A PHASE III RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED CLINICAL TRIAL TO ASSESS THE EFFECTS OF FERAMAX® WHEN ADMINISTERED ORALLY ONCE A DAY ON POSTOPERATIVE FATIGUE LEVELS IN PATIENTS FOLLOWING ELECTIVE CORONARY ARTERY BYPASS GRAFT SURGERY

by

Heather E. Mingo

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DEDICATION

This thesis is dedicated to my family, who have meant, and continue to mean, so much to me. I would like to thank my parents, Sandy and Millie Mingo, who are no longer with us. They instilled in me the value of hard work and a drive to never to give up on my dreams. Both my mother and father were always proud supporters of whatever path I chose. I miss and think of them every day.

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ABSTRACT

Fatigue is one of the most prevalent and troublesome symptoms experienced by patients after undergoing coronary artery bypass graft (CABG) surgery. It is often associated with significant morbidity, impairments in mobility, and reduced quality of life (QOL). The etiology of postoperative fatigue (POF) is complicated and multifactorial with several contributing mechanisms. It is not routinely assessed clinically, and treatment is currently based on limited empirical evidence. Effective treatment of fatigue would significantly decrease symptom burden related to CABG surgery. The purpose of this randomized controlled trial (RCT) was to examine whether a single intervention – the administration of a once-daily oral iron tablet – would have an effect on the reported experience of postoperative fatigue among a population of patients undergoing CABG surgery. A sample of 121 patients was recruited, and of those 121 patients, 109 were randomized to a control or an intervention group. Five patients withdrew the day after randomization, and no medication was consumed. One hundred-four patients were entered into the data analysis using the intention to treat approach. Symptom Management Theory (SMT) formed the conceptual and theoretical basis for the study.

Results obtained from this study failed to reject the null hypothesis in that there was no statistically significant difference between the primary study outcome of reported fatigue between the control and the intervention groups. Findings from the study do, however, contribute to our knowledge of this poorly understood symptom and provide suggestions for future research. Study results point to the need for refinement of the SMT framework and the need for more structured clinical assessment, focused patient education, and greater attention to the impact of fatigue on postoperative recovery.

LIST OF ABBREVIATIONS USED

ASA	American Association of Anesthetists
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CDCD	Center for Disease Control and Prevention
CRP	C – reactive protein
GI	Gastrointestinal
LVEF	Left Ventricular Ejection Fraction
QOL	Quality of Life
FACT-An	Functional Assessment of Cancer Therapy Anemia
Hgb	Hemoglobin
ICFS	Identity Consequences Fatigue Scale
ITT	Intention to Treat
MI	Myocardial Infarction
POF	Postoperative Fatigue
POMS	Profile of Mood States
SF-36	Short Form 36
SMT	Symptom Management Theory
6MWT	Six-Minute Walk Test
SSI	Surgical Site Infection
TIBC	Total Iron Binding Capacity
VAS	Visual Analog Scale

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CHAPTER 1 INTRODUCTION

1.1 Background

All people experience varying levels of fatigue at some point during their lives. Fatigue is considered a common, non-specific, subjective symptom that is difficult to characterize. Patients may describe the fatigue symptom as sleepiness, weakness, depressed mood, or lack of energy (Wright & O'Connor, 2014). Acute or physiologic fatigue is usually of short duration resulting from mental stress, repetitive or overactive physical activity, and sleep deprivation or health status unrelated to a medical condition (Aaronson et al., 1999; Rosenthal, Majeroni, Pretorius, & Malik, 2008; Wright & O'Connor, 2014). Symptoms of acute fatigue range from feelings of generalized tiredness to exhaustion (Schumann & Rodriguez, 2000) usually experienced by healthy people and relieved by rest or proper nutrition (Ruffin & Cohen, 1994; Wright & O'Connor, 2014).

Over time, acute fatigue can transition into chronic fatigue, presenting 50% of the time, not alleviated by rest, and lasting longer than six months (Rosenthal et al., 2008; Ruffin & Cohen, 1994; Schumann & Rodriguez, 2000). Chronic fatigue is debilitating and usually triggered by an underlying cause or symptom of a disease, such as hypothyroidism, renal dysfunction/ failure, multiple sclerosis, chronic fatigue syndrome, cancer, and coronary artery disease (CAD) (Heesen et al., 2006, Lee et al., 2004; Rosenthal et al, 2008; Smets, Garssen, Schuster-Uitterhoeve, & de Haes, 1993). Patients diagnosed with chronic disease or cancer experiencing anemia may also suffer from fatigue (Rosenthal et al., 2008). Chronic fatigue can further be distinguished from chronic fatigue syndrome. This syndrome, also known as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), is due to a possible association with immune dysfunction

and neuropathology (Haney et al., 2015; Unger et al., 2016; Viner & Christie, 2005). Myalgic Encephalomyelitis/chronic fatigue syndrome refers to a complex, debilitating disease described as persistent, disabling fatigue that worsens with physical, cognitive, and emotional effort (Chan et al., 2014; Haney et al., 2015; Unger et al., 2016). This multisystem disease has unknown etiology, nonrestorative sleep, and lasts longer than six months (Chan et al., 2014; Haney et al., 2015; MacLachlan et al.; 2017; Schumann & Rodriguez, 2000; Unger et al., 2016).

Fatigue, acute or chronic, is one of the most distressing and highly prevalent symptoms reported in individuals with CAD (Bunevicius, Stankus, Brozairiene, Girdler, & Bunevicius, 2011) and following coronary artery bypass graft surgery (CABG) (also known as cardiac revascularization) (Barnason et al, 2008; Hall & Salmon, 2002; Kop, 1999; Kehlet, 1997; Miller, Evangelista, Giger, Dracup, & Doering, 2013; Pedersen & Middel, 2001; Schroeder & Hill, 1993). Coronary artery disease leads to a decrease in circulating oxygen-rich blood, which, in turn, may result in angina, decreased exercise capacity, and fatigue (Bunevicius et al., 2011; Staniute, Bunevicius, Brozaitiene & Bunevicius, 2014). Fatigue is prevalent in 35 to 75% of CAD patients (Kop, 1999; Miller et al., 2013; Pedersen & Middel, 2001). Fatigue is considered an independent predictor of future cardiac events, for example, myocardial infarction (MI), repeat cardiac revascularization, recurrent angina, and readmission to a hospital (Kop et al., 1994; Miller et al., 2013; Smith, Kupper, Denoilet & de Jonge, 2011).

Coronary artery disease is the most common form of heart disease, affecting approximately 2.4 million Canadians and is the second leading cause of mortality in Canada (Government of Canada, 2017). This disease is associated with known

cardiovascular risk factors such as advancing age, sex, hypercholesterolemia, diabetes mellitus, smoking, hypertension, and chronic kidney disease (Government of Canada, 2017; Mancini et al., 2014) and results from a condition called atherosclerosis. Atherosclerosis is a condition of which coronary atherosclerotic plaque builds up in the lining of the coronary artery walls causing CAD (Government of Canada, 2017; Insull, 2009; Pragodpol & Ryan, 2013). The plaque is a waxy substance containing fatty deposits, cell waste, blood clotting material (fibrin), cholesterol, and calcium (Insull, 2009). This condition can cause people to develop angina, MI, heart failure, or cardiac arrhythmias. Over time, the disease progresses with further plaque build-up, causing narrowing and hardening of the arteries. Also, the plaque can rupture, creating a blood clot or thrombus formation at the rupture site (atherothrombosis). The thrombus can partially or entirely block oxygen-rich blood flow to a coronary artery resulting in acute cardiac events. An imbalance in myocardial oxygen supply and demand restricts blood flow to the heart muscle causing anginal pain (Hansson, 2005). The thrombus can completely block the artery causing death to part of the heart muscle (myocardial infarction) (Hansson, 2005). Earlier detection of CAD and cardiac revascularization are increasing life expectancy, but CAD is still causing mortality and morbidity (Hawkes, Nowak, Bidstrup & Speare, 2006). Coronary artery bypass graft surgery, a surgical treatment for CAD, can alleviate symptoms, reduce mortality, and improve functionality and QOL (Hawkes et al., 2006).

1.2 Background of Patient Population

Postoperative fatigue (POF) persists following one of the most common surgical procedures, CABG, delaying recovery, and functionality. These issues warrant further

research; therefore, this study investigated the fatigue effect through the use of iron supplementation among CABG patients. Postoperative CABG symptoms are well documented in the literature, describing both the physical (e.g., pain, dyspnea, fatigue, sleep disturbances, and edema) and psychological (e.g., anxiety disorders and depression) components (Al-Daakak, Ammouri, Isac, Gharaibeh, & Al-Zaru, 2016; Cowper et al., 2006). Following uncomplicated major surgery including CABG, fatigue continues to be a chief complaint which may prevail longer than surgical pain and can persist longer than physical symptoms (Barnason et al, 2008; DeCherney, Bachmann, Isaacson, & Gail, 2002; Kahokehr, Thompson, Thompson, Soop, & Hill, 2012; Zargar-Shoshtari & Hill, 2009). Fatigue can be accompanied by feelings of frustration, depression, and cognitive impairment affecting recovery (DeCherney et al., 2002; Zargar-Shoshtari & Hill, 2009). Fatigue can occur immediately following CABG surgery and tends to peak two to four weeks post-discharge (Barnason et al., 2008; Tsai, Tsay, Moser, Huang & Tsai, 2019; Zimmerman, 2002).

Preoperatively, the prevalence of fatigue ranges from 35% -75% in patients with CAD or other medical conditions, and these patients are reported to be at an increased risk for POF following CABG surgery (Hall & Salmon, 2002; Kehlet, 1997; Kop,1999; Miller et al., 2013; Schroeder & Hill, 1993). Fatigue has been identified as an independent prognostic indicator of CAD morbidity and mortality with a two- to three-fold increase in potential cardiac complications (e.g., readmission, MI) (Miller et al., 2013; Smith, Kupper, Denollet, & de Jonge, 2011). Postoperative fatigue is often associated with significant morbidity, impairments in mobility, compromised QOL, and prolonged recovery following CABG surgery (Barnason, Zimmerman, Anderson, Mohr-

Burt, & Nieveen, 2000; Barnason et al., 2008; Zargar-Shoshtari & Hill, 2009), especially in the elderly population (Whitson et al., 2011). This symptom is associated with muscle atrophy, decreased functional capacity, and cardiac deconditioning. These substantive changes can reduce independence and postpone the resumption of usual daily activities (Hall & Salmon 2002; Zargar-Shoshtari & Hill, 2009). A number of other preoperative risk factors that are predictive of morbidity and mortality following CABG surgery include advanced age (Hosseini, Amouei & Alemohammad, 2014), reduced renal function, diabetes mellitus, cerebral vascular disease, morbid obesity, chronic lung disease, left ventricular dysfunction, anemia (Barnason et al., 2008; Higgins et al., 1992; Miles et al., 2018; Miller et al., 2013), and psychosocial stressors (anxiety and depression) (Ramesh et al., 2017).

With earlier discharges, surgical complications, such as surgical site infections (SSI), tend to occur post-discharge and are treated in the outpatient setting (Anthony & Sendelbach, 2007). Any postoperative difficulties can negatively impact recovery, increase the patient burden, and require home care services (Stoicea et al., 2017). Postoperative fatigue can also have a direct impact on an individual's well-being and recovery, contributing to delays in return to normal daily activities, such as housekeeping, childcare, and family (Yu et al., 2015). Delay in recovery can place a significant strain on the family (Barnason et al, 2008; Bisgaard et al., 2001; DeCherney et al., 2002; Plach, Hendrich, & Jeske, 2006) and impact patients' return to work (Yu et al, 2015) and income (Zargar-Shoshtari & Hill, 2009). Greater POF severity can worsen physical, functional, and emotional outcomes, thus increasing demands on primary care and communities (Yu et al., 2015). Early assessment, identification, and secondary

prevention of fatigue by the healthcare provider could reduce the risk of disease progression and minimize further cardiac complications (Miller et al., 2013; Smith et al., 2011).

1.4 Definition

The definition of fatigue has been widely debated and remains poorly understood. Generally, the fatigue symptom has been characterized as a multidimensional phenomenon and is challenging to measure objectively (Rodriguez, 2000). Kennedy (1988) described POF as a feeling of tiredness, exhaustion, or strain during convalescence. Postoperative fatigue has been defined as a distressing, unpleasant, ongoing symptom impacting QOL following surgery (Rubin, Hardy, and Hotopf, 2004b). DeCherney et al. (2002) referred to POF as a factor delaying recovery in the postoperative period. Yu et al. (2015) defined POF as a subjective feeling of discomfort, leading to a loss of ability to participate in activities of daily living and regular work. Furthermore, Zargar-Shoshtari and Hill (2009) defined POF as a collection of multidimensional (physical and psychological) symptoms that delay return to normal activities. The definition by Zargar-Shoshtari and Hill for POF will be used for the current study as POF has a multidimensional etiology, and there is a reduction in postoperative activities.

1.5 Measurement

Due to fatigue's subjective nature and multidimensional components, the symptom is often overlooked by physicians. Standardized measures designed to assess the prevalence and severity of fatigue and fatigue-related symptoms do exist; many of the scales have been used for both clinical and research purposes. One of the most common

scales is the Fatigue Visual Analog Scale (VAS) (Christensen, Bendix, & Kehlet, 1982), which is a unidimensional tool measuring fatigue on a 100 mm continuum scale of 1 (no fatigue) to 10 (worst fatigue ever). The VAS provides an instant assessment of fatigue intensity or severity but lacks the evaluation of the physical and psychological components (de Oliveira et al., 2016). Multidimensional scales include the Identity Consequence Fatigue Scale (ICFS) (Paddison et al., 2006); the Profile of Mood States (POMS) (Fawzy et al., 1990); and the Multidimensional Fatigue Inventory (MFI) (Smets, Garssen, Bonke, & De Haes, 1995), which seeks to collect data on history and symptoms and to measure the multidimensions of fatigue. The development of instruments that are valid and reliable has been challenged by the absence of a consistent, standard definition of fatigue and by the varied nature of its associated subjective symptoms. Objective measures of work capacity (e.g., bicycle ergometer) and measuring muscle strength (e.g., hand grips) may be appropriate; however, the use of objective measures in the clinical setting has been limited (Zargar-Shoshtari & Hill, 2009). There is no single scale to capture all dimensions of fatigue symptomatology. Thus, the complexity of this multifaceted symptom and its varying effects following surgery make fatigue challenging to define, assess, and ultimately treat.

1.6 Contributing Factors

Postoperatively, many factors contribute to the etiology of POF, such as surgical stress, pain, anesthetic agents, sleep disturbances, nutritional deficiencies, and functional mobility (Salmon & Hall, 1997). Data show that POF is strongly associated with psychological and physiological factors, anemia, QOL, and functional capacity, thus prolonging recovery (Kahokehr et al., 2012).

The initial diagnosis of POF includes a history and physical assessment and identification of the treatable or reversible contributing causes of POF, such as poor nutrition, sleep disorders, anemia, and depression (Kahokehr et al., 2012). Various treatment interventions (e.g., analgesia, thoracic and spinal anesthesia, human growth factor (HGH), and steroids) that have been trialed by anesthesia to treat underlying pain; reported limited benefits in reducing POF (Rubin & Hotopf, 2002; Zargar-Shoshtari & Hill, 2009). Management and treatment interventions for fatigue symptoms can potentially improve recovery and achievement of optimal outcomes from CABG surgery (Barnason et al., 2008). Currently, there is no standard of care for managing or treating POF (Rubin & Hotopf, 2002; Zargar-Shoshtari & Hill, 2009).

1.7 Rationale for the Study

A significant reason for embarking on this study was the magnitude of the patients having CABG surgery. Approximately 14,000 CABG surgeries are performed in Canada annually (Canadian Institute for Health Information [CIHI], 2017). According to a national Cardiac Care Quality Indicators Report, Canadian mortality rates (1.3%) within 30 days of isolated CABG surgery and 30-day hospital readmission (9.5%) for isolated CABG are comparable to other countries (CIHI, 2017). While this is positive news for Canadians, opportunities for improving QOL, and patient outcomes remain. The widely reported prevalence of POF and its impact on individuals, families, and communities provide another rationale for this treatment intervention study.

Despite the frequency with which CABG surgery is performed, limited research has been conducted to examine management and interventions aimed at decreasing POF in these individuals. A few studies have indicated that iron deficiency could cause fatigue

symptoms (Patterson, Brown, & Roberts, 2000; Hogan, Klein, & Richards, 2015; Vaucher, Druais, Waldvogel, & Favrat, 2012; Verdon et al., 2003). Iron deficiency anemia is a common complication and present in over 90% of patients following surgery (Beris et al., 2008). Postoperative anemia can be explained by perioperative blood loss, cardiopulmonary bypass, phlebotomy, and hemodilution. Surgery-induced inflammation causes a blunted erythropoietic response, therefore decreasing iron availability and iron metabolism (Beris et al., 2008). A randomized controlled trial by Garrido-Martin et al. (2012) assessed intravenous iron, oral iron, and placebo and showed no improvement in Hgb or decreased red blood cell transfusions among cardiac surgery patients (n=159) at discharge. Fatigue was not a reported outcome in this study. Two randomized controlled trials examined the effect of oral iron supplements among non-anemic, iron-deficient women with unexplained fatigue in primary care (Vaucher et al., 2012 and Verdon et al., 2003). Verdon et al. (2003) examined non-anemic women (n=136) using ferrous sulfate (FeSO4) versus placebo for four weeks, with the primary outcome being a change in the level of fatigue. Study results indicated that fatigue levels were decreased by 29% after one month in the iron group compared with the placebo arm (13%). Vaucher et al. (2012) compared oral FeSO4 versus placebo in nonanemic menstruating women (n= 198) with ferritin levels of less than 50 μg/L experiencing fatigue of unknown origin for 12 weeks. Results obtained from the Current and Past Psychological Scale revealed a significant improvement in fatigue scores (fatigue decreased by 47% in the intervention group compared to a decrease of 28% in the placebo group, -18.9%, 95% CI -34.5 to -3.2; p = 0.02). There was no significant difference in fatigue scores related to QOL, depression,

and anxiety. There was, however, a significant increase in Hgb ($p<0.002$) and ferritin ($p< 0.001$) level at six weeks following iron supplementation (Vaucher et al., 2012).

Krayenbuehl and colleagues (2011) compared intravenous iron and placebo in non-anemic, premenopausal women (n = 90) with ferritin ≤ 50 µg/L over six weeks. Results showed improvement in fatigue scores of the Short Performance Inventory (SPI) of 65% in the iron group and 40% in the placebo group ($p = 0.02$) baseline to six weeks. Anker et al. (2009) compared IV iron and placebo among chronic heart failure patients (n = 459) and iron deficiency with or without anemia. Results showed a 50% decrease in fatigue score in the iron group compared to a 28% reduction in the placebo group (OR 2.51; 95% CI 1.75 to 3.61) between baseline and 12 weeks. Patients with anemia and those without anemia reported similar results. Therefore, iron supplementation showed a significant decrease in fatigue levels compared to the placebo group.

Other studies looked at oral iron treatment interventions (five randomized controlled trials [RCT] s one in cardiac surgery and four in orthopedic surgery), which did not demonstrate an improvement in postoperative Hgb when patients received oral iron supplements. Fatigue was not assessed as an outcome in these studies. However, fatigue is known to be associated with iron deficiency anemia (IDA) and iron deficiency without anemia. An Austrian longitudinal study of menstruating women showed a relationship between iron deficiency, general health, and fatigue (Patterson, Brown, Powers & Roberts, 2000). Two studies have shown that cognitive function has been reduced in iron-deficient adults, which can affect daily function (Brown et al., 1998; Patterson et al., 2000). These RCTs show promise in that there was a significant reduction in fatigue levels following the oral iron supplementation, especially in the

absence of anemia. Currently, there have been no studies examining the use of oral iron therapy to decrease fatigue levels following surgery and specifically in CABG surgery.

There are differences between the sexes related to CAD. Women with CAD tend to be older, have smaller cardiac vessels, stiffer heart muscle, and more comorbidities (e.g., hypertension, hypercholesterolemia, diabetes, peripheral vascular disease, and angina) compared to males with CAD (Papakonstantinou, Stamou, Baikoussis, Goudevenos, & Apostolakis, 2013). In this study, women represented 10% of the sample. Similarly, the Miller et al. (2013) sample contained only 10% of women. This rate of participation by women limits the feasibility of subgroup analysis related to sex and also raises the question of whether gendered roles influence the participation of women in clinical trials.

The majority of studies conducted on fatigue were observational, focusing on prevalence and impact. Prior treatment intervention studies (e.g., educational techniques) related to investigating POF among CABG patients have been reported. These studies had conflicting results, and no study examined oral iron supplementation as a treatment intervention for POF in the CABG surgical population. Lack of clinical research represents a gap in our knowledge of how to treat fatigue in CABG surgery patients. The extent of the fatigue experience is associated with impaired physical function and decreased QOL (Barnason et al., 2008; Miller et al., 2013).

1.8 Purpose

The purpose of this study was to identify changes in fatigue state in CABG surgery patients undergoing oral iron therapy following discharge from the hospital. This novel study is potentially relevant to health professionals who care for CABG patients.

1.9 Research Objectives

The objective of this research study was to examine how an oral iron supplement (FeraMAX®) might influence fatigue during late postoperative recovery (at 12 weeks) among CABG patients, and the effects on recovery outcomes (e.g., QOL, functional capacity, anemia, and medication adherence). This research objective aimed to answer the following questions:

1. Is oral iron effective in reducing POF as measured by the multidimensional Identity Consequence Fatigue Scale (ICFS) throughout 12 weeks?
2. Is oral iron effective in improving fatigue, functional capacity, QOL, and anemia?
3. To what degree do patients taking oral iron to adhere to the prescribed medication?

1.10 Statement of Hypotheses

The research hypothesis guiding the design and conduct of this study was based on previous research by Zargar-Shoshtari et al. (2009). The study was designed to test the effectiveness of an intervention to treat POF among abdominal surgery patients. For the current study, the null hypothesis assumes that there was no difference in reported fatigue levels between patients receiving interventional medication (FeraMAX®) and those receiving the placebo medication.

The next chapter presents a review of the relevant literature related to this current study.

CHAPTER 2 LITERATURE REVIEW

The purpose of this research was to examine fatigue in adults who underwent CABG surgery and to examine the effects of fatigue on patient outcomes during the recovery period. The current study aimed to investigate the impact of FeraMAX® oral iron supplements on fatigue levels, anemia, functional capacity, and QOL postoperatively in patients scheduled for CABG surgery utilizing an experimental method.

The literature review provides a synthesis of existing evidence on iron, POF, functional capacity, anemia, and QOL in CABG patients in the early postoperative recovery period and identifies the gaps in research. Fatigue is a common symptom that can affect people in their daily lives from a feeling of tiredness at the end of a workday to complete exhaustion. This symptom is usually short-lived and corrected by rest. Conversely, POF is ubiquitous after CABG surgery and can last weeks to months. Postoperative fatigue can prolong return to a preoperative level of independence or dependence in daily activities and work. This delay in normality (e.g., physiological, psychological, and social factors) during recovery can cause frustration to both patient and family members.

