful to your health or well-being;
- There is new information that shows that being in this study is not in your best interests;

If you are withdrawn from this study, a member of the research team will discuss the reasons with you.

If you withdraw your consent, the information about you collected before you left the study will still be used. No new information about you will be collected without your permission.

12. WHAT ABOUT NEW INFORMATION?

You will be told about any other new information that might affect your health, welfare, or willingness to stay in the study and will be asked whether you wish to continue taking part in the study or not.

13. WILL IT COST ME ANYTHING?

There are no costs to participants for being part of this study and participants will not be paid to participate. Additionally, out of pocket expenses (ex. parking costs) will not be reimbursed.

Research Related Injury

If you become ill or injured as a direct result of participating in this study, necessary medical treatment will be available at no additional cost to you. Your signature on this form only indicates that you have understood to your satisfaction the information regarding your participation in the study and agree to participate as a subject. In no way does this waive your legal rights nor release the principal investigator, the research staff, the study sponsor or involved institutions from their legal and professional responsibilities.

14. WHAT ABOUT MY PRIVACY AND CONFIDENTIALITY?

Protecting your privacy is an important part of this study. Every effort to protect your privacy will be made. If the results of this study are presented to the public, nobody will be able to tell that you were in the study.

However, complete privacy cannot be guaranteed. For example, the principal investigator may be required by law to allow access to research records.

If you decide to participate in this study, the research team will look at your personal health information and collect only the information they need for this study. "Personal health information" is health information about you that could identify you because it includes information such as your;

- Name,
- Address,
- Telephone number,
- Age or month/year of birth (MM/YY),
- Information from the study interviews and questionnaires;
- New and existing medical records, or
- The types, dates and results of various tests and procedures.

a) Access to Records

Other people may need to look at your personal health information to check that the information collected for the study is correct and to make sure the study followed the required laws and guidelines. These people might include:

- Dr. Greg Hirsch, Primary Investigator
- Dr. Ansar Hassan, Co-Investigator
- Emma Wilson-Pease, Research

- The Nova Scotia Health Authority Research Ethics Board (NSHA REB) and people working for or with the NSHA REB because they oversee the ethical conduct of research studies within the Nova Scotia Health Authority.

b) Use of Your Study Information

Any study data about you that is sent outside of the Nova Scotia Health Authority will have a code and will not contain your name or address, or any information that directly identifies you.

De-identified study data may be transferred to:

- Nova Scotia Health Authority

Study data that is sent outside of the Nova Scotia Health Authority will be used for the research purposes explained in this consent form.

The research team and the other people listed above will keep the information they see or receive about you confidential, to the extent permitted by applicable laws. Even though the risk of identifying you from the study data is very small, it can never be completely eliminated.

The research team will keep any personal health information about you in a secure and confidential location for 7 years and then destroy it according to NSHA policy. Your personal health information will not be shared with others without your permission.

After your part in the study ends, we may continue to review your health records for safety and data accuracy until the study is finished or you withdraw your consent.

You have the right to be informed of the results of this study once the entire study is complete.

The REB and people working for or with the REB may also contact you personally for quality assurance purposes.

c) Your access to records

You have the right to access, review, and request changes to your study data.

15. DECLARATION OF FINANCIAL INTEREST

The Canadian Frailty Network (CFN) is reimbursing the principal investigator and/or the principal investigator's institution to conduct this study. The amount of payment is sufficient to cover the costs of conducting the study.

16. WHAT ABOUT QUESTIONS OR PROBLEMS?

For further information about the study call **Dr. Greg Hirsch**. Dr. Hirsch is in charge of this study at this institution (he is the "Principal Investigator"). Dr. Hirsch's work telephone number is (902) 473-7890. If you can't reach the Principal Investigator (Dr. Hirsch), please refer to the attached Research Team Contact Page for a full list of the people you can contact for further information about the study.

The Principle Investigator is **Dr. Greg Hirsch**
Telephone: (902) 473-7890

Your Research Coordinator is **Emma Wilson-Pease**

Telephone: (902) 473-5780

17. WHAT ARE MY RIGHTS?

You have the right to all information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction before you make any decision. You also have the right to ask questions and to receive answers throughout this study.

If you have any questions about your rights as a research participant, contact Patient Relations at (902) 473-2133 or healthcareexperience@nshealth.ca

If you are calling us long distance (NS, NB and PEI), please use our toll free number 1-855-799-0990.

In the next part you will be asked if you agree (consent) to join this study. If the answer is "yes", please sign the form.

18. CONSENT FORM SIGNATURE PAGE

I have reviewed all of the information in this consent form related to the study called:

Impact of Frailty on Cardiac Surgery Outcomes

I have been given the opportunity to discuss this study. All of my questions have been answered to my satisfaction.
I authorize access to my personal health information, and research study data as explained in this form.
This signature on this consent form means that I agree to take part in this study. I understand that I am free to withdraw at any time without affecting my future care.

_____	_____	_____/ _____ / ____
Signature of Participant	Name (Printed)	Year Month Day*
_____	_____	_____/ _____ / ____
Signature of Person Conducting Consent Discussion	Name (Printed)	Year Month Day*
_____	_____	_____/ _____ / ____
Signature of Investigator	Name (Printed)	Year Month Day*
_____	_____	_____/ _____ / ____
Signature of Participant's Substitute Decision Maker	Name (Printed)	Year Month Day*
_____	_____	_____/ _____ / ____
Signature of Impartial Witness	Name (Printed)	Year Month Day*

If the consent discussion has been conducted in a language other than English, please indicate: _____
Language

_____	_____	_____/_____ / ____
Signature of Translator	Name (Printed)	Year Month Day

I will be given a signed copy of this consent form.

2. FACT questionnaire

Addressograph/Sticker

Participant Report on Overall Health

Instructions: To be completed by **the participant** (1) First, answer the two yes/no questions on the top row. (2) Then, in each column, check THE BOX that **BEST** describes your **USUAL** abilities at home.

	ARE YOU **WALKING** AT YOUR USUAL LEVEL TODAY? ☐ yes ☐ no			ARE YOU YOUR USUAL SELF TODAY IN TERMS OF MEMORY? ☐ yes ☐ no
	Usual Mobility (getting round)	**Social**	**Daily Tasks**	**Memory**
1	O Fit, exercise regularly (e.g. swimming, exercise class)	O I'm in charge of organizing social events	O I still work at a job or do a high level hobby (e.g. building model airplanes)	O Impress others with memory and thinking
2 & 3	O Active/exercise occasionally	O Socialize weekly and have someone to count on if needed	O I can do all the things I used to do without any help, but finds it harder	O I am worried about my memory, but my family (caregiver) is not concerned
4	O Starting to slow down and often tired during the day	O Socialize less than weekly OR might not have someone to count on if needed	O I am not dependent on others but my symptoms often limit activities	CONCERNS: (choose any that apply)
5	O Walking slower and regularly need a cane or walker	O Socialize rarely	O I need help with some everyday activities that I could previously do alone such as housework, or banking, or taking medications correctly	O Trouble remembering details of current news and/or recent events
6	O I need the help of another person when using stairs, walking on uneven ground or getting in/out of the bath OR O I have fallen **more than** once in the past 6 months (not on ice)	O Mostly house-bound	O I need help with all activities outside the home (e.g. banking, shopping) and reminders for some activities in the home such as choosing appropriate/ fresh clothes for the day or reminders to bathe	O Often repeat stories or questions
7	O I always need someone's help or supervision when walking OR O I need help using a wheelchair	O House-bound and isolated: OR O Caregiver stress/or no available caregiver to meet care needs	O I need the help of another for bathing, toileting or dressing	O Often forget the names of close family members such as adult children
8	O I am unable to get out of bed and need help from others to move from bed to chair	O Unable to participate in any social exchange, even when visited	O I depend on others for all aspects of daily life	O Trouble remembering almost everything

Name of Participant_____ **Signature (participant)**_____ **Relationship with collateral**_____

path clinic
PALLIATIVE AND THERAPEUTIC HARMONIZATION

FACT Cognitive Assessment

Explanation for testing: "*Part of my role is to look at your overall health, so I'm going to ask you some questions which may not seem to be related to the reason that you're here today"*

1. Ask the patient to, "Repeat the following 3 words and remember them for later:

   APPLE PENNY WATCH

2. Have the patient "Draw a clock" on a separate piece of blank paper (provided) "and place the hands of the clock at ten minutes after eleven."

3. Ask the patient "What were those words I asked you to remember?" and record their answer in the space below:

   Answers must be exact (e.g. "clock" is not acceptable).