This chapter is separated into five sections, which offer a review of the literature up to the start of the study. Before completion of this thesis, a further search of the electronic databases was performed to obtain any recent evidence about the subject matter. The first section presents the background of the issues related to POF and CABG surgery. The second section provides an overview of studies that examined intervention strategies to treat POF following surgery, with an emphasis placed on oral iron treatment modalities that are associated with recovery. The third section offers factors associated

with POF. The theoretical framework that grounds this study is described in section four. Additionally, a review of the symptom management theories is presented along with an exploration of a symptom management theory that was used in the study to guide this research inquiry of symptom management of POF. Study outcome variables are described in detail in the final section.

2.1 Search Strategy

A search was conducted on published English language peer-reviewed studies between 1980-2019 using PubMed, CINAHL, EMBASE, Google Scholar, and Cochrane Review electronic databases. This 39-year timeframe was selected because pivotal studies on fatigue began at that time, led by Christensen et al. (1982). MESH keywords, singly or in combinations (coronary artery bypass graft or grafting, and coronary, or cardiac, or heart, and fatigue, or vital exhaustion, or symptom, and postoperative, or surgery and intervention, or treatment or management) were identified from studies related to POF. Studies included in the review that met the inclusion criteria consisted of double-blind interventions versus placebo, interventions versus routine care, or nearly identical interventions initiated pre-or-post-surgery. Articles excluded in the search included patients aged 19 years or under and patients who have undergone cancer therapy or cancer-related surgery.

Initially, titles and abstracts were reviewed to identify interventional studies with an outcome of POF among CABG patients. Additional relevant studies gleaned from the bibliographies of the selected articles were added for further review. A new search was conducted to identify clinical trials examining an intervention with an outcome of POF in any surgical procedure.

The search strategy was repeated in February 2019 to determine if any new relevant articles should be added to the existing literature review. Searches were run in OVID Medline, CINAHL, and EMBASE databases. Results were limited to English; methodological filters were used to limit retrieval to randomized controlled trials or systematic reviews. Search strategies consisted of controlled vocabulary and keywords with assistance from the Maritime Strategy for Patient-Orientated Research Support Unit.

2.2 Background of Coronary Artery Bypass Graft Surgery

2.2.1 Coronary artery disease. Coronary artery disease (CAD) occurs when there is a narrowing or blockage of a coronary artery or arteries of the heart (Government of Canada, 2017). In Canada, CAD is the most common form of heart disease and the second leading cause of death for both men and women (Government of Canada, 2017). According to data from the Public Health Agency of Canada's database 2012/2013, approximately 48,000 deaths were attributed to significant cardiovascular disease, and 2.4 million (1 in 12) people in Canada are diagnosed with CAD (Government of Canada, 2017). Men are at a higher risk of CAD before the fifth decade, and women's risk of CAD increases about ten years later, post menopause (Jabagi, Tran, Hessian, Glineur, & Rubens 2018; Kornowski et al., 1997; Pathak, Shirodkar, Ruparelia, & Rajebahadur, 2017; Shah, Palaskas & Ahmed, 2016; Yusuf et al., 2004).

Coronary artery disease arises from atherosclerosis, causing plaque buildup narrowing the lumen within the vessels and therefore decreasing oxygen-rich blood perfusion and resulting in fatigue (Eckhart, DeVon, Piano, Ryan & Zerwic, 2014; Government of Canada, 2017; Pragodpol & Ryan, 2013). Symptoms of fatigue are associated with a decrease in exercise capacity and poor function (Eckhart et al., 2014).

Fatigue affects approximately 35 to 75% of CAD patients (Kop, 1999; Miller et al., 2013; Pedersen & Middel, 2001) and is considered an independent predictor of future cardiac events, e.g. myocardial infarction (MI), recurrent angina pectoris, (Appels & Mulder, 1989; Kops, Appels, Mendes de Leon, de Swart, & Bar, 1994; Miller et al., 2013; Williams et al; 2010), repeat revascularization, (Kops et al., 1988), and death (Smith et al., 2011; Williams et al; 2010). Patients who were experiencing fatigue from CAD (Ai, Wink, & Shearer, 2012) or other related preoperatively medical conditions were found to be at an increased risk of POF following CABG surgery (Hall & Salmon, 2002; Kehlet, 1997; Schroeder & Hill, 1993).

The symptoms of CAD can be improved by medical therapy and modifying risk factors such as smoking, hypertension, high blood cholesterol, physical inactivity, obesity, and diabetes (Yusuf et al., 2004). Myocardial perfusion can also be enhanced by procedures such as percutaneous coronary intervention (PCI) or a surgical procedure called coronary artery bypass graft (CABG) (Hillis et al., 2011).

2.2.2 Coronary artery bypass graft surgery. Globally, CABG surgery is a standard treatment option for coronary revascularization to alleviate the symptoms of CAD and improve survival (Hillis et al., 2011). Coronary artery bypass graft is a well-established surgical procedure where a patient's vein or artery is used as a conduit to bypass narrowed or blocked native coronary arteries allowing reperfusion of the myocardium (Hillis et al., 2011; Taggert, Boyle, de Belder, & Fox, 2010). This surgical procedure provides benefits of improved ventricular function, relieves ischemia, reduces anginal symptoms, prolongs survival, and prevents the progression of MI (Hillis et al., 2011; Solimene, 2010). Advances in surgical and cardiopulmonary bypass techniques in

CABG surgery have resulted in fewer perioperative complications, reduced cardiac-related mortality, improved functionality, and QOL (Hillis et al., 2011). Postoperatively, the presence of physical symptoms such as shortness of breath (Tsai et al., 2019; Zimmerman et al., 2010); incisional pain (Tsai et al., 2019; Watt-Watson, Stevens, Katz, Costello, Reid & David, 2004); swelling and sleep disturbances (Tsai et al., 2019; Zimmerman, Barnason, Nieveen & Schmaderer, 2004); appetite problems (Ammouri, Al-Daakak, Isac, Gharaibeh, & Al-Zaru, 2016); fatigue (Tranmer & Parry, 2004; Tsai et al., 2019; Zimmerman et al., 2004); and psychological symptoms consisting of anxiety and depression (Al-Daakak, Ammouri, Isac, Gharaibeh & Al-Zaru, 2016) are a concern for patient recovery. Empirical studies have reported that post CABG patients experience multiple surgery-related symptoms or symptom clusters, which could cause a burden and consequently delay recovery and interfere with activities of daily living and emotional well-being (Redeker & Hedges, 2002). Symptom clusters are defined as two or more concurrent symptoms that may or may not be related to a common cause (Abbott, Barnason, & Zimmerman, 2010; Dodd, Miaskowski, & Lee, 2004; Miaskowski, Dodd, & Lee, 2004; Zimmerman, Barnason, Young, Tu, Schulz & Abbott, 2010). Zimmerman et al. (2010) conducted a secondary analysis of an RCT, testing the effects of a homecare intervention on functional outcomes among elderly CABG patients (n=226). This study revealed patients (greater than 50% of patients) experienced a higher symptom presence of fatigue (51%), appetite problems (53%), and pain (58%) before discharge (Zimmerman et al., 2010). Shortness of breath, fatigue, and pain were the most reported symptoms preoperatively due to ischemic changes, whereas fatigue, sleep disturbances and shortness of breath were expressed one year following CABG surgery – especially in

the elderly (Fukuoka, Lindgren, Rankin, Cooper & Carroll, 2007; Zimmerman et al., 2010). Most studies related to POF in CABG surgery patients were conducted between 1980 and 2012.

Approximately 14,000 CABG surgeries are performed in Canada annually, with approximately 600/year CABG surgeries carried out in Nova Scotia at one regional centre (CIHI, 2017). According to a national Cardiac Care Quality Indicators (CCQI) report released in October 2017, Canadian mortality rates (1.3%) within 30 days of isolated CABG surgery and 30-day hospital readmission (9.5%) for isolated CABG are comparable to other countries (CIHI, 2017). Historically, CABG surgery results were evaluated by outcome measures of mortality and morbidity. Even though the CCQI report reported positive outcomes (CIHI, 2017), there are still opportunities for improving QOL.

2.3 Fatigue

2.3.1 Definition. Fatigue is a complex symptom that has been studied across several different fields (e.g., nursing, physiology, psychology, and medicine) and to date, there is no widely accepted definition (Piper, Lindsey, & Dodd, 1987; Piper, Dodd, Ferketich, Paul, & Weller, 1989; Zargar-Shoshtari & Hill, 2009). The various definitions come from many sources, including popular and/or grey literature. The Oxford Dictionary of Nursing defines fatigue as extreme tiredness resulting from mental or physical exertion (Oxford, A Dictionary of Nursing, 2017). Alternatively, www.emedicinehealth.com (2017) defines fatigue as a feeling tired, exhausted, and a lack of energy and motivation that can be physical, mental, or both. Fatigue is very subjective, meaning the symptom is only observed by the individual experiencing it (DeCherney et al., 2002; Salmon & Hall, 2001; Zargar-Shoshtari et al., 2009). Defining fatigue has been

both difficult and challenging for researchers due to the complex interaction of biological, psychosocial, and behavioural factors (Aaronson et al., 1999; Zargar-Shoshtari & Hill, 2009). From a nursing perspective, Ream and Richardson, (1996) defined fatigue as a "subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion, creating an unrelenting overall condition which interferes with individuals' ability to function to their normal capacity" (pg. 519). Zargar-Shoshtari and Hill (2009) defined fatigue as a loss of energy or malaise. Fatigue is a universal phenomenon commonly observed in the general population. As well, fatigue occurs in chronic diseases such as renal dysfunction/ failure, multiple sclerosis, chronic fatigue syndrome, cancer and cancer treatments such as chemotherapy or radiotherapy, cardiac disease and side effects of medications (Heesen et al., 2006, Smets et al., 1993, Lee et al., 2004; Lee, Dziadkowiec, & Meek, 2014; Lerdal, Lee, Bakken, Finset, & Kim, 2012).

Fatigue is a common symptom following surgery, and complaints of POF can be present weeks to month's post-surgery (Barnason et al., 2008; Kehlet & Wilmore, 2002; Redeker, 1993; King & Parrinello, 1988; Miller et al., 2013; Rubin, Hotopf, Papadopoulos & Clear, 2005; Rubin, Hardy, & Hotopf, 2004; Tack & Gillis, 1990). Postoperative fatigue is the focus of this study.

2.3.2 Postoperative fatigue. The term POF was derived from definitions in engineering science related to metal fatigue, which is the weakening of a structure affecting the strength of the material from repeated stress (Salmon & Hall, 1997). Physiological and metabolic changes that occur during surgical convalescence can cause weakness from surgical stressors (Salmon & Hall, 1997). Moreover, POF can delay the

ability to perform activities and impact daily life following surgery (Zargar-Shoshtari & Hill, 2009; Rubin & Hotopf, 2002). It is not unreasonable to assume that the experience of fatigue could have considerable effects on wellbeing. Kennedy (1988) described POF as a feeling of tired, exhaustion, or strain during convalescence. Postoperative fatigue has been defined as a distressing, unpleasant, ongoing symptom impacting QOL following surgery (Rubin, Hardy, and Hotopf, 2004b). DeCherney et al. (2002) referred to POF as a factor delaying recovery in the postoperative period. Yu et al. (2015) defined POF as a subjective feeling of discomfort, leading to a loss of ability to participate in activities of daily living and regular work.

Furthermore, Zargar-Shoshtari and Hill (2009) expressed POF as a collection of physical and psychological symptoms that delay return to normal activities. These two authors added the idea of recovery to their definition of fatigue, meaning they were interested in POF and not just general fatigue. The definition by Zargar-Shoshtari and Hill (2009) will be used in the current study as it is comprehensive in that it takes into consideration that POF has a multimodal etiology and has more clarity in terms of reduction in postoperative activities than previous definitions.

Postoperative fatigue can present in isolation, or as part of a larger picture that involves multiple physiological (e.g., mobility, nutrition, sleep disturbances, and anemia) and psychological (e.g., depression and anxiety) factors (Barnason et al, 2008; Fortes, Recôva, Melo, & Novaes, 2010; Zargar-Shoshtari & Hill 2009). The degree of physiological and psychological factors can be attributed to the severity of fatigue and disrupt normal function (Hall & Salmon, 2002) and hence is clinically significant.

Patients experiencing POF can also experience a decrease in QOL, muscle atrophy, decreased functional capacity, and cardiac deconditioning, all of which can postpone the return to regular daily activities (Hall & Salmon 2002; Zargar-Shoshtari & Hill 2009).

2.3.3 Postoperative fatigue in CABG patients. Fatigue is one of the most frequently reported complaints that have a profound impact on function following CABG surgery (Barnason et al., 2008). The overall prevalence of fatigue is approximately 55% among patients following CABG surgery (Barnason et al., 2008). Symptoms of fatigue following any surgery have been reported to last from weeks (Barnason et al., 2008; Rubin, Cleare, & Hotopf, 2004a; Rubin, Hardy, & Hotopf, 2004b) to months (Barnason et al., 2008; King & Parrinello, 1988) depending on the study and methods. Acute fatigue usually corrects in 50% of patients in eight weeks (Barnason et al., 2008; Christensen et al., 1982; King & Parrinello, 1988; Redeker, 1993; Schroeder & Hill, 1993; Tack & Gillis, 1990), but studies have reported that 10% of patients continue to experience fatigue after 12 weeks (Rubin, Hardy & Hotopf, 2004b). Though the prevalence of fatigue is high and continues beyond the initial postoperative period of six weeks, patients' fatigue continuously improves over time.

Postoperative fatigue can interfere with the individual's overall ability to function to his/her normal capacity (Ream & Richardson 1996). The specific manifestations of POF can be biomedical, physical, or psychological. A variety of influencing factors such as CAD, pain, sleep disorders, anemia, mood, endocrine/metabolic disturbance, and mobility seem to have a complex interaction during the onset and persistence of POF. The etiology of POF appears to be multifactorial (Zargar-Shoshtari & Hill, 2009).

Regardless of the etiology, patients experiencing preoperative fatigue from CAD

or other medical conditions were found to be at an increased risk of POF (Hall & Salmon, 2002; Kehlet, 1997; Miller et al., 2013; Schroeder & Hill, 1993). Hall and Salmon (2002) reported that the level of preoperative fatigue was a predictor of POF following primary hip arthroplasty. Moreover, POF did not correlate with other preoperative characteristics (age, gender, and nutritional status), duration of surgery, or anesthesia (Christensen, 1995). A variety of socio-demographic and clinical characteristics (e.g., age, sex, body mass index, smoking, diabetes, and hypertension) were associated with fatigue in cardiac patients (Miller et al., 2013). Women reported higher levels of fatigue preoperatively compared to men (Miller et al., 2013; Smith et al., 2011; Williams et al., 2010). The levels of fatigue between males and females were similar at 16 weeks following CABG surgery.

Patients having CABG surgery are generally characterized by older age (65 years and older) and multivessel disease. Evidence suggests that fatigue symptom management strategies among patients having CABG surgery may benefit from a specific and tailored intervention such as a telehealth device called Health Buddy ® (Barnason et al., 2008). Fatigue can occur before surgery and then persist or can develop as a new symptom following CABG surgery (Barnason et al., 2009). Successful CABG surgery is one method to alleviate CAD and potentially improve mobility, functionality, and QOL (Lee, Tu, Chong, & Alter, 2008; Plach et al., 2006). Fatigue has mainly been associated with physiological factors preoperatively, but there are other physiological factors (e.g., muscle atrophy, decreased functionality, cardiac deconditioning) (Barnason et al., 2008; Hall & Salmon, 2002) that contribute to this symptom.

Rubin et al. (2004a) found a significant difference in the extent of POF in major

surgery (e.g., abdominal and cardiac) compared to minor surgery. However, major surgery such as joint arthroplasty did not show significant POF (Aarons, Forester, Hall & Salmon, 1996). Zimmerman et al. (2002) performed a pilot study (n=35) comparing CABG and minimally invasive direct CABG (MIDCABG) patients' recovery patterns in the early postoperative period. Fatigue was the most prominent symptom at two, four, and six weeks in >50% of patients in both groups. The duration and type of surgery were not associated with the extent of POF (Aarons et al., 1996; Rubin et al., 2004a; Zimmerman et al., 2002).

2.3.4 Symptom progression. Patients experience substantial fatigue in the first few weeks following surgery due to a decrease in oxygen-carrying capacity as a result of perioperative anemia. At the time of hospital discharge, up to 80% of CABG patients experience fatigue (Barnason et al., 2008; Miller et al., 2013). Fatigue remains prominent one week after discharge in up to 94% of CABG patients (Barnason et al., 2008; Miller et al., 2013). Postoperative fatigue is not limited to just the immediate postoperative recovery and at six weeks postoperatively. Fatigue continues to persist in 95% of CABG patients, lengthening recovery, and prolonging the return to activities of daily living. Fifty percent of patients > 65 years of age still complain of fatigue eight weeks after CABG surgery (Barnason et al., 2008). Other studies have shown that fatigue is a significant problem that can persist for months to years.

Most of the earlier studies on POF were conducted on the general surgery population more than a decade ago and focused mainly on its prevalence. In those studies, fatigue was investigated as a concurrent symptom or secondary outcome, not as the primary outcome. Fatigue following CABG surgery has a similar incidence and

duration. These findings are not surprising, considering these patients may have difficulty expressing their fatigue due to other competing postoperative physical or mental issues. These postoperative issues, including sleep disturbances, malnutrition, functional decline, surgical stress, and altered mental status, can lead to more extended hospitalization. The introduction of a cardiac fast track program has facilitated shortened hospital stays and enhanced recovery (Engelman et al., 2019; Schulte, Antoniou, & Attia, 2018). This program consists of preoperative optimization of Hgb, lung function, exercise capacity, smoking cessation, and weight loss. In addition, patients receive counselling regarding the postoperative period. Intraoperative optimization includes mini cardiopulmonary bypass circuits, normothermic management, and short-acting anesthetics. Postoperative optimization includes early extubation, intense management of fluid, pain, and nausea/vomiting. Also included in the postoperative period are early removal of lines and drains, timely ambulation, and use of high protein drinks (Schulte et al., 2018). The potential impact of POF can prolong recovery, contribute to morbidity and mortality, and have a negative effect on the patient's QOL, including physical, psychological, and social components.

Patient complaints can range from lack of energy to exhaustion, all of which interfere with the patients' overall ability to function to their normal capacity and ultimately affect well-being (Ream & Richardson, 1996; Zargar-Shoshtari & Hill, 2009). Postoperative fatigue can result from both surgical and postoperative physical and psychological factors, which can delay convalescence.

The recognition and treatment of both primary and secondary POF have often been overlooked in assessment, treatment, and monitoring responses to interventions

(Dittner, Wessely, & Brown, 2002) due to its subjective nature and lack of understanding regarding etiology and pathophysiology. Recovery after surgery is a complex process encompassing multiple dimensions, including biological (e.g., sex differences) and physiological variables; symptoms; physical, emotional, social, and economic function; health perception; and overall QOL (Neville et al., 2014). Therefore, research is essential for improving patient care and/or practice by applying the best available evidence.

2.4 Factors associated with Postoperative Fatigue

After surgery, many precipitating factors contribute to the etiology of POF, such as surgical stress, anesthetic agents, sleep disturbances, nutritional deficiencies, and functional mobility (Salmon & Hall, 1997). POF is strongly associated with psychological and physiological mechanisms, anemia, QOL, and functional capacity prolonging recovery (Kahokehr et al., 2012). Previous investigators assumed that POF resulted from the physical effects of surgery; however, investigators have been unsuccessful in finding a physiological cause for POF (Christensen & Kehlet, 1993; Salmon & Hall, 1997). In other words, POF is under-diagnosed due to its complex presentation and multifactorial etiology.

Theories regarding the etiology of fatigue have been proposed and evaluated, but the phenomenon remains poorly understood. One theory by Christensen (1995) proposed that the inflammatory effects of the surgical stress response along with decreased nutrition and impaired mobility resulted in reduced skeletal muscle mass, causing POF (Rubin & Hotopf, 2002). Salmon and Hall (1997) theorized that POF resulted from emotional and motivational changes caused by surgical trauma. Depression has been seen as another critical factor that is experienced in fatigued CABG patients (Barnason et al.,

2008). The prevalence of depression is approximately 30 to 40% in CABG patients and seen in older patients with comorbidities (Tully & Baker, 2012). Depression has been associated with younger age (Fraguas et al., 2007), and being female (Mitchell et al., 2005). Depression has been seen as another risk factor for the development of CAD and 30-day mortality (Krannich et al., 2007; Pirraglia, Petersen, Williams-Russo, Gorkin, & Charleson, 1999). In contrast, the presence of anxiety was observed in approximately 50% of patients with CAD and 34% of patients with clinically relevant anxiety scores following CABG surgery (Rymaszewska, Kiejna & Hahrys, 2003). Other investigators suggested subclinical mineral deficiencies (Cordova, Perez-Gallardo & Navas, 1995), cytokine production (Jakeways & Carli, 1993; Kehlet, 1999; Rubin & Hotopf, 2002), elevated tryptophan levels (McQuire et al., 2003; Meyer et al, 2010; Miller et al., 2013; Yamamoto et al., 1997), sleep disturbances (Fan, Yuan, Ji, Yang & Gao, 2017; Kehlet & Rosenberg, 1997; Rosenberg-Adamson, Kehlet, Dodd, & Rosenberg, 1996), and negative mood (Salmon & Hall, 1997) may impact POF.

These studies examined single factors, whereas other researchers have explored the idea that POF is multifactorial with an uncertain etiology (Christensen, 1995; Christensen & Kehlet, 1993; Rubin, Hardy, & Hotopf, 2004b; Salmon & Hall, 1997; Zargar-Shoshtari & Hill, 2009). The etiology is complicated by influencing biological and psychological factors such as depression and anxiety (Zargar-Shoshtari & Hill, 2009). The biological factors can be divided into physiological (e.g., surgical trauma and stress), nutritional deficiency, and reduced physical activity, which can lead to impairment of muscular weakness (Zargar-Shoshtari & Hill, 2009).

2.4.1 Surgical stress. Surgery triggers a local inflammatory response consisting of endocrine and metabolic changes referred to as surgical stress or systematic inflammatory stress syndrome (SIRS) (Burton, Nicholson & Hall, 2004; Desborough, 2000; Zargar-Shoshtari & Hill, 2009). The extent and duration of the response are dependent on the amount of tissue injury (Desborough, 2000). Surgical stress has been considered to be associated with POF.

Surgical stress can be triggered by surgical trauma to the entire body, which causes damage to the red blood cells and impairment of platelet function during cardiopulmonary bypass. Surgical trauma is considered a significant factor of POF (Yu et al., 2015; Zargar-Shoshtari & Hill, 2009) as it has been shown to produce a physiological effect caused by the metabolic and hormonal response of impaired muscle function. This physiologic effect causes an inflammatory response releasing cytokines in the circulation, which have been associated with POF and linked to the surgical stress response (Christensen, Hjortso, Mortensen, Riis-Hansen, & Kehlet, 1986; Kehlet, 1988; Maier et al., 1998; Salmon & Hall, 1997; Zargar-Shoshtari & Hill, 2009). These physiologic responses revert to preoperative values within days to a few weeks postoperatively (Salmon & Hall, 1997). Paddison and colleagues (2008) demonstrated the correlation between Neopterine and cytokines in the peritoneal fluid and POF. Previous research has demonstrated that there is a higher inflammatory response in the abdomen than the extremities due to surgical injury (Aarons, Forester, Hall & Salmon, 1996; Cruickshank et al., 1990).

The magnitude of surgical injury also has a significant role in the degree of fatigue (Christensen, Hoügard & Kehlet, 1985). Christensen et al. (1985) found that

major abdominal surgery patients experienced higher levels of fatigue compared with minor ear surgery or orthopedic surgery, with no correlation between the duration of surgery and anesthesia and POF. Rubin et al. (2004a) found a significant difference in the extent of POF in major surgery (e.g., abdominal and cardiac) compared to minor surgery. Major surgery, such as joint arthroplasty, did not, however, show significant POF (Aarons et al., 1996). Researchers proposed that this could be explained because abdominal surgery was a treatment for a condition or disease where orthopedic surgery improved mobility (Christensen et al., 1985).

Zimmerman et al. (2002) performed a pilot study (n = 35) comparing CABG and minimally invasive direct CABG (MIDCABG) patients' recovery patterns in the early postoperative period. Fatigue was the most prominent symptom at two, four, and six weeks in > 50% of patients in both groups. The duration and type of surgery were not associated with the extent of POF (Aarons et al., 1996; Rubin et al., 2004a; Zimmerman et al., 2002). More recently, evidence reports the duration of major abdominal surgery has an interrelationship with POF due to inflammation of the peritoneum (Kahokehr et al., 2012; Paddison, Sammour, Kahokehr, Zargar-Shoshtari, & Hill, 2011; Zargar-Shoshtari, Paddison, Booth, & Hill, 2009).

2.4.1.1 Interventions. A controlled trial by Zargar-Shoshtari and colleagues (2009) demonstrated an improvement in POF and POF correlated with local peritoneal cytokine levels in colorectal surgery patients. Glucocorticoids given 90 minutes preoperatively were effective in reducing fatigue in the general surgery patients (Zargar-Shoshtari et al., 2009; Schulze, Moller, Bang, Rye, & Kehlet, 1990; Schulze et al., 1992). This effect was explained by the immunosuppressive response of the steroids and steroids

mood-enhancing property to improve emotional distress.

The response to the surgical injury is activated by a systemic reaction resulting in hormonal changes initiated by the neuronal activation of the hypothalamic-pituitary-adrenal axis (Desborough, 2000). The hypothalamus plays an important role in assembling energy stores and secreting corticotropin-releasing factor (CRF), which stimulates the anterior pituitary gland to secrete the growth hormone (GH) and adrenocorticotropic hormone (ACTH) (Smelzer & Bare, 2004). The adrenocorticotropic hormone stimulates the adrenal cortex to produce glucocorticoids (Smelzer & Bare, 2004). The GH stimulates protein synthesis, lipolysis (the breakdown of lipids), and glycogenolysis (conversion of glycogen to glucose). At the same time, the body prepares for "fight or flight" by stimulation of the sympathetic nervous system and releases hormones such as catecholamines (Desborough, 2000). An increase of secretions of various other stress hormones (e.g., cortisol, glucagon, aldosterone, and antidiuretic hormone) occurs during surgery and remains elevated for a few days postoperatively (Desborough, 2000). Cortisol and catecholamines are principal mediators acting as neurotransmitters, hormones, or both (Desborough, 2000).

Catecholamines (e.g., epinephrine, norepinephrine, and dopamine) are also released into the bloodstream by the adrenal medulla in response to stress (Smelzer & Bare, 2004). The catecholamine release increases heart rate, blood pressure, mental acuity, blood flow to skeletal muscle, and blood glucose (Smelzer & Bare, 2004). Oxygen and glucose are also increased to maintain energy expenditures (Smelzer & Bare, 2004). These hormonal responses generate a cascade of metabolic events leading to gluconeogenesis (production of glucose), catabolism (break down of various body

components into energy) of stored body fuels (carbohydrates, fat and protein), sodium and water retention, and potassium excretion (Desborough, 2000; Smelzer & Bare, 2004). The stress response combines not only physiological (hormonal, metabolic, hematological, and immunological) and psychological effects (e.g., malaise), but behavioural (reluctance to move) and subjective responses (Salmon & Hall, 1997; Zargar-Shoshtari & Hill, 2009). A reduction in the stress response with therapeutic treatments that include pain management, increased nutritional intake, exercise, and the use of glucocorticoids can reduce the development of POF (Salmon & Hall, 1997; Zargar-Shoshtari & Hill, 2009).

Besides the physiological response, behavioral and subjective responses are clinically important. Feelings of malaise and reluctance to mobilize following surgery can impair muscle function causing immobilization, impairment of cardiovascular fitness, and decline in nutritional status (Barnason et al., 2008; Christensen, et al., 1982; Christensen, & Kehlet, 1993; Christensen, Nygaard, Stage, & Kehlet, 1990; da Costa Torres, Ramos dos Santos, Lima Reis, Paisani, & Chiavegato, 2016; Kehlet, 1997; Kehlet & Moesgaard, 1996; Salmon & Hall, 1997; Zargar-Shoshtari & Hill, 2009).

Strategies such as anesthetic agents and neuraxial blockade have been developed to decrease the harmful effects of the stress response and reduce POF. Techniques to reduce catabolism include regional and local anesthesia, early oral nutrition, and mobilization, which have been reported to reduce POF (Carli & Schricker, 2000; da Costa Torres et al., 2016; Kehlet & Dahl, 2003; Zargar-Shoshtari & Hill, 2009). Epidural anesthesia, anesthetic agents, and opioids, such as morphine, are used in cardiac surgery to decrease myocardial ischemia and suppress or reduce the stress response (Desborough

& Hall, 1989; Desborough, 2000; Mangano, Browner, Hollenberg, & Tateo, 1992; Zargar-Shoshtari & Hill, 2009). Reduction in opioid anesthesia and analgesia, steroids, and minimally invasive surgery are also strategies to reduce the surgical stress response (Kehlet & Dahl, 2003).

Surgical stress also has been shown to affect the length of recovery and alter physiological reserve, which can result in postoperative complications, such as sepsis (Watters, Clancey, Moulton, Briere & Zhu, 1993). A prolonged stress response may result in exhaustion of essential body components (e.g., proteins, fat, glucose, minerals), resulting in fatigue, weight loss, loss of lean body mass and muscle wasting, impaired wound healing, immobilization, increased risk of infection, and increased morbidity and mortality (Velickovic, Yan & Gross, 2002). These detrimental effects of the stress response can be reduced by reducing surgical stressors and preempting metabolic changes (Velickovic et al., 2002).

2.4.2 Cytokines. Inflammatory cytokines (e.g., interferons, tumor necrosis factor (TNF), and interleukins (IL)-1,-6, -8 and -10) are natural cell proteins that are produced by the white cells and provide cell to cell communication throughout the body (Burton et al., 2004; Desborough, 2000). Interleukins are involved in stimulating or suppressing the immune system or inflammation (as in surgical stress) and are named individually (e.g., IL1, IL2….IL37). Research by Wright, Strike, Brydon, and Steptoe (2005) examined healthy subjects following injection of the Salmonella typhi vaccine, which increased plasma levels of interleukin (IL)-6; the authors reported a considerable decrease in the subjects' mood but no change to other physical symptoms.

The systemic inflammatory and immunologic response that occurs from surgical

trauma is mainly caused by an activation of cytokine production, which may predispose patients to major complications postoperatively (Desborough, 2000). Recently, there has been an interest in the role of cytokines in surgery and prophylactic treatment therapies to reduce the inflammatory burden on the patient (Desborough, 2000).

A pilot study (n = 27) by Paddison et al. (2008) examined inflammatory markers (cytokines and neopterin) in the peritoneal fluid and serum over two weeks. The ICFS scale was used to measured fatigue trajectory over two months. A relationship between the fatigue experience and IL-6 and IL-10 and TNF-α was significant in the first 24 hours following colorectal surgery. Patients with elevated levels of neopterin had more severe and sustained POF. In other words, a reduction in the inflammatory response following major surgery could decrease the effects of fatigue in the recovery period. Later, an RCT by Zargar-Shoshtari and Hill (2009) investigated a relationship between POF and peritoneal cytokines. Zargar-Shoshtari and Hill examined the use of preoperative injections of steroids (Dexamethasone) on inflammatory response in colectomy patients (n = 60). The researchers found that steroids were associated with a reduction in peritoneal cytokine concentrations, decreasing inflammation postoperatively, and a significant reduction in early POF. These studies confirm that a reduction in cytokine production in the peritoneum is associated with a decrease in POF. Prophylactic therapies can reduce the inflammatory response and therefore reduce POF among this population of patients.

Two other studies examined local vs. systemic cytokine response, one in abdominal surgery (Badia et al., 1996) and the other in joint arthroplasty (Kristiansson et al., 1998). The findings in both studies demonstrated an increase in plasma cytokine

levels, but the local concentration of cytokines was less in the hip arthroplasty compared to abdominal surgery. The magnitude and duration of the surgical stress response were proportional to the cytokine concentration at the surgical site and may significantly influence the length of recovery and POF (Desborough, 2000).

Cytokines, specifically proinflammatory cytokines (e.g., IL-1-β, TNF-α, IL-6, IL-8, and IFN-γ) are released at the site of tissue injury and may augment the inflammatory response. The main cytokines released at surgery are interleukin-1 (IL-1), IL-6, and TNF-α. IL-6 is the main cytokine responsible for the production of acute-phase reactants, such as C-reactive protein (CRP), in the liver (Burton et al., 2004). Interleukin-6 peaks within 24 hours of the incision and correlates with the extent of the injury, duration of surgery, and postoperative complications (Burton et al., 2004). C-reactive protein also increases after the surgery, and the peak value is two-three days after incision (Bruno, De Falco, & Iolascon, 2015; Johnson-Wimbley & Graham, 2011). The CRP response is proportional to the extent of surgery (Bruno et al., 2015; Burton et al., 2004; Johnson-Wimbley & Graham, 2011).

Proinflammatory cytokines are elevated after CABG surgery and may be linked to POF (Zargar-Shoshtari & Hill, 2009). Surgical techniques (e.g., laparoscopic procedures), avoiding sleep disruptions, and pain control helps to decrease tissue damage and reduce surgical stress response (Burton et al., 2004). Surgical stress causes an inflammatory response characterized by an increase in cytokines (specifically IL-6), which blocks iron metabolism and the production of Hgb. This response results in anemia of inflammation. Due to the limited laboratory testing availability at the study site of IL-6 and TNF, CRP will measure the extent of inflammation after surgery for the current

study. CRP increases in response within hours of tissue injury (such as surgery) or infection (Johnson-Wimbley & Graham, 2011).

2.4.3 Biological sex. Female sex is another risk factor that has been correlated with fatigue following major surgical procedures (Tolver, Strandfelt, Rosenberg & Bisgaard, 2013). Sex is a classification based on genetic, biological, and physiological characteristic differences (Welch et al. 2017). A case-controlled study (n=50) assessing sex differences in fatigue following laparoscopic groin hernia repair reported that women experienced significantly more fatigue compared to men ($p<0.02$) and that fatigue continued to impact women on day 0-3 following the procedure (Tolver et al., 2013).

2.4.3.1 Sex differences in CAD. Sex gaps in diagnosis and treatment of CAD persist as women present with different signs and symptoms of ischemia from CAD than male patients (e.g., shortness of breath; epigastric pain; nausea; pain radiating to shoulder, neck, and arms; and fatigue) (Mannsverk et al., 2012). CAD is the leading cause of death among women, and mortality is seven times higher for CAD than for breast cancer globally (Benjamin et al., 2018), and these rates are the same in Canada (CIHI, 2017). One in three women dies from heart disease per day compared to one in thirty-four deaths per day from breast cancer (Benjamin et al., 2018; Garcia, Mulvagh, Bairey-Merz, Buring, & Manson, 2016; Mehta et al., 2018). Coronary artery disease risk increases with age in women, especially after a transition to menopause (Government of Canada, 2017; Garcia et al., 2016). Women's rate of mortality following MI and CABG surgery is double that of men (Mannsverk et al., 2012), with only 34% of women undergoing CABG surgery (Hillis et al., 2011; Zimmerman, 2011; Zimmerman et al., 2007). This increase in mortality could be due to advanced age, comorbidities, and

ineffective treatment (Mannsverk et al., 2012). Women have a smaller body size and smaller coronary arteries, which can play a factor in mortality. In women, coronary artery disease is poorly understood. There are substantial sex differences in epidemiology, symptoms, diagnosis, progression, and management of the disease that is often overlooked as treatment response may differ with men versus women (Mannsverk et al., 2012). For many decades, women have been underrepresented in cardiovascular clinical trials hindering appropriate management. In 2011, the Canadian Institute of Health Research required research applications to indicate whether sex and gender were addressed (Welch et al., 2017), and in 2015, the National Institute of Health developed guidelines that all research included sex as a co-variant or justification for why it was not included (Farahani, Gaeeni, Mohammadi, & Seyedfatemi, 2014; Welch et al., 2017). Over the last decades, mortality rates in CAD have decreased in men. In both sexes, older than 65 years, there has also been a decline in mortality. However, there has been an increase in mortality in women of the age group 35-54 years compared to a decline in death for men of the same age group (CIHI, 2017). Sex differences in people with CAD is another factor that can predispose patients to POF.

Nontraditional risk factors unique to women include pregnancy and related complications, hormone therapy, menopause, and autoimmune disorders, such as Systemic Lupus Erythematosus and rheumatoid arthritis; all are associated with an increased risk of CAD (Schmidt, Landin-Wilhelmsen, Brannstrom, & Dahlgren, 2018). Even though there is an overlap of non-traditional factors with the nine traditional CAD risk factors, hypertension, diabetes mellitus, tobacco use, dyslipidemia, physical inactivity, reduced intake of fruits and vegetables, alcohol use, obesity, and psychosocial

factors such as depression, as identified in the INTERHEART study (Yusuf et al, 2004) between men and women, there is a lack of clinical recognition and regular risk assessment in women (Bairey Merz, Pepine, Walsh, & Fleg, 2017). In addition, 48% of women have three or more traditional risk factors of CAD and receive suboptimal management of the risk factors (Vaccarino, 2010). Women who smoke have an increased hemoglobin level and escalated progression of CAD, and women who smoke also have a two-fold increased risk of MI compared to men (Mehta, Wei & Wenger, 2015). Women who smoke and take OCP are associated with an increased risk of venous thrombosis and MI compared to men (Vaccarino, 2010). Women diagnosed with hypertension and who use OCP are likely to have an increase in blood pressure (Vaccarino, 2010).

Ethnic minorities, especially among premenopausal women in this category, experience worse outcomes compared to age-matched men (Benjamin et al., 2018; Garcia et al., 2016). One of many ethnically identified disparities in women is that African American women have a higher prevalence of hypertension compared to Caucasian women and men (Vaccarino, 2010). The CDC (2010) created a report on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in African American men over a time span of 1988-2006. African American men have a disproportionally higher burden of hypertension compared to Caucasian or Mexican American men and African American women. Older women also have a higher risk of uncontrolled hypertension (Vaccarino, 2010). Even though the disease process and the traditional risk factors are the same, the cumulative effect of the risk factors are nearly a two-fold relative increased risk of MI in older women and an eight-fold relative increased risk in younger women compared to men (Schmidt et al., 2018), This risk signifies the importance of sex

differences and the need for recognition and aggressive management of the CAD. There are many misconceptions surrounding CAD. Coronary artery disease was always thought of as a man's disease. Women have different anatomy, physiology of the myocardium, and sex hormones than men, which can affect the progression of the disease (Gorodeski, 2002). Subsequently, women have a higher symptom burden, lower functional capacity before and after surgery, participate in less physical activity, are slower to return to daily living activities, and experience a higher rate of adverse outcomes (Ammouri et al., 2016; Zimmerman et al., 2011). The symptom burden could be related to women being older, having more comorbidities, being more in need of immediate surgery, and having less physical function compared to men (Abbott et al., 2005). Women experience a decreased awareness of the burden of CAD, possibly due to the misconception of the cardio protective effect of premenopausal endogenous estrogen (Maas & Appelman, 2010) and lack of understanding of the sex differences (Schmidt et al., 2018). Earlier clinical trials, including the well-known Women's Health Initiative (WHI) (Writing Group for the Women's Health Initiative Investigators, 2002) and the Heart and Estrogen-Progestin Replacement Study (HERS) (Hulley et al., 1998), were unable to demonstrate a reduced risk of CAD events in women with established CAD with menopausal hormone therapy. Women present with CAD approximately ten years later than men, commonly after menopause (Yusuf et al., 2004). Chest pain, pressure, or discomfort is common in both women and men; however, the severity of pain in women may vary considerably. Women may present more often than men with symptoms different than chest pain. For example, shortness of breath, pain in one or both arms, nausea, vomiting, sweating, and lightheadedness, indigestion, and unusual fatigue (Papakonstantinou et al., 2013).

Penckofer et al. (2005) examined fatigue levels among CABG surgery patients (men versus women). The researchers reported that more women indicated symptoms of fatigue at one, three, and six weeks post-surgery than men and fatigue persisted in 84% of women (n = 61) at 12 weeks after CABG surgery. Another study compared men versus women (n = 65) at 12 weeks after CABG surgery. Women experienced a higher level of fatigue (74% vs. 35%) compared to men (Schulz, Zimmerman, Barnason & Nieveen, 2005). Results showed that women had higher symptom scores of fatigue at every time point than men for 12 weeks (Schulz et al., 2005). On the other hand, a small study by Keresztes, Merritt, Holm, Penckofer, & Patel, (2003) showed no difference in a fatigue subscale postop CABG surgery among men (n = 40) compared to women (n=40) at both time points of one and 12 weeks. These studies, however, showed an overall trend in the reduction of fatigue longitudinally. Fatigue is more prevalent in women than men after CABG surgery (Schulz et al., 2005; Zimmerman et al., 2010).

Crane (2005) examined fatigue in older women (n = 84) ages 65 to 88 years old six to twelve months after MI. Researchers found that 67% of the women experienced fatigue that they perceived to be different from fatigue before the MI (Crane, 2005). Fatigue was associated with depression and sleep quality. Even though 60% reported participating in physical activity, fatigue was not associated with physical activity. Older women participate less in physical activity and are at a higher rate of MI reoccurrence than men within the first six years (35% versus 18%), respectively (Crane, 2005). This decrease in physical activity could be related to sex, SOB, and fatigue (Schulz et al., 2005). A longitudinal study (n = 155) examined changes in fatigue at sixteen weeks and two years following an MI. Fatigue in the sample was reduced, with nearly 50% of the

total group still experiencing fatigue two years post-MI (Alsén & Brink, 2013). Eighteen percent of participants self-reported fatigue along with depression at two years, whereas 30% reported fatigue without depression (Alsén & Brink, 2013). In this study, men experienced lower fatigue scores than women, being less mentally fatigued and more active and motivated after MI (Alsén & Brink, 2013).

Barnason et al. (2006) reported fatigue as the main obstacle to physical activity in participants (n = 37) at two, four, and six weeks following percutaneous coronary invention (PCI). Appels et al. (2005) examined the effects of treating fatigue in angioplasty patients (n = 710) with behavioural intervention and demonstrated that fatigue is a prognostic indicator of future cardiac events such as MI. The findings of these studies are consistent with POF's high prevalence and longer duration in women compared to men among cardiac patients. In another study, Ammouri et al. (2016) reported that perceived symptoms of fatigue following CABG surgery were a significant burden and were related to demographic variables (e.g., age and sex). A higher level of sleep disturbances and reduced appetite were also experienced by women (Ammouri et al., 2016). Following CABG surgery, compared to men, women are known to have a higher cardiac risk profile, more significant symptom burden, and impaired physical function (Zimmerman, 2011).

2.4.4 Psychological factors. Physiological factors can influence POF and delay recovery, but the psychological components such as anxiety and depression are often overlooked (Hall & Salmon, 2002). These psychosocial symptoms are predictive of increased morbidity and mortality in the first six months following CABG surgery (Abbott et al., 2010; Blumenthal et al., 2003; Burg, Benedetto, Rosenburg & Soufer,

2003). Mallik et al. (2005) found that, in CABG patients (n = 963) with higher levels of documented depressive symptoms preoperatively, the symptoms were significant ($p < 0.0001$) for poorer physical functioning in the first six months postoperatively, and 25% of the patients had impaired function at one year (Mallik et al., 2005). Depression is considered an independent risk factor for CAD due to hypercortisolemia or an autonomic imbalance (Krannich et al., 2007) and causes an increase in atherosclerotic plaque to form. Depression plays a critical factor in the relationship between fatigue and the cardiac population (Barnason et al., 2008). A series of studies identified that patients who experience fatigue after MI were often depressed, resulting in poorer cardiac outcomes (Crane, 2005; Crane et al., 2016; Griego, 2000; Marchionni et al., 2000; Mayou et al., 2000; McGowan et al., 2004).

Friedman and Griffin (2001) pointed out that fatigue is also related to depression in heart failure. McGowan et al. (2004) examined patients following MI and reported that fatigue was experienced, but it was not linked to depression. Females, the elderly, and patients with inadequate social support experienced fatigue but not necessarily with depression (McGowan et al. (2004). A convenience sample of 100 Jordanian patients was studied following CABG surgery, and 3% of participants reported depression in the early recovery period (Ammouri et al., 2016). Previous studies have concluded that preoperative anxiety and depression contribute to these symptoms postoperatively among CABG patients and can contribute to cardiac mortality (Khawaja, Westermeyer, Gajwani & Feinstein, 2009; Gallagher & McKinley, 2009; Ghoneim & O'Hara, 2016). These symptoms could be related to age, sex, functional capacity, and comorbidities. A study conducted by Zimmerman et al. (2010) among elderly CABG patients identified higher

physical functioning and improved recovery when patients experienced low levels of anxiety and depression at discharge. Patients experiencing moderate symptoms had higher levels of depression and anxiety (Zimmerman et al., 2010).

2.4.5 Sleep disturbances. Another major contributor to surgical recovery and POF is sleep disturbances. A review on sleep disturbances by Chouchou, Khoury, Marc-Chauny, Denis, and Lavigne (2014) reported a variation in the quality and quantity of sleep following major surgery. The reasons for the variation could be due to many confounding factors such as age, surgical procedure and duration, narcotic use, and psychological disorders. Following cardiac surgery, the review revealed that patients experienced sleep disruption, decreased total sleep time, and decreased duration of slow-wave sleep and rapid eye movements sleep stages for three to weeks postoperatively (Chouchou et al., 2014; Edéll-Gustafsson, Hetta & Arén, 1999; John, Bruce, & Masterton, 1974). Sleep disruption among patients who had CABG surgery in the early postoperative period has been reported to be caused by environmental and physical factors such as incisional pain, noise, and cardiac function, whereas following discharge, altered sleep patterns can be attributed to more psychological factors, including anxiety and mood disturbances (Liao, Huang, Huang & Hwang, 2011).