   _____ _____ _____

4. Determine a cognitive score by following the Cognitive Flow Sheet

3. EQ-5D-3L & EQ-VAS

Health Questionnaire

English version for Canada

By placing a check-mark in one box in each group below, please indicate which statements best describe your own state of health today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

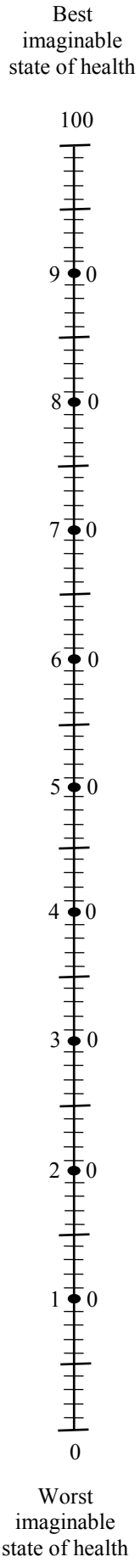
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad their state of health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.

Your own state of health today



APPENDIX B Power Calculations for Adverse Outcomes

Figure 1. Sample size necessary for MACE outcome, using Overall sample size distribution.

Power for Cohort Studies

	Input Data
Two-sided confidence interval (%)	95
Number of exposed	203
Risk of disease among exposed (%)	18.26
Number of non-exposed	26
Risk of disease among non-exposed (%)	0.87
Risk ratio detected	21
Power based on:	
Normal approximation	61.97%
Normal approximation with continuity correction	49.96%

Figure 2. Sample size necessary for MACE outcome, using Daily Tasks sample size distribution.

Power for Cohort Studies

	Input Data
Two-sided confidence interval (%)	95
Number of exposed	107
Risk of disease among exposed (%)	14.78
Number of non-exposed	121
Risk of disease among non-exposed (%)	4.35
Risk ratio detected	3.4
Power based on:	
Normal approximation	77.82%
Normal approximation with continuity correction	69.93%

Figure 3. Sample size necessary for mortality +/- MACE outcome, using Overall sample size distribution

Power for Cohort Studies

	Input Data
Two-sided confidence interval (%)	95
Number of exposed	203
Risk of disease among exposed (%)	19.56
Number of non-exposed	26
Risk of disease among non-exposed (%)	0.87
Risk ratio detected	22

Power based on:	
Normal approximation	65.91%
Normal approximation with continuity correction	54.53%

Figure 4. Sample size necessary for mortality +/- MACE outcome, using Daily Tasks sample size distribution

Power for Cohort Studies

	Input Data
Two-sided confidence interval (%)	95
Number of exposed	107
Risk of disease among exposed (%)	16.09
Number of non-exposed	121
Risk of disease among non-exposed (%)	4.35
Risk ratio detected	3.7

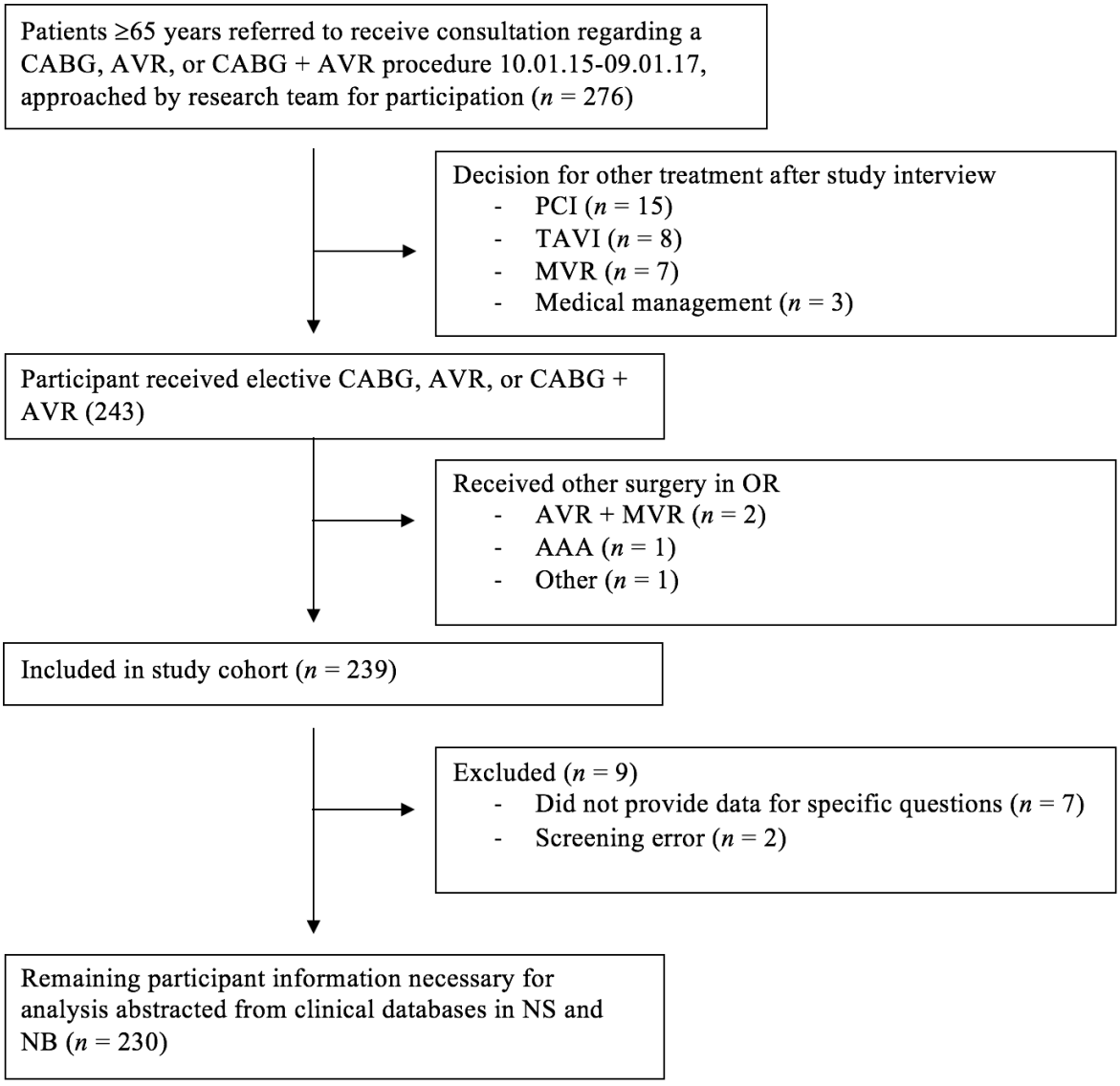
Power based on:	
Normal approximation	84.8%
Normal approximation with continuity correction	78.57%

Results from OpenEpi, Version 3, open source calculator--PowerCohort
Print from the browser with ctrl-P
or select text to copy and paste to other programs.

*All calculations performed using OpenEpi software - Version 3, open source calculator (98).

APPENDIX C Supplementary Tables & Figures

Supplementary Figure 1. Participant flow throughout study recruitment and analysis



Supplementary Table 1. Frequencies of unadjusted in-hospital outcomes by frailty domain, stratified by frailty status

	Overall	Mobility	Social	Daily Tasks	Memory
MACE					
Frail	42/44 (95.45%)	37/44 (84.09%)	16/44 (36.36%)	34/44 (77.27%)	17/44 (38.64%)
Not frail	2/44 (4.54%)	7/44 (15.90%)	28/44 (63.63%)	10/44 (22.72%)	27/44 (61.36%)
Mortality +/- MACE					
Frail	4/47 (95.74%)	40/47 (85.10%)	20/47 (42.56%)	37/47 (78.72%)	22/47 (46.80%)
Not frail	2/47 (4.26%)	7/47 (14.89%)	27/47 (5.44%)	10/47 (21.28%)	25/47 (53.19%)

*Overall frailty score was calculated using the highest frailty score from across the four domains, and dichotomized into two groups for analysis due to small sample size, into the following categories: 1-3 Not frail, 4-8 Frail; N = 230

Supplementary Table 2. EuroSCORE II effects in adjusted models remain unchanged after addition of FACT scores

	EuroSCORE II OR (95% CI)	***P-value***
Mortality and/or MACE		
EuroSCORE II alone	1.09 (1.02-1.16)	0.009
+ Overall	1.09 (1.02-1.16)	0.011
+ Mobility	1.09 (1.02-1.16)	0.009
+ Social	1.07 (1.01-1.15)	0.035
+ Daily Tasks	1.09 (1.01-1.16)	0.016
+ Memory	1.09 (1.02-1.16)	0.014
MACE		
EuroSCORE II alone	1.12 (1.05-1.20)	0.001
+ Overall	1.12 (1.04-1.20)	0.001
+ Mobility	1.12 (1.05-1.20)	0.001
+ Social	1.10 (1.04-1.19)	0.003
+ Daily Tasks	1.12 (1.05-1.21)	0.001
+ Memory	1.12 (1.05-1.20)	0.001

*P-values derived by regression analysis; FACT overall score calculated by taking the highest overall score from the four domains; FACT dichotomized into two groups for analysis due to small sample size, into the following categories: 1-3 Not frail, 4-8 Frail; N = 230

Supplementary Table 3. Logistic regression models of FACT on primary adverse outcomes, adjusted for EuroSCORE II, comparing the most parsimonious model (Social, Daily Tasks, and Memory domains) with the initial model.