Beydon et al. (1994) examined sleep quality among 176 general and orthopedic surgery patients from preoperative to two weeks post-discharge. Patients reported poor sleep quality postoperatively with a decrease in nocturnal sleep and increased daytime sleep and napping related to hospital environmental factors, including pain and noise. Changes in sleep patterns, including sleep loss and fragmented sleep, occur immediately after surgery, causing disturbances in cognitive impairment, memory formation, and

emotional state, especially in the elderly (Edéll-Gustafsson et al., 1999). Sixty to eighty percent of patients reported these disturbances during the early recovery period in the intensive care unit, and this is usually self-limited (Edéll-Gustafsson et al., 1999). A meta-analysis examined sleep disturbances and changes in sleep duration, which were associated with an increased risk of cardiac morbidity and mortality (Cappuccio, Cooper, D'Elia, Strazzullo, & Miller, 2011). In a systematic review of altered sleep patterns after CABG surgery, over 50% of patients reported poor sleep quality lasting up to six months following surgery (Liao et al., 2011). Even though sleep quality continues to improve over time, the disruption of sleep can amplify concurrent symptoms (Liao et al., 2011) and affect psychosocial and physiological outcomes and a patient's QOL. Sleep provides restorative, protective, and energy-conserving functions and is essential for survival (Liao et al., 2011).

Few studies have individually examined the incidence of fatigue in the intensive care unit (ICU), though fatigue emerges as a significant issue. In a small study examining ICU survivors (n = 39) over six months, investigators reported 50% of patients experienced decreased vitality, physical function, and a reduction in home responsibilities (Kelly & McKinley, 2010). Other studies identified that patients experienced prolonged fatigue after discharge from the ICU setting (Eddleston, White & Guthrie, 2000; Hofhuis et al., 2008). A cross-sectional study by Redeker et al. (2010) examined 173 patients with heart failure with sleep-disordered breathing and reported associated symptoms of fatigue, depression, excessive daytime sleepiness, and altered functional performance. There was no statistically significant relationship between sleep disorders and fatigue in linear regression. Sleep disturbances could be a contributing factor to POF; however, a

direct relationship between POF and sleep disturbances in the acute care setting requires further research to demonstrate a correlation (Rosenburg-Adamsen, Kehlet, Dodd & Rosenburg, 1996; Zargar-Shoshtari & Hill, 2009).

2.4.6 Other related symptoms. Several studies reported additional troublesome symptoms following CABG surgery that have correlated with fatigue, including incisional pain, leg swelling, poor appetite, and shortness of breath (SOB) (Ammouri et al., 2016). A descriptive study by Ammouri et al. examined symptoms experienced by 100 patients following CABG surgery. The most frequently reported symptom was sternal incision pain, followed by leg swelling at 60%. These symptoms impact daily activities, walking, and QOL (Bruce et al., 2003). Poor appetite was found to be significantly worse in the elderly (> 60 years), women, and patients with comorbidities. Poor appetite was felt to be attributed to antihypertensive medications (Ammouri et al., 2016; Grap, Savage & Ball, 1996). Researchers also reported symptoms of anxiety, depression, sleep disturbance, and fatigue in early recovery (six-week post-surgery) lasting up to 12 weeks, impairing function, and interfering with psychological recovery (Abbott et al., 2010; Zimmerman et al., 2007). Patients having CABG surgery usually experience multiple symptoms both before and after surgery. The more symptoms patients experience, the poorer psychosocial and physiological outcomes compared to patients experiencing fewer symptoms (Abbott et al., 2010; Zimmerman et al., 2007).

2.4.7 Anemia. Anemia is another influencing factor associated with POF and adverse cardiac outcomes following CABG surgery (Barnason et al., 2008; Bracey et al., 1999; Rodriguez, 2000; Steptoe, Wikman, Molloy & Kaski, 2012). As previously mentioned, anemia is defined as a decrease in the oxygen-carrying capacity of red blood

cells, and without treatment, the rate and completeness of the Hgb rebound are uncertain (Muñoz, Garcia-Erce & Remacha, 2011). Red cell mass reduction results in diverse symptoms such as fatigue, dyspnea, headaches, lightheadedness, and even myocardial ischemia (Nappi, 2003; Ross et al., 2003). Coronary artery bypass graft surgery can result in significant blood loss and a subsequent decrease in Hgb, resulting in perioperative anemia. Perioperative anemia is a strong predictor of blood transfusion, which can result in perioperative complications and adverse patient outcomes. Over the last few decades, transfusion practice has changed with preoperative Hgb optimization, lower transfusion triggers, appropriate blood utilization, and tolerance of anemia (LaPar et al., 2018). Perioperative anemia has also been associated with fatigue, a higher rate of myocardial ischemia, cardiac morbidity, and reduced QOL (Nelson, Fleisher & Rosenbaum, 1993; Piednoir et al., 2011). Correction of anemia depends on several factors (cause, the degree of anemia, patient's general health, and bone marrow health).

Zindrou, Taylor, and Bagger (2002) investigated the risks of anemia in a prospective, observational trial of 2059 consecutive patients undergoing cardiac bypass surgery. The results similarly demonstrated patients with a preoperative Hgb level less than 100 g/L had a five-fold higher in-hospital mortality rate following surgery (17% vs. 3.4%, $p = 0.001$) compared with those with a Hgb level greater than 100 g/L, despite intraoperative transfusion. Results suggested that low preoperative Hgb levels are a marker of disease severity and have a major effect on mortality.

Other recent studies reported preoperative anemia as a predictor of poor outcomes for patients undergoing CABG surgery (de Santo et al., 2009; Ranucci et al., 2013; Williams, He, Rankin, Slaughter & Gammie, 2013). Low preoperative Hgb is a risk

factor for increased blood transfusion requirement, morbidity and mortality (Karkouti et al., 2008; van Straten et al., 2009; Williams et al., 2013), and an increase in cardiac events were due to other factors related to preoperative anemia (Kulier et al., 2007). The findings support preoperative anemia investigation and Hgb optimization. Furthermore, oral iron has been used to treat preoperative anemia, but the association between oral iron therapy and POF has never been studied.

2.4.7.1 Iron deficiency. Piednoir et al. (2011) conducted an observational study that examined preoperative iron deficiency (n = 100) in cardiac surgery patients to determine the prevalence and relationship to perioperative anemia, RBC transfusions, and fatigue. Preoperative anemia can increase RBC transfusion risk perioperatively (Piednoir et al., 2011). Thirty-seven of the 100 study patients were diagnosed with iron deficiency preoperatively, and this factor was associated with the presenting anemia (Piednoir et al. (2011). Subsequently, these patients had a higher postoperative transfusion rate in the first week (62% vs. 35%, $p = 0.019$) (Piednoir et al., 2011). One-quarter of the patients were iron deficient without anemia, and they received (2 units vs. 0 units, $p < 0.05$) RBC transfusions more than patients who were neither iron-deficient nor anemic (Piednoir et al., 2011). Piednoir et al. also found a relationship between preoperative iron deficiency and POF on day 7 ($p = 0.01$).

Miles et al. (2018) conducted a single-centre, respective study of non-anemic patients (n = 277) undergoing cardiac surgery. The postoperative hospital stay of those who were iron deficient was longer than those who were not.

Preexisting anemia and or surgical blood loss can cause postoperative anemia and worsening outcomes for patients having CABG surgery (Nappi, 2003; Ranucci et al.,

2012). Ranucci et al. compared postoperative morbidity and mortality of a severely preoperative anemic group with a propensity-matched group of nonanemic or moderately preoperative anemic cardiac patients. In a sample of 802 patients divided into severely anemic (Hgb <100g/L; hematocrit <30%) (n = 401) versus non-severely anemic (n = 401), results confirmed that there was approximately double the operative mortality in the severely anemic vs. non-severely anemic patients (Ranucci et al., 2012). These studies show that anemia can also increase morbidity and operative mortality in CABG patients.

Researchers also found an increased risk of stroke, prolonged mechanical ventilation, and longer length of hospital stay in severely anemic patients (Ranucci et al., 2012). The symptom of anemia can harm many aspects of QOL (e.g., exercise tolerance) (Ranucci et al., 2012) and cognitive function (Ludwig & Strasser, 2001). The relevant contribution that anemia has to POF is more difficult to ascertain (DeCherney et al., 2002). Researchers frequently evaluate the physical factor of anemia but do not address the functional, social, and psychological components, as evident in the literature. This current study examines whether iron supplementation impacts fatigue and improves patient outcomes (e.g., anemia, QOL, functional capacity). A systematic review was conducted with ten studies (prospective, retrospective, and meta-analysis) reporting the use of oral or IV iron supplementation and or erythropoietic stimulating agents (ESAs) in elective orthopedic surgery patients (Steuber, Howard & Nisly, 2016). The review supported the use of oral or IV iron with or without ESAs preoperatively to optimize Hgb levels and decrease blood transfusion requirements. In the intraoperative or postoperative setting, the authors concluded that conflicting results were reporting a statistically significant reduction in blood transfusions versus no statistically significant difference.

The use of iron supplementation with or without ESAs may help prevent postoperative anemia and reduce blood transfusion requirements (Steuber et al., 2016). Iron supplementation is an inexpensive medication that could potentially improve recovery outcomes.

Kulier et al. (2007) investigated the effect of preoperative Hgb concentration in patients (n = 4804) having CABG surgery. This study revealed that anemia was a risk factor for postoperative complications and that the degree of risk is proportional to the level of anemia. This large epistemological study looked at older adults, mean age 64, and only 20% were women. The findings indicated that the incidence of anemia tends to increase with age and that older persons are frequently at a higher risk for coexisting comorbidities. Another reported finding was that a preoperative Hgb level was an independent risk factor for postoperative non-cardiac-events in particular renal events. These studies identified the importance of interventions to optimize preoperative Hgb and anemia. Iron deficiency and iron-deficiency anemia should be treated with iron supplementation to prevent end-organ ischemia and further progression of anemia (Auerbach & Delonghery, 2016).

Sarnak et al. (2002) reported an observational study (n = 14410) to evaluate whether subjects from the general population that met a criterion for low Hgb were at high risk of developing cardiovascular disease (CVD). The data were stratified for sex and the presence of anemia. The results demonstrated that the presence of anemia is an independent risk factor for developing symptoms of CVD. Sarnak et al. (2002) reported the first population-based study to link anemia to cardiovascular outcomes in the general population. The presence of multiple risk factors dramatically increases an individual's

probability of cardiovascular morbidity and mortality (Sarnak et al., 2002). A limitation of these studies was that the researchers did not determine the causal relationship of anemia, which could potentially increase the cardiac risk (Sarnak et al., 2002). This study also supports the importance of correcting anemia through methods other than blood transfusions to minimize negative outcomes. Further clinical trials are required to identify the relationship between anemia, fatigue, and cardiovascular disease.

2.4.7.2 Postoperative anemia. Postoperatively, the prevalence of anemia in elective surgical patients is estimated to be as high as 90%, depending on the definition used by the researchers (Beris et al., 2008; Shander et al., 2004). Red blood cell transfusion is generally the treatment of choice for anemia and improves oxygen delivery to the tissues for postoperative patients (Corwin et al., 2007; Goddard, James, McIntyre, & Scott, 2011; Hebert, Wells, & Blajchman, 1999; Scott, Seifert & Grimson, 2008). Blood transfusions could potentially worsen patient outcomes and have been associated with an increase in both morbidity and mortality (Corwin et al., 2007; Hebert et al., 1999; LaPar et al., 2018; Piednoir et al., 2011; Scott, Seifert & Grimson, 2008; Vincent et al., 2002). Forty-five percent of critically ill patients received an RBC transfusion with an average of 4.5 units while in an ICU (Corwin et al., 2004; Pape, Stein, Horn & Habler, 2009; Vincent et al., 2002). The efficacy of RBC transfusions has not been demonstrated in hemodynamically stable and critically ill patients. Trauma patients and patients with cardiovascular disease have increased morbidity and mortality if they received allogeneic blood. Blood transfusions are still used for hemorrhage and symptomatic patients but are not without risks. Transfusion practice has changed substantially, and the restriction of transfusions improves patient outcomes by decreasing length of stay, postoperative

infections, morbidity and mortality (Corwin et al., 2007; Hebert et al., 1999; LaPar et al., 2018; Piednoir et al., 2011; Vincent et al., 2002).

Hebert et al. (1999), in a multi-centered, randomized, controlled study of transfusion requirements in the critical care setting (TRICC) (n = 838), examined whether a restrictive strategy of RBC transfusion was equal to a liberal RBC transfusions strategy. The researchers concluded that a restrictive strategy of RBC transfusion (Hgb levels between 7-9 g/dL) was as effective or superior to a liberal transfusion strategy (maintaining Hgb level above 10g/dL) with the possible exclusion of patients with acute cardiac symptoms (MI and unstable angina pectoris) (Hebert et al., 1999). Outcomes of the trial showed a significantly lower overall rate of in-hospital mortality in the restrictive-strategy group compared to the liberal-strategy group (22.2% vs. 28.1%, p = 0.05) (Hebert et al., 1999). There were differences in 30-day mortality; however, the mortality rate did not reach statistical significance (Hebert et al., 1999).

These studies show that a strict transfusion protocol could decrease inappropriate RBC exposure and adverse transfusion events. Transfusion decisions should not be based on transfusion triggers, but physiologic need (Hebert et al., 1999; LaPar et al., 2018; Piednoir et al., 2011).

Myocardial infarction, a complication postoperatively, can occur as a result of anemia in both cardiac and noncardiac surgery patients, especially with increased blood loss (Nappi, 2003). Previous studies suggest that correcting Hgb levels could decrease complications, improve function, and decrease fatigue (LaPar et al., 2018; Piednoir et al., 2011). Conversely, Christensen and Kehlet (1984) found there was no correlation between fatigue and an increase in Hgb or transferrin levels 30 days postoperatively in a

small group (n = 36) of general surgery patients. The inflammatory response following surgery may block Hgb synthesis; therefore, there is no significant increase in Hgb or transferrin. Based on the small sample size, the results also cannot be generalized to the broader population. Postoperative anemia is relatively common and affects convalescence. Interventions other than blood transfusions should be considered to reduce postoperative complications.

2.4.8 Functional capacity. Another risk factor for POF is functional capacity, which is impacted by symptoms, such as pain (Bruce et al., 2003) and psychological function after CABG surgery (Abbott et al., 2010). Together these factors further affect QOL. Fatigue, SOB, and sleep disturbances were the most frequently reported symptoms following CABG surgery in elderly patients, who reported significantly more inferior function (Fukouka et al., 2007; Schulz et al., 2011).

Patients undergoing CABG surgery now require shorter hospital stays and are expected to be more engaged in self-management following discharge, which in turn causes significant functional challenges. A review of 35 studies examining outcomes of inpatient adult mobilization by Kalisch and colleagues (2013), identified the benefits of mobilizing patients to prevent functional decline and postoperative complications. Several studies from this review reported that ambulation, a key element of nursing care, was missed in up to 88.7% of the inpatient stays (Brown, Friedkin, & Inouye, 2004; Callen et al., 2004; Kalisch et al., 2013). Postoperative immobility correlates with POF, and, when combined with inadequate nutritional intake, can worsen the level of fatigue (Salmon & Hall, 1997). Following major surgery, there is a prolonged period of inactivity and hospitalization that can result in a decline in muscle function and endurance

(Covinsky et al., 2003; Kehlet, &Wilmore, 2002; Suetta, Magnusson, Beyer & Kjaer, 2007). Since the implementation of a cardiac fast track program, patients are mobilizing earlier, receiving adequate pain control, and early nutrition to potentially decrease length of stay and surgical complications (Parks, Routt, & De Villiers, 2018). Healthy young adults were observed on bed rest and demonstrated impairment in muscle strength and functioning (Edwards, Rose & King, 1982; Hortobágyi et al., 2000; Rubin et al., 2004a). Early mobilization even for healthy people is essential to improve muscle mass and strength. During the first week postoperatively, a patient can lose one to six percent of muscle strength per day from immobilization (Appell, 1990; Convertino et al., 1997; Suetta et al., 2007).

Cardiovascular fitness can also decline following surgery (Zargar-Shoshtari & Hill, 2009). Cardiac fitness was objectively measured, and results indicated that there was a correlation with POF greater than 20 days after surgery (Christensen et al., 1990; Christensen et al., 1982; Christensen, Stage, Galbo, Christensen, & Kehlet., 1989). Christensen et al. (1982) observed an association with fatigue levels and an increase in pulse rate secondary to orthostatic stress in patients following abdominal surgery. Both impairments in muscle function and cardiovascular fitness have been associated with the development of POF (Christensen & Kehlet, 1993). Houborg et al. (2006) randomized patients to either strength and aerobic exercise or placebo following colorectal surgery and demonstrated a moderate decrease in fatigue during early recovery but not an improvement in the decline of physical function. Further examination of fatigue and recovery outcomes such as early mobilization, pain control, and early nutrition is required to reduce cardiovascular deconditioning and muscular impairment.

Despite improvements in surgical practice, cardiopulmonary bypass techniques, and type of anesthesia that have occurred over the last several decades, POF continues to be one of the most frequently reported symptoms that all patients will experience to some degree during their early recovery phase. There has been research in the area of POF (Kahokehr et al., 2012; Zargar-Shoshtari & Hill, 2009); however, there is no consensus concerning the underlying mechanisms (e.g., hormonal, inflammatory). To compound this situation, POF has multiple contributing factors, including psychological issues, nutritional deficiencies, surgical stress, and impaired muscle function for this clinical problem. (Christensen & Kehlet, 1993; Christensen, 1995; Rubin, Hardy, & Hotopf, 2004b; Salmon & Hall, 1997; Zargar-Shoshtari & Hill, 2009). Postoperative fatigue, therefore, may adversely affect patient outcomes and QOL.

The varied underlying mechanisms and contributing factors can pose a challenge for the healthcare provider attempting to diagnose and treat POF. Recognition of the impact of fatigue is an essential first step to help the patient with the symptom experience.

2.4.9 Quality of life. Fatigue can adversely affect QOL and recovery outcomes in cardiac surgery patients (Barnason et al., 2008). Quality of life can be described as an individual's subjective perception of their present physical, psychological, social, and general wellbeing (Cella & Tulsky, 1990; Guyatt et al., 1997; Ross & Ostrow, 2001). As noted above, previous research has demonstrated that POF can negatively affect QOL (Barnason et al., 2008; DeCherney et al., 2002). Several studies on QOL following CABG surgery focused on preoperative risk factors related to mortality, physical functioning, and mental health but not specifically on the fatigue outcome (Hawkes &

Mortensen, 2006; Hawkes et al., 2006; Koch et al., 2003; Lindsay, Smith, Hanlon, & Wheatley, 2001; Sawatzky, & Naimark, 2009) as a primary outcome. Zimmerman et al. (2004) examined the use of an educational intervention (Health Buddy) on elderly CABG patients over six months, and fatigue was reported as the most significant obstacle in physical activity and enjoyment of life. Barnason et al. (2009) studied the association between fatigue and outcomes at six weeks and 12 weeks following CABG surgery. Fatigued (n = 66) and non-fatigued (n = 53) patients were compared using the self-reporting of POF. There was significant impairment in physical functioning, psychosocial functioning, social, mental functioning, anxiety, and depression at six weeks in the fatigued group. Although fatigue has a substantial impact on QOL after CABG surgery, there has been relatively little evidence generated related to the treatment of POF in this population (Barnason et al., 2009; DeCherney et al., 2002; Kahokehr et al., 2012; Rubin & Hotopf, 2002).

An intervention to relieve POF symptoms in the early recovery period after discharge may improve QOL and function. While numerous studies looked at the effects of CABG on patients' QOL focusing on preoperative risk factors related to mortality, physical functioning, and psychological health, none of the studies looked specifically at the effect of fatigue as a primary outcome (Hawkes, Novack, Bidstrup, & Speare, 2006; Hunt, Hendrata, & Myles, 2000; Koch et al., 2003; Lindsay et al., 2001; Sawatzky & Naimark, 2009). The current study investigates the effect of fatigue levels as the primary outcome following CABG surgery.

2.5 Perioperative Interventions to Reduce Fatigue

Rubin et al. (2004a) carried out a meta-analysis of sixty-six RCTs (n = 4289)

examining intervention strategies for decreasing levels of POF. The study identified fatigue-related interventions for any surgical procedure, which included 17 analgesic intervention studies; 16 psychosocial intervention studies; eight early nutrition postoperative studies; early mobilization studies; surgery technique studies; anesthestic technique studies; human growth hormone (HGH) studies; and glucocorticoids and sleep hygiene studies. Each intervention is discussed in the following sections.

2.5.1 Analgesic interventions. An interventional study using analgesia reported a reduction in fatigue levels on postoperative day one. Investigators used epidural analgesia (Schulz et al., 1988; Zeiderman, Welchew, & Clark, 1991) and non-steroidal anti-inflammatory agents (Schulz et al., 1988) to provide adequate postoperative pain control in an attempt to alter pain-related endocrine and metabolic changes. Findings suggest there was no change in fatigue levels when multimodal analgesia was used (Rubin et al., 2004a). Although one study reported that Ketorolac, a non steroidal anti-inflammatory drug, administered on the evening preoperatively to surgery, significantly improved the level of POF relative to placebo in abdominal hysterectomy patients (n = 198), the results did not show significance in the days following surgery (Parker, Holtmann, Smith, & White, 1994). Non-steroidal anti-inflammatory agents are no longer used to provide postoperative pain control because benefits were inconsistent in reducing pain (Fransen et al., 2006; Gan, 2017).

Observational studies have shown that combining perioperative strategies, such as early postoperative oral nutrition, early mobilization, and optimal pain control, decreased length of hospital stay, postoperative morbidity, and readmission (Bardam, Funch-Jensen, Jensen, Crawford & Kehlet, 1995; Basse, Hjort Jakobsen, Billesbolle Werner & Kehlet,

2000; Kehlet & Mogensen, 1999; Moiniche, Bulow, Hesselfeldt, Hestbaek & Kehlet, 1995). The limitations of these studies were their inability to establish a causal relationship.

2.5.2 Nutritional intervention. Postoperative nutrition supplementation improved muscle mass and weight gain in patients (n = 46) having colorectal surgery but did not affect POF (Jensen & Hessov, 1997). Rubin and Hotopf (2002) conducted a systematic review of RCTs of interventions for POF and found no evidence to support the use of nutritional interventions to reduce POF.