	Adjusted		*S, DT, M model (adjusted)*	
	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*
Mortality and/or MACE				
EuroSCORE II	--	--	--	--
+ Overall	2.89 (0.65-12.82)	0.163	--	--
+ Mobility	1.16 (0.47-2.85)	0.746	--	--
+ Social (S)	2.67 (1.25-5.69)	0.011*	1.85 (0.82-4.16)	0.136
+ Daily Tasks (DT)	3.38 (1.56-7.33)	0.002*	2.90 (1.32-6.38)	0.008*
+ Memory (M)	2.45 (1.20-5.00)	0.014*	1.86 (0.87-3.99)	0.112
MACE				
EuroSCORE II	--	--	--	--
+ Overall	2.95 (0.66-13.21)	0.157	--	--
+ Mobility	1.18 (0.48-2.90)	0.751	--	--
+ Social (S)	2.43 (1.13-5.24)	0.023*	1.74 (0.76-3.95)	0.188
+ Daily Tasks (DT)	3.58 (1.64-7.84)	0.001*	3.15 (1.422-6.99)	0.005*
+ Memory (M)	2.05 (0.99-4.24)	0.052	1.55 (0.71-3.39)	0.270

*P-values derived by regression analysis; FACT overall score calculated by taking the highest overall score from the four domains; FACT dichotomized into two groups for analysis due to small sample size, into the following categories: 1-3 Not frail, 4-8 Frail; N = 230

Supplementary Table 4. Multivariable model fit statistics for each adverse outcome event occurring post-discharge, relative to a baseline model with EuroSCORE II, examining additional models involving the most predictive domains (Social, Daily Tasks, and Memory)

	AUC (95% CI)	AIC	BIC	LR
Mortality and/or MACE				
EuroSCORE II	0.62 (0.52-0.71)	218.09	224.95	--
+ Overall	0.64 (0.55-0.73)	217.58	227.87	0.11
+ Mobility	0.62 (0.52-0.71)	219.98	230.27	0.74
+ Social (S)	0.65 (0.55-0.74)	213.95	224.24	0.01*
+ Daily Tasks (DT)	0.69 (0.61-0.77)	209.29	219.58	0.00*
+ Memory (M)	0.63 (0.54-0.73)	214.22	224.51	0.00*
+ Cumulative	0.71 (0.63-0.80)	208.24	228.82	0.00*
+ S, DT, M	**0.71 (0.62-0.80)**	**207.83**	**225.02**	**0.00***
+ S, DT	**0.71 (0.62-0.80)**	**208.29**	**222.04**	**0.00***
MACE				
EuroSCORE II	0.64 (0.54-0.73)	215.26	222.12	--
+ Overall	0.66 (0.56-0.75)	214.67	224.96	0.11
+ Mobility	0.64 (0.54-0.73)	217.13	227.42	0.72
+ Social (S)	0.67 (0.57-0.76)	212.39	222.68	0.03*
+ Daily Tasks (DT)	0.71 (0.62-0.79)	205.64	215.93	0.00*
+ Memory (M)	0.64 (0.55-0.74)	213.62	223.91	0.06
+ Cumulative	0.72 (0.64-0.80)	206.99	227.57	0.00*
+ S, DT, M	**0.72 (0.64-0.81)**	**206.56**	**223.75**	**0.00***
+ S, DT	**0.73 (0.64-0.81)**	**205.75**	**219.50**	**0.00***

*Each model included the base model (EuroSCORE II) with the addition of each domain (overall, mobility, social, daily tasks, and memory) alone. The cumulative model included all four domains, not including overall frailty, in one model together. AUC indicates area under the receiver operating curve; CI, 95% confidence interval; AIC, Aikaike Information Criterion; BIC, Bayesian Information Criterion, LR, likelihood ratio test (each model compared to EuroSCORE II model alone); outcomes based on

event rates at discharge; FACT overall score calculated by taking the highest overall score from the four domains; FACT dichotomized into two groups for analysis due to small sample size, into the following categories: 1-3 Not frail, 4-8 Frail; N = 230

Supplementary Table 5. Logistic regression models of FACT on primary adverse outcomes, unadjusted for EuroSCORE II, with altered cutpoint for frailty FACT scores

	Unadjusted	
	OR (95% CI)	*P-value*
Mortality and/or MACE		
EuroSCORE II	--	--
+ Overall	1.77 (0.90-3.51)	0.100
+ Mobility	1.07 (0.45-2.51)	0.882
+ Social	4.17 (1.84-9.44)	0.001*
+ Daily Tasks	1.72 (0.67-4.39)	0.258
+ Memory	3.73 (0.96-14.54)	0.058
MACE		
EuroSCORE II	--	--
+ Overall	1.91 (0.97-3.75)	0.061
+ Mobility	1.24 (0.54-2.83)	0.613
+ Social	4.33 (1.91-9.84)	0.000*
+ Daily Tasks	1.66 (0.65-4.24)	0.287
+ Memory	3.62 (0.93-14.09)	0.063

*P-values derived by regression analysis; FACT overall score calculated by taking the highest overall score from the four domains; FACT dichotomized into two groups for analysis due to small sample size, with altered cutpoint, into the following categories: 1-4 Not frail, 5-8 Frail; N = 230

Supplementary Table 6. Sensitivity analysis on logistic regression models of FACT on primary adverse outcomes, comparing cutpoints (adjusted for EuroSCORE II)

	Adjusted – Cutpoint at 4		*Adjusted – Cutpoint at 5*	
	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*
Mortality and/or MACE				
EuroSCORE II	--	--	--	--
+ Overall	2.89 (0.65-12.82)	0.163	1.65 (0.82-3.32)	0.159
+ Mobility	1.16 (0.47-2.85)	0.746	0.99 (0.41-2.40)	0.986
+ Social	2.67 (1.25-5.69)	0.011*	3.56 (1.50-8.41)	0.004*
+ Daily Tasks	3.38 (1.56-7.33)	0.002*	1.56 (0.59-4.12)	0.370
+ Memory	2.45 (1.20-5.00)	0.014*	3.15 (0.76-13.04)	0.113
MACE				
EuroSCORE II	--	--	--	--
+ Overall	2.95 (0.66-13.21)	0.157	1.76 (0.87-3.55)	0.117
+ Mobility	1.18 (0.48-2.90)	0.751	1.14 (0.48-2.73)	0.766
+ Social	2.43 (1.13-5.24)	0.023*	3.12 (1.30-7.49)	0.011*
+ Daily Tasks	3.58 (1.64-7.84)	0.001*	1.46 (0.54-3.96)	0.453
+ Memory	2.05 (0.99-4.24)	0.052	2.97 (0.69-12.75)	0.143

*P-values derived by regression analysis; FACT overall score calculated by taking the highest overall score from the four domains; FACT dichotomized into two groups for analysis due to small sample size, into the following categories: 1-3 Not frail, 4-8 Frail; N = 230

Supplementary Table 7. Sensitivity analysis on logistic regression models of FACT on primary adverse outcomes, comparing 3 frailty levels and frailty cutpoint of five, adjusted for EuroSCORE II

	Adjusted – 3 Frailty Levels		*Adjusted – Cutpoint at 5*	
	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*
Mortality and/or MACE				
EuroSCORE II	--	--	--	--
+ Overall	1.67 (0.95-2.95)	0.076	1.65 (0.82-3.32)	0.159
+ Mobility	1.05 (0.60-1.85)	0.860	0.99 (0.41-2.40)	0.986
+ Social	**1.86 (1.21-2.85)**	**0.005***	**3.56 (1.50-8.41)**	**0.004***
+ Daily Tasks	**2.00 (1.21-3.28)**	**0.006***	1.56 (0.59-4.12)	0.370
+ Memory	**2.11 (1.19-3.71)**	**0.010***	3.15 (0.76-13.04)	0.113
MACE				
EuroSCORE II	--	--	--	--
+ Overall	1.75 (1.04-1.20)	0.157	1.76 (0.87-3.55)	0.117
+ Mobility	1.12 (0.63-1.98)	0.694	1.14 (0.48-2.73)	0.766
+ Social	**1.75 (1.13-2.70)**	**0.012***	**3.12 (1.30-7.49)**	**0.011***
+ Daily Tasks	**2.02 (1.23-3.33)**	**0.006***	1.46 (0.54-3.96)	0.453
+ Memory	**1.86 (1.05-3.32)**	**0.033***	2.97 (0.69-12.75)	0.143

*P-values derived by regression analysis; FACT overall score calculated by taking the highest overall score from the four domains; N = 230