2.5.3 Minimally invasive interventions. Schwenk, Böhm, and Müller (1998) investigated patients (n=60) having laparoscopic cholecystectomy versus the conventional laparotomy procedure. Similarly, patients enrolled in the Enhanced Recovery After Surgery (ERAS) experienced less fatigue ($p < 0.05$) day one to day seven after the minimally invasive procedure. Patients in the laparoscopic surgical group experienced significantly decreased fatigue up to one month postoperatively compared to the control/open procedure group for major colonic surgery, as well as fewer consequences of fatigue (Zargar-Shoshtari et al., 2009; Jakobsen, Sonne, Andreasen & Kehlet., 2006). However, POF has not been investigated in minimally invasive cardiac surgery.

2.5.4 Psychosocial interventions. Psychosocial techniques, such as emotional preparation, enhancing coping skills, and education sessions, were not able to demonstrate a significant effect on fatigue at any time points day 0 - day 30 (Rubin & Hotopf, 2002). Postoperatively, guided imagery, a cognitive technique that has been used to manage stress, anxiety, and depression versus relaxation versus control were

investigated in patients (n = 60) undergoing abdominal surgery. Although patients reported a decrease in perioperative stress, the study did not demonstrate a significant difference in POF, pain intensity, recovery of pulmonary function, or duration of postoperative ileus (Hasse, Schwenk, Hermann & Müller, 2005). Ai and colleagues (2006) investigated faith-based coping and optimum effect preoperatively in cardiac surgery patients (n = 481). The analysis resulted in a reduction of physical fatigue postoperatively but no correlation with mental fatigue.

2.5.5 Symptom management intervention. Barnason et al. (2009) conducted a descriptive study on older adults (n = 232) following a CABG surgery assessing symptom management (SM) telehealth device called Health Buddy ® (Bosch Healthcare Incorporated; Palo Alto, CA, USA) which assessed symptoms and provided strategies to manage symptoms compared with usual care. The investigators found an improvement in fatigue levels at six weeks postoperatively in the SM group. A small subset analysis of the previous study examined women (n = 40) following CABG surgery assessed POF using an SM device compared with routine care (Zimmerman & Barnason, 2007). The intervention group showed a significant reduction in fatigue at six weeks (Zimmerman & Barnason, 2007).

2.6 Interventions

2.6.1 Pharmacological therapy. A variety of drug interventions have been evaluated for the management and treatment of POF. Fan et al. (2017) investigated the effect of perioperative melatonin vs. placebo on postoperative cognitive decline in 139 elderly patients (ages > 65) undergoing hip arthroplasty. Subjective assessments sleep quality, general well-being, pain, and POF were measured using outcome specific VAS

scales. The Folstein Mini-Mental State Examination (MMSE) assessed the cognitive function. Researchers showed a significant reduction in the MMSE score in the control group after surgery compared with the preoperative value or the intervention group and a significant increase in POF in the control group as compared to those who received the intervention group at postoperative days one, three, and five. The MMSE scores in the intervention group remained constant over the seven postoperative days of assessment. Significant impairments in sleep quality, well-being, and POF were found in the control group compared to the intervention group (Fan et al., 2017).

Steroid prophylaxis remains controversial in light of evidence from published RCTs and meta-analysis. Evidence indicates that pharmacological agents can alter the inflammatory response to surgical trauma and reduce the POF in perioperative outcomes. Schulze et al. (1990) and Schulze et al. (1992) used glucocorticoids preoperatively in major abdominal surgery, which showed an improvement in POF. However, although patients may demonstrate improvement in the quality of recovery, there may be an increased risk of postoperative infection. Murphy et al. (2011) used low dose steroids vs. placebo preoperatively in CABG patients (n = 170) and found significant improvement in POF, as well as the quality of recovery scores, pain, and emotional and physical domains.

Kissmeyer-Nielsen, Jensen, and Laurberg (1999) conducted a RCT using human growth hormone vs. placebo in younger adults (ages 18-50) having major abdominal surgery and showed that both groups were equally fatigued at day 10 after surgery, but at day 30 and 90 the human growth hormone group was less fatigued than the placebo. There was no statistical difference between groups at 30 days; however, there was a statistically significant difference between groups at 90 days. Limited interventional

studies, specifically examining pharmaceutical therapies, were conducted in cardiac surgery patients.

2.6.1.1 Iron supplementation. Oral iron supplements are routinely prescribed to treat iron deficiency (ID). In the adult surgical population, oral iron is recommended six to eight weeks preoperatively to treat ID and iron deficiency anemia (IDA) and therefore improve iron storage in the body, increase Hgb levels, and decrease blood transfusion rates (Leal-Noval et al., 2013; Muñoz et al., 2017). The Anesthesia International guidelines (2017) and Seville consensus document (2013) strongly recommend that oral iron supplements should not be prescribed immediately postoperatively to treat postoperative anemia. This recommendation is due to oral iron's poor absorption and potential side effects. Several RCTs were conducted among hip fracture (Parker, 2010), hip and knee arthroplasty (Mundy, Birtwistle, & Power, 2005; Sutton, Cresswell, Livesey, Speed, & Bagga, 2004), and CABG (Crosby, Palarski, Cottington, & Cmolik, 1994) patients to evaluate the effects of oral iron versus placebo on postoperative anemia. The results concluded there were no significant differences in red cell mass and iron stores between study groups (Crosby et al.; Leal-Noval et al., 2013; Mundy et al., 2005; Parker, 2010).

Fatigue is a common symptom of both anemia and postoperative CABG surgery, and the correlation between these conditions and their potential impact needs further investigation. Both fatigue and anemia are common co-morbid factors in CABG surgery patients at hospital discharge. As noted above, postoperative anemia, but not POF, has been treated with oral iron supplementation as an intervention for iron deficiency (Muñoz et al., 2017). Oral iron is an inexpensive and effective treatment for iron deficiency that

occurs from acute surgical blood loss during surgery. Two randomized placebo-controlled intervention studies examined the effect of oral iron supplements that measured fatigue as a primary outcome using oral iron in menstruating women (Vaucher et al., 2012; Verdon et al., 2003). Vaucher et al. (2012) compared oral ferrous sulphate vs. placebo in non-anemic women with ferritin < 50 µg/L (n = 198) and unexplained fatigue for 12 weeks. Results showed a decrease in fatigue scores of 47.7% in the iron group and 28.8% in the placebo (19% difference in fatigue score between groups), but no significance in QOL, depression, and anxiety. However, there was a significant increase in Hgb ($p < 0.002$) and ferritin ($p < 0.001$) at six weeks following iron supplementation (Vaucher et al., (2012). Verdon et al. (2003) examined anemic women (n = 136) in the primary care setting using FeSo4 versus placebo for four weeks with the primary outcome of change in the level of fatigue. Results showed that the level of fatigue was decreased by 29% after one month in the iron group compared to the placebo (13%); women benefited from oral iron if ferritin levels were below 50 µg/l.

Both studies demonstrated a significant decrease in fatigue levels following oral iron supplementation in this non-surgical population. Verdon et al. (2003) designed a shorter study (one month) and did not measure Hgb post-treatment, whereas the study by Vaucher et al. (2012) was more extended in duration (12 weeks); included only non-anemic women; and measured other outcomes, such as QOL, Hgb, ferritin, and soluble transferrin receptor levels. There have been no reported studies that used oral iron supplementation to assess the impact of oral iron on fatigue levels in both male and female adult CABG surgery patients.

2.7 Iron Metabolism

Iron is an essential trace element in the body that provides many vital metabolic processes and is an essential component in blood formation (Johnson-Wimbley& Graham, 2011). This metal has a crucial role in cellular respiration, energy production, temperature regulation, immune function, and cognitive development (Johnson-Wimbley & Graham, 2011; Muckenthaler, Rivella, Hentze & Galy, 2017). Iron's primary functions are to bind and transport oxygen to the red blood cells (erythrocytes) and also is a critical component of Hgb (Muckenthaler et al., 2017). Hemoglobin is a protein that is synthesized in the production of erythrocytes and is an oxygen carrier from the lungs to peripheral organs and tissues (Muckenthaler et al., 2017). Approximately two-thirds of the body's iron is found in Hgb within the red blood cells (Johnson-Wimbley & Graham, 2011; Muckenthaler et al., 2017). Ninety percent of iron is stored in the body, and, when the iron is needed for Hgb production, it is transported bound to transferrin to the bone marrow, and the rest of the iron is excreted (Johnson-Wimbley & Graham, 2011). Small amounts of iron are stored in the muscles as myoglobin, which is necessary for muscle contraction (Johnson-Wimbley& Graham, 2011).

An excessive amount of iron in the body can be toxic to organs and tissues (e.g., heart disease and liver damage) (Johnson-Wimbley & Graham, 2011). The body maintains iron homeostasis by various mechanisms to avoid iron overload or iron deficiency. These mechanisms include the control of dietary iron absorption of the intestinal cells (enterocytes), iron transfer to the circulation, cellular recycling by macrophages, and storage in the hepatocytes of the liver (Johnson-Wimbley & Graham, 2011). The average adult body contains 4-5 g of daily iron with only 1-2mg of iron

absorbed from the diet daily (CDCP, 1998; Government of Canada, 2019; Johnson-Wimbley& Graham, 2011). Iron is absorbed in the enterocytes of the intestines, mainly in the upper duodenum, to maintain iron stores. Iron in the amount of 1-2mg/day is excreted through sloughing of the duodenum, physiological losses of menstruation, bleeding, sweat, and epithelial skin cells. A replacement of additional dietary iron is required daily to maintain iron homeostasis, as 10% is excreted from the body. If this iron loss is not replaced, an iron deficiency may result. Too little iron can affect the body's vital functions and is associated with increased morbidity and mortality (Johnson-Wimbley& Graham, 2011). The average recommended daily dietary iron intake for adults is 10-20mg/ day (Government of Canada, 2019; Institute of Medicine, 2001). Postmenopausal women require the same iron intake as men (Government of Canada, 2019; Institute of Medicine, 2001). However, premenopausal women tend to store less iron than men due to menstrual blood loss, and they require 10 mg more of iron daily than men, according to the Dietary Reference Intakes (Government of Canada, 2019; Institute of Medicine, 2001; Johnson-Wimbley& Graham, 2011).

The dietary forms of iron are classified into heme and non-heme. Food from an animal source (e.g., meat), provides ample heme iron and is better absorbed than non-heme. Non-heme iron is found in plant sources (e.g., cereals, beans, grains, and green vegetables). The acidic environment of the stomach, Vitamin C, or Vitamin C rich foods can help the body absorb the non-heme iron-containing foods (Johnson-Wimbley & Graham, 2011; Zhang & Enns, 2009). The dietary iron is required to replace the 10% that is excreted from the body daily. If this iron is not replaced, an iron deficiency will result. This deficiency in iron leads to iron deficiency anemia.

2.8 Iron Deficiency

Iron deficiency is the most common nutritional deficiency worldwide (CDCP, 1998: Johnson-Wimbley& Graham, 2011). The terms iron deficiency and iron deficiency anemia have been used interchangeably, but iron deficiency refers to subnormal iron stores because of decreases in dietary iron intake, poor intestinal absorption, or increased iron losses (Haas & Brownlie, 2001). These low iron levels trigger a decrease in Hgb production and reduction in the availability of oxygen to the working muscles and tissues, causing fatigue, tachycardia, hypotension, shortness of breath, and decreased physical endurance (Haas & Brownlie, 2001; Ross et al., 2003). Iron deficiency in the early stages occurs without anemia and can present without apparent symptoms. As iron stores continue to deplete, the Hgb synthesis is compromised, and the Hgb level will start to drop below the normal reference value (Table 1), causing iron deficiency anemia. The evaluation of iron deficiency is characterized by a decreased serum iron (circulating iron), increased transferrin concentration (transport protein for iron), decreased transferrin saturation (amount of iron bound to transferrin), and ferritin concentration (iron storage) (Clark, 2009). Diet improvement and iron supplementation are the most common treatments for hemodynamically stable patients with iron deficiency and iron deficiency anemia (Blanc et al., 1968; Clark, 2009; National Institute of Health, 2019).

Table 1. *Stages of Iron Deficiency and Iron Deficiency Anemia*

Stage	Hemoglobin	Serum Ferritin (mcg/ml)	Serum Iron	Transferrin Saturation %
Normal	Normal	> 30	Normal	> 16
Iron Stores Deplete	Normal	< 30	Normal	> 16
Iron Deficiency	Normal	< 15	Decreased	< 16
Iron Deficiency Anemia	Decreased	< 15	Decreased	< 16

2.9 Iron Supplements

Iron supplementation can be utilized to replenish iron stores and increase Hgb. Oral iron supplements are available in two preparations containing either ferrous or ferric forms of iron. Ferrous forms (ferrous gluconate, ferrous sulfate, and ferrous fumarate) of iron are the most common over the counter preparations and the better absorbed of the two preparations. The ferrous forms differ by elemental iron content that is available for absorption, containing 12%, 20%, and 33%, respectively (NIH, 2019). The recommended daily dosing of elemental iron ranges from 150 mg/day to 180 mg/day (Centers for Disease Control and Prevention, (CDCP) 1998; Johnson-Wimbley& Graham, 2011). A recommendation to help further promote iron absorption is that a Vitamin C supplement is taken with iron supplements. These iron supplements can cause gastrointestinal (GI) side effects (e.g., nausea, vomiting, diarrhea, constipation, and abdominal discomfort) and turn the stool black. In a study by Swerdlow (1992), patients prescribed oral iron therapy using ferrous salts experienced side effects such as constipation, gastric irritation and diarrhea 25% of the time, and, as a result, had poor adherence to the drug regimen. The frequency of GI side effects is the main reason for poor adherence to the medication (Swerdlow, 1992). Arcangelo and Peterson (2006) found that 20 % of patients

discontinued oral iron therapy because of GI effects. As a result, a newer formulation of oral iron has been developed to decrease side effects and improve adherence to the medication.

FeraMAX® (polysaccharide iron complex) is a newer heme iron preparation that contains 150 mg of elemental iron - nearly triple the elemental iron in ferrous sulphate. This formulation has a non-ionic coating to avoid a breakdown in the stomach and therefore decreases gastric side effects (FeraMAX.com, 2019). FeraMAX® is a standard iron treatment ordered by the Perioperative Blood Management at the clinical investigative site. The CDCP (2011) recommends the treatment of 50-60 mg of oral elemental iron twice a day for 12 weeks (Johnson-Wimbley& Graham, 2011).

2.10 Anemia of Chronic Disease

Postoperatively, patients may present with low serum Hgb levels, reduced serum iron, serum transferrin concentration, and transferrin saturation along with an elevated ferritin concentration characteristic of anemia of chronic disease (ACD) (Madu & Ughasoro, 2017; Weiss & Goodnough, 2005). Anemia of chronic disease is the second most common type of anemia and is associated with chronic disease or inflammation (Weiss & Goodnough, 2005). Surgery causes an inflammatory response, which alters iron metabolism. This inflammation contributes to a state of hypoferraemia (iron deficiency) with the presence of adequate iron stores. A decreased serum iron concentration reflects iron deficiency and transferrin saturation, decreased red blood cell survival, a blunted erythropoietic response in the bone marrow, and erythropoietin production (the hormone that regulates the production of red cells) for a few weeks following surgery (Weiss & Goodnough, 2005). During the early postoperative period, even if iron stores are

adequate, they are unavailable for Hgb synthesis and erythropoietic response. This response may result in a functional iron deficiency and ongoing anemia (Weiss & Goodnough, 2005). During the immediate postoperative period, oral iron supplements may not be effective in restoring Hgb levels because the synthesis of Hgb is impaired. Once the surgical inflammation ceases, oral iron may enhance red cell production, normalize Hgb levels, and replenish iron stores. Anti-inflammatory drugs would not be recommended as these drugs cause platelet dysfunction, increase risk of bleeding, and are not adequate for pain control.

In addition to perioperative anemia, patients who had CABG surgery may also present with symptoms such as pain, fatigue, and dyspnea (shortness of breath) (Barnason, Zimmerman, Anderson, Mohr-Burt & Nieveen, 2000). Although these symptoms may not directly cause mortality, they can prolong the recovery period and potentially impact the QOL, especially fatigue (Barnason et al., 2000; Zargar-Shoshtari & Hill, 2009).

2.11 Theoretical Framework

A theoretical framework is a blueprint that guides the development of the research question(s), design, and analysis plan for a research study unless the research is theory generating. For this study, theory and conceptual framework will be used, and this framework provides structure and supports the rationale for studying the management of fatigue following surgery. Three possible theories were reviewed as part of the literature review for suitability to guide the planned research study.

2.11.1 The social cognitive theory. The SCT was developed to provide a theoretical understanding to guide the prediction and understanding of changes in human

behaviour (Bandura, 1989). This theory can guide the development of nursing interventions designed to increase self-efficacy and potentially modify health outcomes. Self-efficacy can be defined as an individual's confidence in being able to perform a specific behaviour (Bandura, 1989). Increased self-efficacy has been reported to be predictive of successful CABG surgery and increased activity following cardiac rehabilitation (Wassem &Dudley, 2003). This construct focuses on the individual's mastering of self-management behaviours and outcomes. The SCT is based on the assumption that people can influence their behaviour and environment, which can affect their outcomes (Bandura, 1989). Postoperatively, patients can improve outcomes by removing barriers such as physical activity, setting goals, and becoming motivated towards their recovery.

The SCT can be applied to postoperative patients experiencing symptoms of fatigue by developing educational strategies to provide positive reinforcement and enhance the effectiveness of intervention program outcomes. Health care providers (HCP) are in a position to influence behaviours that promote health. Health care providers can identify patients that would benefit and be able to design and incorporate self-efficacy strategies in existing health promotion guidelines or education programs. After hospital discharge, self-management programs are essential to support patients to adjust and cope with recovery. Behavioural change theories can be used to test an intervention such as direct education or teaching methods for promoting symptom management and improvement in patient outcomes. For this proposed study, the SCT would not be applicable as the theory's primary focus is behaviour adjustment through self-management interventions. Behaviour change alone cannot modify postoperative

anemia and fatigue because some etiological factors are physiological. There are four essential tenants of the social cognitive theory that are relevant to health behavior change: observational learning, reinforcement, self-control, and self-efficacy (Bandura, 1989). These tenants illustrate how human behaviour is learned both observationally and through modelling (Bandura, 1989).

2.11.2 The theory of unpleasant symptoms (TOUS). The Theory of Unpleasant Symptoms (TOUS) (Lenz, Pugh, Milligan, Gift, & Suppe, 1997) and the Symptom Management Theory (SMT) (Dodd et al., 2001) are two symptom management theories that examine the inter relationship of symptoms and how multiple factors influence the patient's outcomes, either by focussing on the symptom experience or symptom management.

The TOUS provides a theory to help nurses understand the characteristics of a symptom or multiple symptoms, the interaction of the characteristics, and how the characteristics are affected by influencing factors that can ultimately impact patient performance (Lenz et al., 1997). The theory introduces major assumptions about the individual and their health-promoting symptom management activities. One assumption is that prior human behaviour will influence the individual's thinking and the degree to which individuals will engage in the health-promoting behaviour (e.g., exercise for functional performance) (Lenz et al., 1997). Another assumption of the TOUS is that individuals benefit from actively participating in the management of their symptoms (Lenz et al. 1997).

The TOUS was initially developed from two studies examining symptoms of fatigue in pregnancy (Milligan & Pugh, 1994; Pugh & Milligan, 1993). The model of

unpleasant symptoms was revised in 1997 for use in a broader range of clinical problems (Lenz, Suppe, Gift, Pugh, & Milligan, 1995). This revised model focuses on subjective symptoms and how they influence the antecedents or precipitating factors (physiological, psychological, and situational) and their effect on the symptom experience and performance (Lenz et al., 1997). Patient performance is described by the sub-dimensions (of timing, quality, intensity, and distress) of the symptoms (Lenz et al., 1995; Lenz et al., 1997). These sub-dimensions are separate but also related. Outcomes of the TOUS include function, cognition, and physical performance (Lenz et al., 1997).

Patients can experience varying degrees of POF after their CABG surgery, but due to their environment and physical factors, they may experience their symptoms differently. Their functional performance is determined by the way the symptoms present. Multiple symptoms can be experienced simultaneously and can result from a single event (e.g., fatigue is frequently accompanied by dyspnea following surgery) (Lenz et al., 1997). As stated by Lenz et al. (1997), treating one symptom will contribute to the treatment of other symptoms. Involving patients in their care by explaining the concepts of physiological, psychological, and situational factors can positively affect their recovery (Lenz et al., 1997). According to the TOUS, providing educational materials will help the patient in decision-making to promote a healthier lifestyle. Within the TOUS, POF would be conceptualized to be a multidimensional experience influenced by psychological, situational, and physiological factors. These factors, in turn, are conceptualized to interact with and influence each other (Lenz et al., 1997). These elements of the TOUS suggest that certain aspects of the theory fit with the proposed study.

While the TOUS focuses mainly on the symptom experience and how it affects function (Lenz et al., 1997), one limitation to using the theory for this study was that there is no intervention component included in the theory (Brant, Beck, & Miaskowski, 2009).

2.11.3 Symptom management theory (SMT). Nurse scientists from the University of California, San Francisco developed a Symptom Management Model (UCSF-SMM) (Larson et al., 1994), a middle-range theory, to study the experiences of patients, families, and healthcare providers in dealing with the multidimensional aspects of symptom management. In 2001, the Symptom Management Model was revised to clarify the nursing domains of person, environment, and health/illness, and their influence on the three dimensions (i.e., symptom experience, symptom management strategies, outcomes, and their relationships) (Dodd et al., 2001). The revised Model also included a component of adherence to strategies. As a result of further testing of the Model, Humphrey et al. (2008) found that the Model met the requirements for theory and renamed it the Symptom Management Theory (SMT). The SMT now addresses specific symptoms, proposes testable linkages between concepts, and provides a framework for the assessment of symptom management strategies and symptom outcomes (Cwiekala-Lewis et al., 2017; Humphreys et al., 2008). The SMT addresses the interrelationship of symptoms and how multiple factors influence patient experiences, symptom management, and patient outcomes (Humphreys et al., 2008). The SMT has been applied to many acute and chronic disease populations for both research and nursing practice (Humphreys et al., 2008).

The six assumptions underpinning SMT are the following:

1. Perception of the individual experiencing the symptom and his/her self-report; that the symptom does not have to be experienced by an individual to apply this model of symptom management.

2. The individual may be at risk for the development of the symptom because of the influence (impact) of a context variable such as a work hazard.

3. Intervention strategies may be initiated before the individual experiences the symptom.

4. Nonverbal patients (infants, post-stroke, aphasic persons) may experience symptoms, and the interpretation by the parent or caregiver is assumed to be accurate for purposes of intervening.

5. All troublesome symptoms need to be managed; that management strategy may be targeted at the individual, a group, a family, or the work environment.

6. Symptom management is a dynamic process; that is, it is modified by individual outcomes and influences of the nursing domains of person, health/illness, or environment (Dodd et al., 2001, p. 669-670).

The SMT explains that if symptom management strategies are successful, then the outcomes and symptom experience of the patient will improve (Dodd et al., 2001; Larson et al., 1994). Patients may experience unique and multidimensional symptoms (physical and psychological) that are distressful immediately following surgery and through convalescence (Dodd et al., 2001; Larson et al., 1994). The physical and psychological symptoms associated with recovery may result in symptom distress, which can affect QOL through changes in mobility, symptom management, and treatment adherence.

The major dimensions of the SMT are symptom experience (perception, evaluation, and response), symptom management strategies (who, when, where, how, to whom, how much and why), and outcomes of symptom status (functional status, emotional status, self-care, costs, mortality, QOL, morbidity and co-morbidity) (Liehr, 2005).

Dodd et al. (2001) emphasized the interrelatedness of the major dimensions with the use of bi-directional arrows in the conceptual framework, as well as the integration of the nursing domains of person, health/illness, and environment. The SMT dimension of symptom experience comprises three elements: the person's perception of the symptom, evaluation, and response. The dimension of symptom management strategies calls for addressing what, when, where, how, to whom, how much, and why? The dimension of outcomes embodies functional status, emotional status, self-care, mortality, and co-morbidities (Dodd et al., 2001). Outcomes are the result of the combination of symptom experience and management strategies. The SMT is not a fatigue-specific theory but focuses on the multidimensional symptom management process depicted via three bi-directional dimensions and associated nursing domains (see Figure 1) (Dodd et al., 2001; Humphreys et al., 2008).

2.11.4 Studies using symptom management theory. Limited research has been conducted that incorporates a symptom management model in an RCT design, specifically in CABG patients. One RCT was conducted to test the effects of a symptom management strategy using an educational intervention (telehealth intervention vs. routine care) (n = 282) on recovery outcomes in postoperative elderly CABG patients with the measurement at discharge, three weeks, six weeks, 12 weeks and six months

(Zimmerman & Barnason, 2007). Preliminary data suggest that patients discharged with symptom management issues may experience fewer complications with early detection and management (Zimmerman & Barnason, 2007). Similarly, enhanced recovery interventions employed symptom management strategies (Hiltunen et al., 2005; Kleinpell & Avitall, 2007; Tranmer & Parry, 2004; Zimmerman et al., 2004) were conducted among CABG patients. Schultz et al. (2011) performed a subanalysis examining the effects of a home care strategy versus usual care on recovery outcomes among elderly CABG patients.

Other nursing researchers investigated postoperative treatment effects incorporating the SMT strategies: perioperative thirst (Conchon, Nascimento, Fonseca & Aroni, 2015), postoperative pain following day surgery, recovery, sleep disruption, HIV, and pediatric oncology (Linder, 2010).

2.11.5 Symptom experience. The symptom experience is described as complex and subjective and comprises the elements of perception, evaluation, and response (Dodd et al., 2001; Humphreys et al., 2008). The perception (a change in the way individuals feel or behave from their norm), evaluation (the assessment by the individual to describe the symptom experience), and response (the individual's reaction to the symptoms) are interrelated subdimensions of the symptom experience (Dodd et al., 2001, Humphreys et al., 2008). The perception of the individual may be altered and response different due to the progression of the severity of symptoms (Armstrong, 2003). Postoperatively, the perception of the fatigue symptom is based on the self-report of the patient and the awareness they are at risk of experiencing fatigue. This experience is affected by frequency, intensity, and distress of the symptom (Dodd et al., 2001; Humphreys et al.,

2008). Following surgery, a patient experiencing fatigue may continue activities of daily living or may not be able to mobilize. If the fatigue symptom continues with sufficient frequency, and the severity is perceived as distressing and interfering with activities, the patient may seek medical help to eliminate or minimize the symptom and may alter their perception (Dodd et al., 2001, Humphreys et al., 2008).

People with POF may experience a range of progressive symptoms from physiological to psychological. Physiological symptoms include muscle atrophy, decreased functionality, and cardiac deconditioning (Hall & Salmon, 2002), and psychological symptoms may include depression and anxiety (Barnason et al., 2009).

2.11.6 Symptom management strategies. Symptom management strategies are dynamic and characterized as biomedical, professional driven, and self-care strategies used by individuals to manage or prevent the symptoms. The management strategies attempt to alter the symptom experience by recognizing treatments that are encouraging and supportive. Strategies encompass more than self-care, ranging from individualized to combination treatments. Patients with POF may benefit from pharmaceutical interventions. As previously mentioned, a limited number of intervention studies on fatigue management have been conducted, and these suggest that POF is unrecognized and undertreated (Kahokehr et al., 2012; Barnason et al., 2008; Rubin & Hotopf, 2002; DeCherney et al., 2002).

The SMT is a more comprehensive theory than the TOUS. Management strategies include specifics (when, where, what, why, how much, to whom, and how) to help design, develop, and prescribe strategies. The type of intervention strategy depends on the particular symptom, and the strategy may need to be altered due to nonadherence

(Dodd et al., 2001). Adherence was added to the revised SMT because researchers recognized its impact on the intervention strategies, and on symptom outcomes (Brant et al., 2009; Dodd et al., 2001). The intervention strategy used in this current study was potentially challenging because oral iron supplementation is associated with an increased risk for nonadherence. The healthcare provider and family members play a crucial role in improving outcomes by education on side effects, and patient follow up.

2.11.7 Symptom status outcomes. The model is no longer applicable if the fatigue symptom is resolved through an iron intervention, which is the primary outcome for this study. If the fatigue symptom requires further intervention, however, then the model is designed to remain dynamic. Symptom outcomes are the evaluation component of the theory that results from the symptoms associated with symptom experience and symptom management strategies. The outcomes comprise eight indicators: functional status, QOL, self-care, morbidity and co-morbidity, mortality, emotional status, and cost (Dodd et al., 2001; Humphreys et al., 2008). Little information on potential associations between iron, fatigue, Hgb values, and perception of QOL is available. Symptom management can be influenced more broadly than by the dimensions of experience, management, and outcomes. The domains of person, health/illness, and environment contained within the theory, therefore, contribute more comprehensively to explaining the symptom experience (Dodd et al., 2001; Humphreys et al., 2008).

2.11.8 Nursing domains of SMT. Three nursing domains (person, environment, and health and illness) influence all three dimensions (symptom experience, symptom management strategies, and symptom outcomes) of the model. The domain of person refers to characteristics of the individual, including demographics (age and sex,

psychological, sociological and physiological) and the variables are inherent to how the person views and reacts to the symptom experience (Dodd et al., 2001, Humphreys et al., 2008). This domain was examined in terms of demographics for this current study. The domain of health and illness is integrated into the symptom experience and includes risk factors, injuries, or disabilities (Dodd et al., 2001; Humphreys et al., 2008). Risk factors such as co-morbidities have been identified as negatively impacting QOL. The environment is the third domain, which encompasses physical, social, and cultural influences. For this study, the domains of health/illness and the environment were examined.

Following major surgery, patients may experience fatigue, and that fatigue may delay recovery. The perception and response to the symptom differs, depending on the person's situation. The influencing factors of the fatigue experience are decreased mobility, anemia, and QOL, which will affect evaluation and response to the symptom. The patient's perception of fatigue, fatigue interventions, and QOL are illustrated in the adapted Symptom Management Model (Figure 1). This model guided the selection of the variables included in the study and facilitated conceptualizing possible associations among the variables.

Incorporating both individual and environment characteristics into this model is important in studies focused on CABG patients. In the domains of person and environment, previous evidence identifies factors within the person that relates to fatigue in the hospital environment. The perceived symptom is viewed differently depending on personal factors, including demographics, and psychosocial and physiological factors. Postoperative fatigue is affected by physical (e.g., mobility) and psychological factors

(e.g., anxiety and depression), and the severity of fatigue varies according to age and sex. Oral iron supplementation as a management strategy can decrease symptoms such as fatigue, improve functional capacity, and produce changes in lifestyle, thus preventing a negative outcome for the patient.

There are few RCT studies related to this population, and a symptom management model guides only a few. One RCT was conducted to test the effects of a symptom management strategy using an educational intervention (telehealth intervention vs. routine care) (n=282) on recovery outcomes in postoperative elderly CABG patients. At discharge, the effects of the treatment were measured at three, six, 12, and 24 weeks. Preliminary data suggested that patients discharged with symptom management problems experienced fewer complications with early detection and management (Zimmerman, Barnason, Schulz, Nieveen, & Tu, 2012).

Effective symptom management can treat symptoms in the acute phase of postoperative convalescence and enable patients to enjoy an improved QOL. The strength of the SMT is the focus on the interrelationship of the dimensions of symptom experience, management strategies, and outcomes from a patient's perspective. Advancing the science of POF by expanding previous literature and demonstrating the relationship between fatigue and QOL and symptoms associated with fatigue in CABG patients may lead to enhanced patient care.

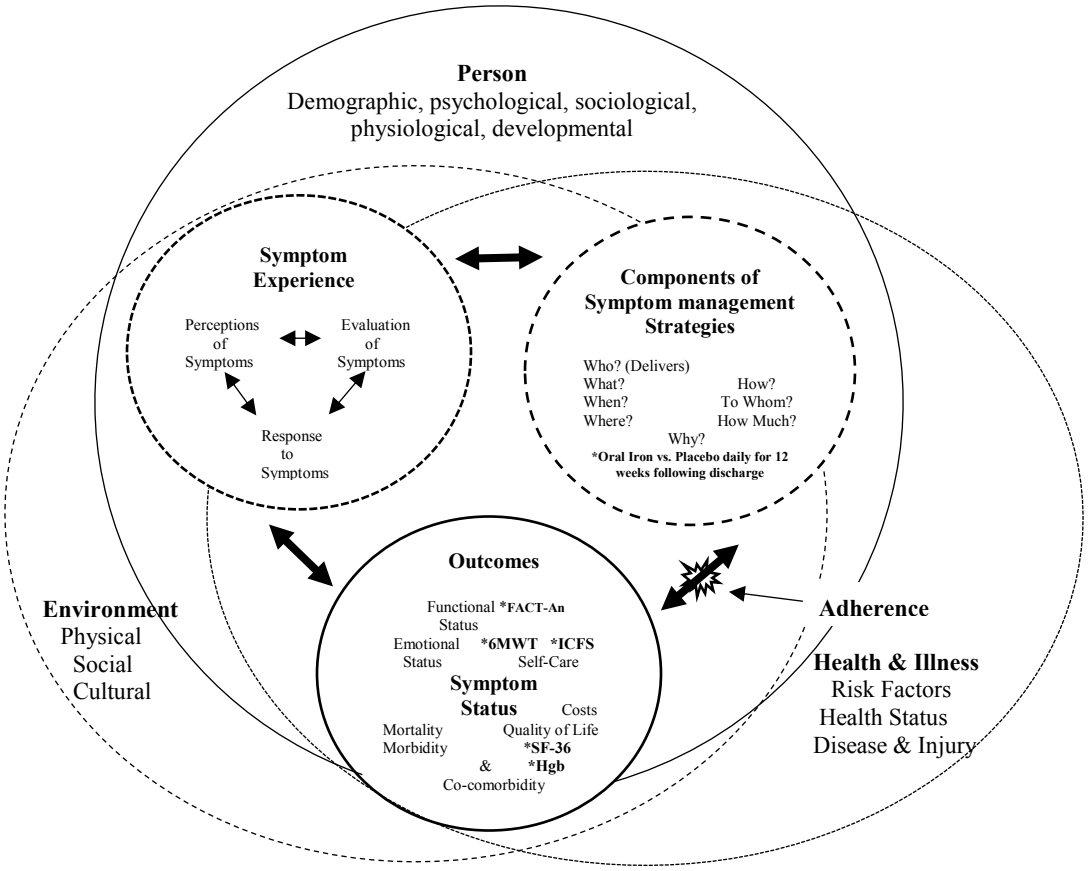

Figure 1. Adapted Symptom Management Model.
Note. *items = intervention strategies in the Symptom Management Strategies Dimension and primary and secondary outcomes in the Symptom Outcomes Dimension.
The fatigue symptom can impact one's sense of well-being, ability to perform daily activities relationships with family and friends, ability to cope with the illness. Dodd et al. (2001). Reprinted with permission

2.12 Summary

POF is a persistent and distressing symptom that can prolong return to work and activities, QOL, cause emotional turmoil and ultimately impact overall recovery (Zargar-Shoshtari & Hill, 2009). Even though fatigue is a more common complaint and has a longer duration than pain, it is often ignored by healthcare providers because of its subjective nature. The fatigue experience can cause a depletion of energy resources over time and worsen patient morbidity and mortality outcomes.

Several studies in this review were observational studies focusing on the prevalence and impact of fatigue on cardiac disease and postoperative cardiac events (e.g., MI) (Barnason et al., 2008; Zimmerman et al., 2007). Few intervention studies (e.g. educational techniques) have been conducted related to investigating fatigue in postoperative CABG patients, and there are no studies examining oral iron supplementation as a treatment for POF. This review provides an opportunity to address the gaps and to introduce an intervention for symptom management of fatigue. The current study addresses the clinical efficacy of this pharmaceutical treatment about fatigue, QOL, functional capacity, and anemia.

There are a number of remaining gaps related to the fatigue experience and management, specifically in CABG surgery, requiring a heightened awareness and further investigation. Clinicians are challenged with proper diagnosis and treatment due to the subjective nature of fatigue, lack of assessment guidelines, lack of clarity of definition, and inadequate measurement. Recognition and a comprehensive assessment of the role POF plays in CABG patients can assist researchers in developing and testing tailored intervention strategies (Yu, Lee, & Wai-Man, 2010) to improve outcomes, such as fewer hospital readmissions, improved patient satisfaction, and decreased morbidity and mortality.

The next chapter will review the methods used to conduct the clinical trial.

CHAPTER 3 METHODS

The purpose of this chapter is to explain the methodological approach as well as the methods used in this study. This chapter contains the research design, sampling plan, data collection, analysis methods, and interpretation of the results. An experimental approach was taken to answer the research questions. A randomized control trial (RCT) design was used to investigate the effects of the pharmaceutical intervention on fatigue in adults who underwent CABG surgery. The aim was to investigate the effect of oral iron administration on selected patient outcomes of fatigue levels, anemia, functional capacity, and QOL postoperatively in patients scheduled for CABG surgery (i.e., non-emergency patients). Ethical considerations for human subjects, validity, and rigor are described. The Symptom Management Theory (Dodd et al., 2001; Humphreys et al., 2008), as described in the previous chapter, guided the research, focusing on the dimensions of symptom experience, symptom management strategies, and symptom outcomes.

3.1 Research Questions

An experimental method was utilized to answer the following research questions:

1. Is oral iron effective in reducing POF among patients having coronary artery bypass graft surgery? A randomized, double-blind placebo-controlled clinical trial.
2. Is oral iron effective in improving fatigue, functional capacity, quality of life, and anemia among patients having coronary artery bypass graft surgery as measured by the Short Form-36, Functional Assessment of Cancer Therapy-Anemia, Six-Minute Walk Test and Hemoglobin biomarker over 12 weeks?

3. To what degree do patients having coronary artery bypass graft surgery take oral iron and adhere to the prescription?

3.2 Study Design

An RCT was chosen to examine the causal relationship between two groups: control and intervention. A two-armed parallel experimental design was selected as a pragmatic, randomized, double-blind placebo-controlled, single-centre study to compare fatigue levels between participants receiving a control (placebo, a harmless, inactive sugar pill) compared to an intervention (oral iron FeraMAX® therapy) during the first 12 weeks after discharge following CABG surgery. Data were collected and analyzed at baseline and at time points two, three, and four. The purpose of employing this method was to explore the effect of the intervention at different time intervals (Spieth et al., 2016).

The medication chosen for this current study is a widely used treatment for iron deficiency anemia (Camaschella, 2015). There is limited research conducted using an experimental design to assess the effect oral iron has on fatigue in the community setting (Vaucher et al., 2012; Verdon et al., 2003). The results of the current study are necessary to provide insight into this phenomenon and establish evidence for a fatigue reduction treatment.

3.3 Setting

This single centre study was conducted at a large regional referral site for cardiovascular surgery affiliated with a university medical school in Eastern Canada. Approximately 600 patients undergo elective CABG surgery annually at the regional centre. Patients are either directly transferred to the cardiology nursing unit from rural

hospitals or admitted from home for elective surgery. Participants were enrolled in the study from the preadmission clinic and inpatient nursing units at the regional centre to optimize recruitment. The sample consisted of elective surgery patients mainly from Nova Scotia; however, some patients resided in the other Maritime Provinces.

3.4 Study Population

The study population consisted of volunteer adults (19 years of age and over) with CAD who were scheduled for elective primary CABG surgery at a large regional centre. The CABG patient population was selected for this study because there was evidence that POF was a prevalent, problematic patient experience, and there was limited literature on treatments of the fatigue experience following CABG surgery (Barnason et al., 2008, King & Parrinello, 1988, Rubin & Hotopf, 2002). Previously published studies have examined the prevalence and contributing factors of fatigue (Rubin, Hardy & Hotopf, 2004b, Zargar-Shoshtari et al., 2009). The symptom experience is well documented in the literature and describes the contributing components: physical (pain, dyspnea, fatigue, sleep disturbances, and edema) and psychological (anxiety and depression) (Al-Daakak et al., 2016, Cowper et al., 2006). While published reports do not suggest that fatigue may directly cause mortality, fatigue has been determined to prolong the recovery period and diminish QOL (Barnason et al., 2000; Zargar-Shoshtari & Hill, 2009). Thus, it is an important clinical phenomenon associated with negative physical and psychological experiences and with real adverse effects for this patient population.

3.5 Study Sample

The sample was derived from a purposive population of patients undergoing CABG surgery, and participants were randomly assigned to two groups. Group

assignment was performed by simple randomization (computer-generated list), and stratification was done by sex.

Intervention outcomes may be affected by known or unknown factors such as sex. Randomization was stratified 1:1 by sex to ensure each group (either FeraMAX® or Placebo) was well-balanced and to ensure an unbiased estimate of the treatment effect (Kahan, Rehal, & Cro, 2015). Stratified randomization was used to ensure that there were similar numbers of males/females in each treatment group to avoid selection bias. The consultant statistician used a computer-generated random sampling software program to create a randomized sampling list of study identification (ID) numbers that allocated 50% of the ID numbers for the intervention group and 50% for the control group before the study commenced. The sealed randomization list was locked in a designated sponsor-investigators' file in the research pharmacy department at the regional centre. This randomization list was used by the research pharmacy technician to dispense the prepared medication (study drug or placebo).

All outpatients were first assessed by cardiovascular surgeons to determine if they required surgical intervention. Once identified as a surgical candidate, all outpatients were further assessed in the preadmission clinic for surgical fitness by anesthesia, and the inpatients were seen by both the cardiovascular surgeons and anesthesia on the nursing units. Once inpatients were accepted for surgery, they were classified by the surgeon as inpatient urgent and scheduled electively for surgery.

3.5.1 Study groups. Participants in both study groups received standard postoperative care. Standard postoperative care includes pulmonary management, pain control, wound care, nutrition management, and mobility. There is no standard of care for

fatigue other than rest periods. At discharge, all CABG patients were invited to enroll in cardiac rehabilitation and seek community resources or support groups.

3.5.1.1 Intervention group. In the intervention group, participants allocated to the oral iron group received standard care during the postoperative period in the hospital. At discharge, they received a 12-week supply of oral iron capsules and were instructed to take one capsule per day starting post-discharge day one. Participants received a package with study medication, discharge instructions, self-report questionnaires for each time point, and a medication symptom diary listing side effects and yes or no replies.

3.5.1.2 Control group. Participants randomized to the control group received in-hospital standard of care during the postoperative period. At discharge, participants received a 12-week supply of placebo capsules and the same package as the intervention group. The package included study medication discharge instructions, questionnaires for each time point, and a medication symptom diary listing side effects and yes or no replies.

3.5.2 Inclusion criteria. Participants were screened for eligibility before enrollment according to the following inclusion criteria:

- nonurgent[1], first time CABG (i.e., nonrepeat)
- American Society of Anesthesia (ASA) physical status I-IV[2]
- aged 19 years and older

[1] Non Urgent classification included patients requiring CABG surgery greater than 24 hours

[2] American Society of Anesthesiologists (ASA) physical status classification is used to categorize physiological status and predict operative risk. ASA Physical Status II refers to a patient with mild systemic disease, Status III refers to a patient with severe systemic disease and Status IV refers to a patient with severe systemic disease that is a constant threat to life (American Society of Anesthesiologists, 2017).

- able to provide informed consent
- able to read and write English at a Grade six academic level

Primary CABG surgery patients were chosen due to a potential higher risk of postoperative complications in patients undergoing a repeat procedure, which could be a confounding factor for a longer recovery.

3.5.3 Exclusion criteria. Exclusion criteria included the following:

- Prior median sternotomy surgery
- Hgb greater than or equal 120 g/L at discharge
- Participating in another prospective study
- Received medical treatment instead of surgery, or had CABG surgery performed at another site.
- History of non-adherence with oral medications as measured by interview
- Received erythropoiesis-stimulating agents (e.g., epoetin alfa and darbepoetin alfa) postoperatively to discharge
- Allergy to iron[3]
- History of hematological disorders (e.g., hemophilia, bleeding disorders) that are deemed clinically significant as per the investigator's clinical judgment
- Received Clopidogrel within two days before surgery, received greater than 81mg of Acetylsalicylic acid 24 hours before surgery, or have received "new oral anticoagulants" (e.g., Apixaban, Rivaroxaban, and Dabigatran) within the

[3] Allergy to oral iron salts is rare (deBarrio et al., 2008, Demir et al., 2014), Adverse GI side effects are more common impacting up to 50% of patients (Tolkien, Stecher, Mander, Pereira & Powell, 2015).

recommended preoperative exclusion period. Patients receiving the "new oral anticoagulants" (e.g., Apixaban, Rivaroxaban, and Dabigatran) postoperatively were not included in the data collection (Herman, Buth, Kent, & Hirsch, 2010)

- History of iron metabolism disorders, such as known iron overload, hemochromatosis, porphyria
- Chronic fatigue syndrome (a condition that is distinguished from other types of fatigue by fatigue lasting more than six months and has at least four other symptoms (e.g., sleep disturbances, headaches, joint pain, and concentration difficulties) that could contribute to increased fatigue) (Afari & Buchwald, 2003)
- Serum transferrin saturation more than 50% at discharge
- History of Fibromyalgia
- Current diagnosis of depressive disorder
- Patient taking iron supplementation ≤ 60 days before surgery and in the postoperative period
- History of hypothyroidism includes uncontrolled thyroid disease (abnormal TSH or T4 at screening visit) as per the investigator's clinical judgment
- Any other unstable conditions as per the investigator's clinical judgment

Contraindications to the 6MWT (this measure was used to measure functional capacity and is discussed further in the chapter)

- Physical disability preventing the safe performance of the walk test
- Resting heart rate > 120 beats/min +/- diastolic blood pressure > 100mm Hg (relative contraindications)
- Resting Sp02 < 85% on room air or prescribed level of supplemental oxygen

The exclusion criteria were identified to isolate POF and eliminate any known confounding variables. Furthermore, emergency and reoperation sternotomy patients tend to be sicker and are at a higher risk of postoperative complications and were excluded from the study. Patients with previous self-reported nonadherence to FeraMAX® would potentially not adhere to the study protocol and were excluded. Also, patients with transferrin saturation greater than 50% are at risk of iron overload, and potential liver failure (Limdi & Hyde, 2003), and so were excluded. During the postoperative period, patients may receive treatment for anemia. Therefore, these patients were excluded from the study. An anemia treatment was defined as the initiation of iron supplementation or erythropoiesis-stimulating agents (e.g., epoetin alfa and darbepoetin alfa). Anemia treatment decisions were made at the discretion of the physician. Postoperatively, the surgical stress response causes inflammation that can induce a blunted erythropoietic response caused by hepcidin blockade, which negatively impacts iron metabolism (Muñoz, Garcia-Erce & Remacha, 2011). Patients were excluded if they had iron metabolism disorders. Another exclusion criterion applied was that of chronic fatigue syndrome, a condition that is distinguished from other types of fatigue by fatigue lasting more than six months and has at least four other symptoms (e.g., sleep disturbances, headaches, joint pain, and concentration difficulties) that could contribute to increased fatigue (Afari & Buchwald, 2003). The extensive exclusion criteria were necessary to isolate the variables associated with fatigue and CAD and eliminate confounding variables.

3.6 Ethical Considerations

Before the commencement of the study, a clinical trials application following the

Tri-Council Policy Statement (TCPS) on clinical research was submitted to Health Canada-Natural and Non-prescription Health Products Directorate (NNHPD). Upon approval of the study protocol (See Health Canada Approval Letter, Appendix A) , a research ethics application was submitted to the NSHA Research Ethics Board (REB) and approval (REB # NSHA-RS/2014-217 Romeo file no. 1015707) was received on December 16, 2014 (see REB Approval Letter in Appendix B). This study was conducted in accordance with applicable Health Canada regulations, International Standards of Good Clinical Practice, and applicable institutional research policies and procedures. Participants were informed of the study when they came to the preadmission clinic or admitted to the nursing unit and invited to participate if they met study criteria. The study protocol was registered at Clinical Trials .gov identifier (NCT019122).

3.6.1 Consent. Following REB approval, the cardiovascular surgeons informed eligible patients about the research study and provided the investigator's contact information to the patient. Eligible patients interested in hearing about the research study were approached by the investigator. The investigator explained the study protocol and the consent form (Appendix C) to each prospective participant who met the study eligibility criteria. Informed consent is a voluntarily process for receiving permission from participants, which was performed in accordance with the Declaration of Helsinki (The World Medical Association, 2013). The Declaration of Helsinki (2013) addresses the voluntary consenting of ethical conduct for research involving human subjects. This consenting process occurred before enrollment and continued through the study period. Participants were informed that participation was voluntary, could withdraw from the study at any point without consequences, and would receive standard care.

Informed consent was ensured by informing the participants both verbally and by providing written information on their rights, the purpose of the study, the procedures to be performed, and the potential risks and benefits of participating in the study. Prospective participants were asked to explain their understanding of the study to confirm that they fully understood the information provided in the written consent. The investigator also provided an opportunity for participants to ask questions. Only when both the investigator and the participant were satisfied that individuals had questions satisfactorily answered and were fully aware of the risks and benefits of participation in the study was written consent to participate in the study obtained by the investigator and signed by the participant. All participants received a copy of the informed consent, and all data were kept confidential. Participant's names only appeared on the consent form, laboratory requisition, and results.

Anonymity was assured for participants by assigning each participant a unique ID number. The participants' names did not appear on any of the paper forms or questionnaires but rather were coded with the study ID. Confidentiality of the data was strictly enforced. All hard copies of completed data collection instruments were stored in a secure, locked file cabinet in the Perioperative Blood Management office. Hard copy data were entered into a hospital computer database, which is password protected using unique participant identifiers. Data were stored and backed up nightly on a hospital desktop computer and accessed only by the research team. All source documents are kept for five years after study closure and then archived offsite to IRON Mountain for long term storage. Research team members were required to sign a confidentiality agreement

regarding participant information. Clinical trial records will be retained for 25 years or longer per REB.

Only the investigator and research team associated with the study have access to the raw data. The results of the study were only shared as aggregate data for this dissertation and subsequent publications. No participant identifiers were reported or published. A study log (a separate document) was prepared that linked patient identifying information (such as name and patient admission data), study ID number, and stored separately from study data. Permission to use instruments was obtained from the developers of ICFS, FACT-An, and SF-36 questionnaires before the commencement of the study. The outcome assessor was kept blinded to the specific treatment allocated to any individual participant. The pharmacy department kept a copy of the randomization list and dispensed the study drug to the investigator.

3.6.2 Human subjects considerations. The REB and the investigator ensured that the research participant's rights were protected by strict adherence to policies and procedures to assure privacy and confidentiality. All study data collected from participants were de-identified and used for statistical purposes. Only aggregate data will be published.

The Belmont Report (1979), provides ethical guidance for investigators conducting research involving human subjects using three underlying moral principles: respect for people, beneficence, and justice. Participants were treated with respect and allowed to make independent decisions regarding participation in the study. When enrolling participants, they were instructed that participation is voluntary, comprehensible, and relevant information was provided during the informed consent

process. Beneficence was addressed by informing participants of the risks and benefits of the research study while the third principle, justice, demonstrated concern and fairness for the participant and society. The exclusion of participants was based on study criteria and not on vulnerability.

3.6.3 Potential risks to participants. Overall risks to participants in the study were assessed to be minimal. The main concerns for participants were the GI side effects of oral iron for the intervention arm. FeraMAX®, an over-the-counter heme based oral iron supplement, was chosen to address the issue of GI side effects for this study. FeraMAX® is a polysaccharide iron complex which reduces GI side effects by breaking down its components in the duodenum, not the stomach, and by promoting better absorption by avoiding the gastric acids (FeraMAX® product monograph, 2019).

3.6.4 Potential benefits to participants. The potential benefits for participants participating in this trial were: (1) they received the pharmaceutical study treatment free of charge; (2) they may have increased exercise capacity and overall activity at physical, cognitive, psychological, and social levels; (3) they may have utilized strategies to decrease POF; (4) they may have improved QOL; and (5) they may have increased independence in returning to work and daily activities. For the intervention group, these participants may have seen the benefit, whereas the control group may have experienced little or no benefit. An outside pharmaceutical vendor compounded the placebo identical to the study medication and used inactive ingredients. The placebo medication was then sent to the study site Pharmacy Department for dispensing.

3.7 Description of Study Outcome Measures

3.7.1 Socio-demographics. A case report form (see Appendix D) was developed

by the investigator to collect data from the participants' health records. The first section recorded demographic data (sex, age, marital status, occupation, employment status), and the second section collected clinical variables (left ventricular ejection fraction [LVEF], alcohol consumption, comorbidities, current medications, history of tobacco use, and ASA physical classification). Data for the medical variables (i.e., operative procedure, transfusion of blood components, length of stay, adverse events, and postoperative complications) were extracted from the participants' health records.

3.7.2 Postoperative fatigue (primary outcome).

3.7.2.1 Identity consequence fatigue scale (ICFS). Paddison et al. (2006) developed the ICFS (Appendix E), a generic tool to correctly measure the comprehensive nature of fatigue and its impact on the post-surgical patient. Only a sample is provided due to copyright restrictions. The ICFS is a 31 item self report instrument measuring five domains of fatigue: feelings of fatigue (five questions), feelings of vigor (four questions), impact on concentration (five questions), impact on energy (six questions) and impact on daily activities (11 questions) (Paddison et al., 2006). This scale provides two summary scales (fatigue experiences and fatigue impacts) (Paddison et al., 2006). The first summary scale, fatigue experiences, combines the first three domains (feelings of fatigue, feelings of vigor, and impact on concentration) and the second summary scale, fatigue impacts, combines the latter two domains' impact on energy and impacts on daily activities scores (Paddison et al., 2006). The fatigue experiences scores were averaged and produced a mean of the first three subscales, and similarly, the fatigue impact summary scores were averaged (Paddison et al., 2006). This tool was administered to

measure the overall POF among CABG surgery patients during the first 12 weeks following discharge in both the intervention and control groups. The participants reported how they had been feeling for the first eighteen items on a six-point Likert scale where: 6 = all of the time; 5 = very often; 4 = fairly often; 3 = some of the time; 2= almost never; 1 = not at all, and for the 19th and 20th items they reported on a five-point Likert scale where: 5 = I strongly disagree; 4 = I disagree; 3 = neutral; 2 = I agree; 1 = I strongly agree. The participants were asked to report how fatigue interfered with their daily activities for the questions 21 to 31 on a six-point Likert scale where: 6 = not applicable, 5 = as often as usual; 4 = nearly as often as usual; 3 = sometimes but less than usual; 2 = only occasionally; 1 = not at all.

Fatigue scores were calculated by direct scoring for the following items: 1, 2, 4, 6, 8, 10, 12, 13, 15-17, and 18. For the remaining items, reverse scoring was performed for items; 3, 5, 7, 9, 11, 14, 19, 20, and 21-31. Feelings of fatigue were calculated with the maximum score of 25 based on five items, question numbers 1, 4, 6, 10, and 12. Feelings of vigor were calculated with the maximum score of 20 based on four items, question numbers 3, 5, 7, and 14. Impact on concentration was calculated with a maximum score of 25 based on five items, questions number 9, 15-17, and 18. Impact on energy was calculated with the maximum score of 28 based on six items, questions number 2, 8, 11, 13, 19, and 20. Impact on daily activities was calculated with the maximum score of 44 based on 11 items questions 21 - 31. A total ICFS score was obtained by calculating the mean of the above five subscales. The two summary scores were calculated as a percentage of the maximum scores (Paddison et al., 2006). The higher the score, the higher the intensity of fatigue.

The ICFS is a comprehensive multidimensional scale in comparison with other fatigue scales (Paddison et al., 2006). As outlined in Table 2, below, the ICFS subscales demonstrated a high internal consistency (α = 0.88 to 0.90) and good stability (test-retest r range = 0.84 to 0.94) (Paddison et al., 2006). Zargar-Shoshtari et al. (2009) found the ICFS to be a valid and reliable measure of fatigue in 70 colon surgery patients. The ICFS scale has been used in other major surgical procedures to detect changes in POF over time (Kahokehr et al., 2012; Paddison et al., 2006). The ICFS scale assessed construct-specific factors using discriminate and convergent validity. Discriminate validity analysis distinguished all the subscales from depression and anxiety (Paddison et al., 2006) and convergent validity compared the ICFS subscales with two fatigue scales, Visual Analog Scale (VAS) and Profile of Mood States (POMS) and confirmed a strong relationship with the Fatigue Identity subscales (Paddison et al., 2006) (See Table 2 for further details). The ICFS has not been used to measure the CABG surgery populations. In this study, Cronbach's alpha was calculated to determine internal consistency (Cronbach, * Warrington, 1951). For this study, the ICFS was chosen to measure POF because it is reliable, sensitive to change, and examines the multidimensions of fatigue.

3.7.3 Fatigue / anemia / QOL (secondary outcomes).

3.7.3.1 Functional assessment of cancer therapy anemia version 4 (FACT)-An.

There are no instruments designed to specifically measure anemia in the postoperative cardiovascular population other than the Hgb biomarker. The FACT-An (See Appendix F) is a disease-specific measure which is comprised of the FACT-G (general scale measuring QOL), and its subscale measuring anemia and fatigue. The FACT-An was selected to assess QOL, anemia, and fatigue in this study (Cella, 1997). This five-point

Likert scale consisted of 48 questions with ratings of 0 (Not at all) to 4 (Very much) and has mainly been used to measure fatigue and anemia symptoms in chronic illness and cancer patients (Cella & Nowinski, 2002). This 48 item scale combined the FACT-General (FACT-G) as a questionnaire base of 28 items, and the FACT-An anemia subscale, which included the FACT- Fatigue (FACT-F) subscale measuring 13 fatigue specific questions, and seven non-fatigue questions relevant to anemia (Cella, 1997). These subscales have been validated in other conditions. Permission was granted from FACIT.org to use the FACT-An the questionnaire and scoring instructions (See Appendix G). In preparation for analysis, negatively worded phrases were reverse coded. The total score resulted from the sum of all subscale scores, and a higher score indicates improved QOL (Cella, 1997). The FACT-An scale scores range from 0 to 80 (Cella, 1997).

The FACT-F and FACT-An were measured on 50 cancer patients Hgb levels of 70-159 g/L and showed high internal consistency with an alpha of 0.95-0.96 and test-retest reliability r = 0.87 (Cella, 1997, Yellen, Cella, Webster, Blendowski, & Kaplan, 1997). The FACT-F and FACT-An total scores differed between Hgb levels ($p < 0.05$) and performance status ($p < 0.001$) (Yellen et al., 1997). FACT-An scale scores range from 0 to 80 (Cella, 1997). The FACT-An and SF-36 were used to assess convergent validity among 79 elderly postoperative hip arthroplasty patient's QOL and Hgb levels. On postoperative day eight, the correlation between Hgb and change in SF-36 was 0.49 ($p < 0.0005$) and FACT-An was 0.46 ($p < 0.0005$) (Conlon, Bale, Herbison & McCarroll, 2008). This may suggest that participants with higher scores have fewer symptoms of fatigue.

3.7.4 Functional capacity (secondary outcome).

3.7.4.1 ***Six-minute walk test (6MWT).*** The 6MWT is a valid and reliable tool that provides consistent results for testing functional capacity postoperatively in the cardiac population (Chen et al., 2018). Balke (1963) developed the 6MWT, a submaximal measure used for assessing functional capacity, later used to assess treatment interventions (Demers, McKelvie, Negassa, & Yusuf, 2001; Guyatt et al., 1984; Guyatt et al., 1985). Cardiovascular patients can be limited in their functional capacity due to dyspnea, fatigue, and pain rather than exertion. Maximal exertion is usually contraindicated or of limited value (ATS Statement, 2002). These patients do not routinely achieve maximal exercise capacity when performing the activities and 6MWT (ATS Statement, 2002). Patients walk at their own pace with options for rest. Daily activities are usually not performed at maximal exertion therefore, the 6MWT is reflective of functional activity (ATS Statement, 2002). The 6MWT was reported as a prognostic indicator of mortality and rehospitalization (Lord & Menz, 2002; Bittner et al., 1993). Previous studies demonstrated the value of > 300m independently protects against mortality and can discriminate patients with different risks in cardiac surgery patients (Cacciatore et al., 2012; Chen et al., 2018; Gremeaux et al., 2011).

The cutoff of > 300m walking distance for the 6MWT was used in this study as a measure of functional walking capacity following CABG surgery (DeFeo, Tramarin, Lorusso, & Faggiano, 2009; de Oliveira et al., 2014; Fiorina et al., 2007). This walking test was previously used and validated in populations with a cardiopulmonary disease (Enright, 2003; Guyatt, 1987; Lipkin, Scriven, Crake, & Poole-Wilson, 1986). Butland, Pang, Gross, Woodstock, and Geddes (1982) compared the 6MWT to other methods of

exercise testing and found a significant correlation with maximum oxygen consumption. The 6MWT has an excellent test-retest reliability r = 0.97 (Balke, 1963). Moderate to strong correlations were demonstrated between the 6MWT and the SF-36 physical function subscale following cardiac surgery at .44 and .54, respectively (Chen et al., 2018). Chen et al. (2018) also examined the responsiveness of the 6MWT between baseline (preoperatively) and discharge, and baseline and 12-week follow-up, the effect sizes were -0.51 and 1.72, respectively. Several studies presented similar results of the 6MWT decreasing significantly from baseline to discharge, then rising significantly from discharge to 12 weeks (Chen et al., 2018; de Oliveira et al., 2014; Opasich et al., 2001).

Before initiating the 6MWT, blood pressure (B/P), heart rate (HR), and dyspnea scores were obtained. Patients were then asked to walk back and forth at their own pace along a premeasured flat corridor for six minutes according to the American Thoracic Society (ATS) protocol, 2002, and the outcome was the distance walked in meters. The patients were given standardized instructions and set phrases of encouragement, such as "good," "keep it up," and "keep going." They could adjust their pace or stop if they displayed symptoms such as dyspnea, dizziness, angina, and muscle pain, and asked to resume when able (ATS statement, 2002; Butland et al., 1982; O'Keeffe, Lye, Donnellan, & Carmichael, 1998).

Phrases of encouragement (Guyatt et al., 1984), staff training, and learning effects have been reported to affect test results by having a positive treatment effect or an improvement in functional capacity (Butland et al., 1982; Guyatt et al., 1984). At the end of the test, the participants were seated, and HR, B/P, and dyspnea scores were recorded on the 6MWT data collection sheet (Appendix H). The goal was to increase the distance

in meters walked with each walking test performed. Twenty-five meters was considered a minimum clinically significant difference (Holland et al., 2010).

3.7.5 Quality of life.

3.7.5.1 Medical outcomes short form 36 (SF-36). The SF-36 was selected for this current study to measure the physiological and psychosocial functioning of health-related quality of life (HRQOL) with a high level of reliability, validity, and quality (McHorney, Ware, Rogers, Raczek, & Rachel, 1992; McHorney, Ware, Lu, & Sherbourne, 1992; Ware et al., 1993; Ware, Gandek, & IQOLA Group, 1994; Ware et al., 1998; Ware, 2003) (See Appendix I, SF-36 Questionnaire). The SF-36 is a widely used standardized generic assessment tool consisting of 36-items and measured on a Likert type scale. The scale was designed to measure eight distinct multi-item domains: Physical Functioning (PF) (6 items), Social Functioning (SF) (2 items), Role Limitations due to Physical Problems (RP) (4 items), Role Limitations due to Emotional Problems (RE) (3 items), Mental Health (MH) (5 items), Vitality (VT) (4 items), Bodily Pain (BP) (2 items), and General Health Perceptions (GH) (6 items) (Ware & Sherbourne, 1992). Response items range from 1-2, 1-3, 1-5, and 1-6 in each of the different domains. The initial responses were first recoded as per the scoring instructions. All items were scored so that the highest score represents the best health state (Ware & Sherbourne, 1992). Next, each item is scored on a range from 0 to 100, where poorer health=0, and better health status=100 (Ware & Sherbourne, 1992; Ware et al., 1995). For example, a low score reflects decreased functional level, and the presence of ischemic pain and a higher score reflects a perception of good health, no functional deficits, and absence of pain (Kapetanakis et al., 2008). A mean is calculated for items in each domain to create the eight subscales.

Missing data were not included in the calculation of the mean scores. Two-component summary scores: Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were derived from the eight domains. The PCS is made up of the domains of physical functioning, role limitation, bodily pain, and general health perceptions, and the MCS domains of vitality, social functioning, mental health, and role emotional. These scores were standardized to a mean of 50 and a standard deviation of 10 (Carli et al., 2002; Ware, Kosinski, & Keller, 1996). Canadian normative data were published in 2000 (Hopman et al., 2000). However, Optum Incorporated, the licensing organization for the SF-36 software (See Software License, Appendix J) License used for this study's data analysis included United States normative data and did not permit the use of the Canadian normative data (Optum, Inc.). A higher score indicates better health, while poorer health is indicated by a lower score. The SF-36 scale is highly reliable with an internal consistency and a Cronbach's alpha of 0.78 - 0.93 (Hays & Shapiro, 1992; Stewart, Sherbourne), and test-retest correlations with a range of 0.76 - 0.80 (Hays & Shapiro, 1992; Stewart, Sherbourne, Hays, & Shapiro, 1992, Ware, 1993).

3.7.6 Adherence.

3.7.6.1 Pill count. A pill count was chosen for this study to measure medication adherence because of its simplicity and objective nature. Medication adherence measures the degree to which patients take their prescribed medication and the rate (reported as a percentage) of medication taken over a specific time frame (Osterberg & Blaschke, 2005). A pill count was calculated by the number of pills taken (number of pills dispensed minus the number of pills counted at 12 weeks), and adherence was assessed to be consistent in both experimental and clinical trials (Lee et al., 2007).

At discharge, participants were asked to bring their pill container to each clinic visit to ensure that the person was taking the right medication and the right dose. All participants received a telephone call at 7 - 10 days post-discharge and a follow-up telephone call monthly to check on adherence to the medication and remind the participant to bring the pill container to the appointment. Study participants were not informed that adherence was being measured.

Table 2 outlines the validity and reliability of the primary and secondary outcome instruments. The ICFS subscales demonstrated a high internal consistency ($\alpha = 0.88$ to 0.90) and good stability (test-retest r range = 0.84 to 0.94) (Paddison et al., 2006). Zargar-Shoshtari et al., 2009 found the ICFS to be a valid and reliable measure of fatigue in 70 colon surgery patients. The ICFS scale has been used in other major surgical procedures to detect changes in POF over time (Kahokehr et al., 2012; Paddison et al., 2006). The ICFS scale assessed construct-specific factors using discriminate and convergent validity. Discriminate validity analysis distinguished all the subscales from depression and anxiety (Paddison et al., 2006) and convergent validity compared the ICFS subscales with two fatigue scales, Visual Analog Scale (VAS) and Profile of Mood States (POMS) and confirmed a strong relationship with the Fatigue Identity subscales (Paddison et al., 2006).

Table 2. *Overview of the Study Instruments*

Instrument Type	**Sample Instrument**	**Developer**	**Validity**				**Reliability**	
			Construct-related validation				Internal Consistency	Test-retest
			Convergent Validity	Comparative Instrument	Discriminant Validity	Comparative Instrument		
Questionnaire 5and 6 point Likert Scale	ICFS	Paddison et al., 2006	0.49-.076 0.49-0.92	VAS POMS	0.72	STAI	0.88-0.90	0.84-0.94
Questionnaire 5-point Likert Scale	FACT An	Cella, 1997	0.75 0.77	Piper Fatigue POMS	$p < 0.013$	Mean Hgb level	0.96	0.87
Questionnaire 6 point Likert Scale	SF-36	Ware & Sherbourne, 1992	0.54- 0.62	FIS	0.925	Subscales	0.78-0.93	0.76-0.80
Functional status	6MWT	Balke, 1963	0.50 0.62	DASI Physical function (SF-36)	0.68	METS	-	0.97

Note. ICFS = Identity Consequence Fatigue Scale; FACT-An = Functional Assessment of Cancer Therapy; SF-36 = Short Form 36; 6MWT = Six Minute Walk Test; VAS = Visual Analog Scale; POMS = Profile of Mood States; FIS = Fatigue Impact Scale; DASI = Duke Activity Status Index; METS = Metabolic equivalents; Spielberger's STAI; Internal Consistency = Cronbach's alpha; test-retest= Pearson correlation.

3.7.7 Blood Biomarkers (secondary outcomes).

3.7.7.1 Laboratory tests. Blood sampling is a medical procedure that removes samples of blood from a peripheral vein by a nurse or phlebotomist. The data on laboratory tests were gathered from the patients' medical/health records and recorded on the case report form (Appendix D). C-reactive protein is an acute-phase reactant that measures the extent of inflammation after surgery (Van Vranken, 2010). Serum ferritin, serum iron, total iron binding capacity (TIBC), and transferrin saturation assess an iron

deficiency. Reticulocytes are immature red blood cells, and a reticulocyte count measures erythropoietic response in the bone marrow.

Normal or abnormal results were assessed using the agency's standard reference range (see Table 3). Hgb level was measured and recorded in g/L. CRP is a serum inflammatory marker and recorded as mg/L. Serum iron was recorded as umol/L. TIBC was recorded as µmol/L. Transferrin saturation was recorded as a percentage. Reticulocyte count was also expressed as a percentage. Serum ferritin was reported as µg/L. Factors such as age, gender, health status, comorbidities, and medications could affect the reliability of blood results (Johnson-Wimbley & Graham, 2011). These biomarkers were chosen to assess the effect of oral iron supplementation at each time point.

Table 3. *Laboratory Reference Range*

Laboratory Test	**Reference Range**
Hemoglobin	120-160 g/L
Reticulocyte Count	0.56-1.52%
Total Iron Binding Capacity	44.75-80.55 µmol/L
Serum Iron	5.00-30.43 µmol/L
Transferrin Saturation	20-55%
Ferritin	22-322 µg/L
C -Reactive Protein	0.00-8.00 mg/L

Department of Pathology and Laboratory Medicine, Nova Scotia Health Authority, 2018

3.7.7.2 Complete blood count. Hematological indices include a complete blood cell count (CBC), which is a broad laboratory test that measures the number of cells (mainly the red blood cells (RBC), white blood cells (WBC), and platelets in the plasma. The components of the CBC include WBC, RBC, Hgb, hematocrit (Hct), mean 6corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), mean

corpuscular hemoglobin concentration (MCHC), red blood cell distribution width (RDW), and platelets which provide valuable diagnostic information for the assessment of anemia.

Iron deficiency can be diagnosed without a decrease in Hgb.

Additional clinical biomarkers used for diagnosing anemia and monitoring treatment response include reticulocyte count, ferritin, iron studies (serum iron, total iron-binding capacity, transferrin saturation (Johnson-Wimbley & Graham, 2011; Northrop-Clewes, & Thurnham, 2013). C-reactive protein is routinely measured to differentiate the type of anemia and a marker of acute or chronic inflammation (Iqbal et al., 2015; Johnson-Wimbley & Graham, 2011) (Table 2). These biomarkers were chosen for this current study. Additional diagnostic biomarkers (e.g., hepcidin and soluble transferrin receptor [sTr]), are useful in the diagnosis of an iron deficiency but have shortcomings (Dignass, Farrag & Stein, 2018).

Hepcidin is a hormone that is secreted into the blood by the liver and a key regulator of iron homeostasis (Johnson-Wimbley & Graham, 2011). Hepcidin, similar to ferritin, decreases in iron deficiency, allowing iron absorption and mobilizing iron stores, whereas hepcidin increases in response to inflammation and iron overload (Dignass, Farrag & Stein, 2018). Soluble transferrin receptor is another marker of assessing iron deficiency or iron overload but is a less reliable test in the presence of inflammation (Dignass, Farrag & Stein, 2018). The laboratory assays for these tests are not readily available in all laboratories, and there is a slow turn around for results (Dignass, Farrag & Stein, 2018). Hepcidin levels are more expensive than the routine laboratory testing for anemia. Hepcidin and sTr tests are not available at the study site laboratories. Yang et al.

(2008) examined plasma ferritin, sTr, and CRP in infants, children, and pregnant women and found that ferritin alone could effectively measure iron status, and in the presence of elevated ferritin due to inflammation, CRP could also be measured.

3.7.7.3 Hemoglobin. Hemoglobin (Hgb) is an essential protein that carries oxygen to the organ tissues. The degree of anemia is based on the Hgb concentration in the blood. A Hgb value less than the cut-off values of the WHO definition would be clinically significant. A Hgb value does not directly measure iron deficiency or differentiate the type of anemia. Further diagnostic testing is required to evaluate anemia.

3.7.7.4 Reticulocyte count. Reticulocytes are immature red blood cells, and a reticulocyte count measures how quickly the immature red blood cells are made in the bone marrow (Bruno, De Falco & Iolascon, 2015). A percentage of reticulocytes are calculated by an automated counter and helps determine the type and cause of anemia.

3.7.7.5 Serum ferritin. Serum ferritin is a protein that is synthesized by the body for iron storage. Ferritin is the most readily available protein and a useful index of iron deficiency. A ferritin value of less than 15 g/L is diagnostic of iron deficiency (Van Vranken, 2010). The ferritin level may be misleading in the presence of inflammation, infection, liver disease, and cancer, as ferritin is an acute-phase protein and can present as normal or elevated (Van Vranek, 2010). An elevated or normal ferritin level can still cause iron deficiency in the presence of inflammation (Johnson-Wimbley & Graham, 2011).

3.7.7.6 Serum iron. Serum iron measures the amount of circulating iron bound to the protein transferrin in the blood (Van Vranken, 2010). When serum iron is measured, the laboratories usually measure transferrin and TSAT (Van Vranken, 2010).

3.7.7.7 Total iron-binding capacity (transferrin). The measurement of transferrin indicates the potential capacity of transferrin to bind with serum iron. Serum iron and transferrin are usually measured to determine the type of anemia (Van Vranek, 2010).

3.7.7.8 Transferrin saturation (TSAT). Transferrin Saturation, a marker of iron availability, is calculated as a percentage to determine how much iron is being carried in the blood (Van Vranken, 2010). A normal range for TSAT is 20 percent to 50% (Bruno, De Falco & Iolascon, 2015). A TSAT of less than 16% is indicative of iron deficiency, whereas a TSAT greater than 50% is considered iron overload (Bruno et al., 2015).

3.7.7.9 C-reactive protein. C-reactive protein (CRP) is a plasma protein that increases in response to inflammation and increases in response within hours of tissue injury (such as surgery) or infection (Bruno et al., 2015). Serum CRP was used to measure the extent of inflammation after surgery (Johnson-Wimbley & Graham, 2011).

3.8 Sample Size

The sample size is the number of participants necessary to answer the research question and detect a clinically meaningful treatment effect (Noordzij, Dekker, Zoccali & Jager, 2011). Determination of a sample size takes into account resources, logistics, available data, and ethical considerations (Gupta, Attri, Singh, Kaur & Kaur, 2016). A sample size that is either too small or too large is unacceptable for clinical, methodological, and ethical reasons (Gupta et al., 2016).

In this study, the sample size was calculated based on a power analysis that contains four factors: population effect size (ES), significance level or alpha (α), power (1-β), and sample size (Gupta et al., 2016). The effect size is the estimate of the magnitude or the size of the difference between the two groups. The sample size was

calculated based on a known effect size of the primary outcome fatigue from previous studies (Vaucher et al., 2012; Verdon et al., 2003). A large treatment effect of (0.62) was chosen for the study to identify an observable and significant effect.

An alpha (α) indicates the level of significance and the probability that the null hypothesis is accepted when it is true (Zhong, 2009). A Type I error can occur if the null hypothesis is true but falsely rejected. The level of significance or alpha of (0.05) is a standard for most research studies (Gupta et al., 2016). A Type II error is related to the statistical power and occurs when you fail to reject a null hypothesis that is false (false negative) (Gupta et al., 2016). For example, when testing medication, and one accepts that the intervention medication had no effect on the outcome, but in reality, the medication actually did have an effect. The power (1-Type II error) can control the Type II error. The power of 0.8 or 80% chance of the effect to be statistically significant is a minimum standard in most clinical trials (Gupta et al., 2016).

A sample size of 100 participants was calculated to be sufficient to detect a 25% change in 12 weeks ICFS total scores with a large effect of (0.62), a power of 80%, and a two-tailed test with an alpha of (0.05). The calculation was based on a planned non-parametric statistical analysis using the Mann-Whitney *U* test *(*Mann & Whitney, 1947*)* for two independent samples. The primary outcome measure was the ICFS, which uses a Likert scale for responses and yields ordinal data. A non-parametric test was used because the intervals of the scale were unequal, and there was a non-normal distribution of the fatigue levels. The power calculation for the RCT study is illustrated in Table 4.

Table 4. *Sample Size Calculations for the Study*

	Change in Fatigue Experience Scores		
Power (1-beta) x 100	15% Δ = 7.0 (46.9 to 39.9)	20% Δ = 9.4 (46.9 to 37.5)	25% Δ = 11.7 (46.9 to 35.2)
Effect size	0.37	0.49	0.62
80%	135	76	50
90%	181	101	66
95%	223	125	81

In addition to the initial sample size calculation, the nature of the study intervention had to be taken into account. According to available medication adherence literature, 20–50% of patients who start taking oral iron therapy (Ferrous Gluconate, Ferrous Sulphate, and Ferrous Fumarate) are nonadherent due to GI effects (Arcangelo & Peterson, 2006, Tolkien, Stecher, Mander, Pereira & Powell, 2015). A newer oral iron preparation, polysaccharide complex FeraMAX®, is a coated formulation that passes through the stomach to the duodenum without any contact with the stomach lining (FeraMAX.com, 2019). This formulation minimizes GI side effects (nausea, vomiting, diarrhea, and constipation), and it has demonstrated better adherence. Also, it contains more elemental iron than other oral iron supplements (FeraMax.com, 2019).

An oversampling of 30% was included to compensate for attrition, potential non-adherence, and missing data. This estimate increased the overall sample enrollment to 130 participants, with 65 participants randomly assigned to each arm of the study (intervention and control). This number would be considered the ultimate sample.

The sampling strategy was to recruit a representative sample of participants. The age range (> 19 years) of the participants was selected because this range represented the incidence of CAD. Only 10% of the sample were women with five in each group. This percentage is a low representation of women who now comprise approximately 30% of

the population undergoing CABG surgery (Hillis et al., 2011; Zimmerman, 2011; Zimmerman et al., 2007). Also, reports indicate that preoperative fatigue increases the risk of POF, and CAD patients tend to experience fatigue related to their disease. For this study, the mean change in fatigue levels was measured at all four-time points.

3.9 Maintaining Rigour

Rigour was assessed for this current study by a variety of design features. The Consolidated Standards for Reporting of Trials (CONSORT) statement provides a reporting structure for completing RCTs and clarity and rigour (Schulz, Altman & Moher, 2010). Participants were randomly selected to either the intervention or control group. This process ensured that the participants were equivalent between groups at randomization. Intention to treat (ITT) approach (Fisher et al., 1990; Gupta, 2011) was conducted on all participants who were randomized to the study. The ITT approach included all randomized study participants according to their randomized treatment allocation and emphasized in the CONSORT guidelines (Gupta, 2011). This approach was used to maintain the integrity of the study and decrease the risk of bias due to nonadherence with the study drug, withdrawal, and dropouts. Dropouts or participants lost to follow-up could reduce the statistical power and provide questionable results (Polit & Gillespie, 2010; Wilder & Barrett, 2005). Strategies for retention of participants during the study included telephone follow up and clinic visits at different time points. Also, to help evaluate scientific rigour for this study, an appropriate selection of valid and reliable outcomes measures, which are discussed later in the chapter, was performed based on the research questions.

3.10 Data Collection Procedure

The study commenced in December 2014, and the first participant consented and was enrolled in July 2015 due to recruiting challenges. Each participant was monitored for 12 weeks post-discharge from the hospital. Data collection was completed in February 2018. Table 4 displays the assessments performed at each time point.

Table 5. *Scheduled Time points (TP) and Assessments of the study*

Assessments	**TP 1**	**TP 2**	**7 to 14 days post-discharge**	**TP 3**	**TP 4**
Consent	X	X[2]			
Inclusion Criteria	X	X[2]			
Exclusion Criteria		X			
Study Enrollment	X				
Randomization		X			
ICFS	X	X		X	X
SF-36	X	X		X	X
FACT-An	X	X		X	X
6MWT	X	X		X	X
Laboratory Tests	X[1]	X[1]		X[1]	X[1]
Medication Dispensed		X			
Collecting and reviewing the list of study drug side effects					X
Follow up telephone calls			X		
Medication and side effects reminders					
SAE collection			X		X

Note. [1] Standard of Care, [2] Confirmation of Continued Eligibility, TP 1 = Preoperative Baseline time point, TP 2 = Postoperative Discharge/Randomization, TP 3 = Six Week Follow-up, TP 4 = Study End 12 Weeks +/-1 week, SAE = Serious Adverse Event

Data were collected at four time points: (time point 1 baseline), the participant was first screened in the preadmission clinic or on the inpatient unit and recruited for the study (five to thirty days). Patients were invited to participate in the research study. The informed consent process occurred at time point 1. At this time point, the patient was briefly interviewed (approximately 15 min) to discuss the study. This visit allowed the patient the opportunity to meet the investigator, to ask questions, and verify their

understanding of the study. Once informed consent was obtained, demographic data and clinically relevant data (See case report form, Appendix D) were abstracted. Blood samples for standard laboratory tests were collected before surgery. Time point 2 (Randomization) occurred at hospital discharge when the patient was randomized to the intervention or control group, and treatment of FeraMAX® or placebo commenced. The third time point was at six weeks, and the fourth time point was at the end of the study treatment, which was 12 weeks post-discharge (verification of ongoing consent at each time point). At each time point, participants were asked if they were willing to continue participation in the study. Table 6 illustrates the data collection procedure at each time point.

Table 6. *Outcome Data for Each Study Time Point*

	Time point 1 Baseline	**Time point 2 Discharge/ Randomization**	**Time point 3 6 Weeks Post-discharge**	**Time point 4 12 Weeks Post Discharge**
Interventions		FeraMAX® or Placebo		
Primary Outcome Fatigue Level	ICFS	ICFS	ICFS	ICFS
Secondary Outcomes				
Quality of Life	SF-36	SF-36	SF-36	SF-36
Anemia/Fatigue	FACT-AN	FACT-AN	FACT-AN	FACT-AN
Hgb, Iron Status, and Inflammation	Laboratory tests	Laboratory Tests	Laboratory tests	Laboratory tests
Functional Capacity	6MWT	6MWT	6MWT	6MWT
Adherence				Pill Count

Note. ICFS= Identity Consequences, FACT-An= Functional Assessment of Cancer Therapy-Anemia, SF-36= Short Form 36, 6MWT= Six-Minute Walk Test, Hgb = Hemoglobin.

3.10.1 Time point 1 (Baseline) Recruitment and Screening. After ethics approval, participants were recruited and screened from the preadmission clinic and inpatient cardiology units at the study site. Recruitment flyers (Appendix K) were posted in the Preadmission Clinic, Cardiovascular Surgery Clinic, and inpatient units to aid in the recruitment of patients.

The cohort of patients scheduled for an isolated CABG surgery was drawn from the preadmission clinic and inpatient nursing units. The Department of Cardiovascular Surgery (seven cardiac surgeons) helped facilitate the recruitment of participants by providing the participants with a summary of the research study. A Waiver of Remote Access for Screening was approved by REB, allowing earlier screening of patient's charts.

According to the Personal Health Information Act (PHIA) 2010 requirements, researchers require a member of the patient's circle of care to approach patients to obtain consent allowing the researcher to contact patients for study consent and to use their personal information (PHIA, 2010). In the preadmission clinic, a member of the circle of care (e.g., preadmission nurse, clinic clerk) approached potential patients to see if they were interested in research. On the inpatient units, a member of the patient's circle of care speaks to patients about the release of patient health information for research purposes. Patients are informed that disclosure of name and contact information could be provided to a researcher if they agree and are willing to sign a PHIA consent form (PHIA, 2010). The circle of care refers to members of a health care team that requires information to provide direct care to an individual (Canadian Medical Protective

Association, 2018). The investigator reviewed the daily preadmission patient list and all CABG patients' health records to determine if the patient met the study criteria.

Every Tuesday, a cardiac catheterization conference is held consisting of representation from cardiology and cardiac surgery to discuss all cardiac catheterization procedures performed the previous week. The group debates whether medical management (e.g., percutaneous cardiac intervention (PCI)) or cardiac revascularization (i.e., CABG surgery) is the best treatment for each patient. For study purposes, every week, a list of all patients that required surgery was sent to the Department of Cardiovascular Surgery and the investigator. The inpatients were assessed by a cardiovascular surgeon and accepted as an inpatient for surgery. If participants met the inclusion criteria for the study, they were approached to participate. The consent process included an explanation of all information regarding the study, risks, and benefits of participation to the prospective participants. The consent form (Appendix C) was completed and signed once all questions were answered, and individuals expressed that they felt fully informed.

Baseline demographic data (sex, age, marital status, residence, and employment status) and clinically relevant data (dyslipidemia, smoking history, diabetes, congestive heart failure, prior myocardial infarction, LVEF, hypertension, renal disease, and previous cardiac surgery) were abstracted through review of the patient health record. Data related to a physical assessment from the preadmission clinic visit were also retrieved from the patient health record. Samples for standard laboratory tests (including Hgb level, reticulocyte count, ferritin, serum iron, total iron binding capacity (TIBC), transferrin saturation, and plasma CRP levels) were drawn in the preadmission clinic or

on the inpatient unit and included in the baseline data. These data were used to make comparisons during the analysis.

Each participant was asked to complete three (3) questionnaires: ICFS (Paddison et al., 2006); SF-36 (Ware and Sherbourne, 1992); and FACT-An (Cella, 1997) as part of baseline data. Functional capacity was assessed using the physical function subscale of the SF-36 and 6MWT (Balke, 1963). The 6MWT assessed walking endurance by having each participant walk up and down a premeasured hallway for six minutes. The investigator recorded the distance in meters walked by each participant. Dyspnea was recorded, but the data were not included in the final analysis as it was not an outcome. The preadmission visit occurred approximately two weeks before scheduled CABG surgery.

3.10.2 Time point 2 (Discharge/ Randomization). Participants confirmed continued participation in the study. Participants who met discharge criteria (no signs of wound infection, stable cardiac rhythm, adequate oral intake, regular bowel function, and independent [or with usual preoperative supportive aids] ambulation), and met study criteria were randomly assigned to one of two research groups on discharge day. The participants were assigned to either a control group (placebo) or an intervention group (oral iron FeraMAX® 150mg elemental iron daily) depending on the randomization sequence. The medication was provided free of charge from the pharmaceutical company BioSyent Inc. to an outside compounding pharmacy, which prepared the placebo identical to FeraMAX® capsule (Conflict of Interest, Appendix L). The prepared product was sent to the study site Pharmacy Department.

A preprinted research prescription was completed and faxed to the study site pharmacy. The pharmacist assigned pre-packed bottles according to a pre-determined randomization schedule. The pharmacy technician then dispensed the drug to the investigator, which was, in turn, given to the participant. The study drug was dispensed in bottles (84 capsules) at discharge. The assigned Study ID number and randomization group were maintained for the duration of the study by the pharmacy. The investigator recorded the group allocation, the date, and unique ID number on the electronic study log.

Participants were instructed to take one capsule daily with 8 ounces of water, from discharge day one until day 84. Participants were also told not to take any other oral natural health products indicated for fatigue during the trial to eliminate effects that could be attributed to the natural health products. The investigator provided oral and written instructions to the participants. (See Instruction sheet for Study Drug, Appendix M) on how and when to take medication, the importance of signs and symptoms (e.g., nausea, vomiting, diarrhea, constipation, and epigastric pain)and what to do if they occurred, and the importance of adherence to the medication. Participants were given a medication side effects list (See Appendix N) for recording a physical assessment of adverse effects related to the drug while at home. Before discharge, participants also had blood work drawn (standard of care), completed the ICFS, FACT-An, SF-36 questionnaires, and the 6MWT.

Participants started their treatment regimen day one post-discharge and continued taking the medication daily for 12 weeks. Instructions were given to the participant to put the side effects list in an opaque envelope labeled with instructions and return them at the

study end visit. Seven to fourteen days following discharge, a telephone call was made to review side effects and to enhance the accuracy of recording symptoms. A follow-up telephone call was made monthly until the end of their participation for both groups.

3.10.3 Blinding. In the study, a double-blind approach was used. That is, both the research team and the study participants were "blind" or did not know which treatment group the study participants were assigned. The research team was unaware of the specific treatment allocated to any individual participant. The research pharmacy technician received a randomized list from the statistician, and the list was kept concealed except under instructions from the investigator. If a physician required a patient to be unblinded, the investigator would contact the Pharmacy Department at the study site, and the Pharmacy Department would unblind the patient according to standard operating procedure.

An outside pharmaceutical vendor compounded the placebo medication and put both the iron supplement and placebo into capsules that were identical in appearance, volume, weight, smell, and taste. The drug capsules were sent to the pharmacy department for packaging. The hospital pharmacy technician prepared sequential participant study medication bottles s, which were kept in the Pharmacy Department at the study site for use as participants were randomized. The bottles were prepared in a 12-week supply with only corresponding Study ID numbers and randomization numbers.

All research team members were blinded to the study groups, but blinding of the participants could not be assured because of the potential side effects of oral iron supplementation. Participants could potentially differentiate the iron capsule from the placebo by experiencing GI effects and observing changes in stool color. Participants

were given a list of study drug side effects at discharge and instructed to check the appropriate box of side effects daily or record any observations on the list (see Appendix N). The lists of study drug side effects were returned to the investigator at the end of the study.

3.10.4 Time point 3 (Six weeks). The informed consent process continued by asking participants a willingness to continue participation in the study. At six weeks, participants completed the same questionnaires (ICFS, FACT-An, SF-36), Six Minute Walk Test (6MWT), and had blood samples drawn. A list of study drug side effects was reviewed with study participants either over the telephone or at a clinic visit whereby yes or no responses were recorded.

3.10.5 Time point 4 (12 weeks) Post-testing. The informed consent process continued to the end of the study. Each participant completed the study after taking 12 weeks of medication or placebo. The investigator administered the same questionnaires (ICFS, FACT-An, SF-36), 6MWT, drew blood samples, collected a list of study drug side effects, and conducted a pill count. The questionnaires were completed with participants either over the telephone or during a clinic visit. If participants were unable to return for the 12-week clinic visit, they were instructed to have blood work and mail the questionnaires, a list of study drug side effects, and a pill bottle to the investigator.

3.11 Data Analysis

Data analysis for this study was generated using SAS STAT 14.3 software, Version 9.4 (SAS Institute Inc., Cary, NC, USA). SAS Statistics® is a software program that is widely used for performing quantitative statistical analysis in social sciences, including health research. Data were retrieved from the case report form, questionnaires,

laboratory tests, and observations. The ITT approach was used to analyze the results. That is, all randomized participants in the groups to which they were randomly assigned, were included in the analysis regardless of whether they received or adhered to the allocated intervention (Gupta, 2011; McCoy, 2017).

Data were checked and cleaned by the investigator, including checks for out of range values, and corrections were made when appropriate. Data from self-reported questionnaires were recoded before the analysis. Descriptive analysis was performed to examine all participants' demographic characteristics and clinical data. Missing or random data and outliers were examined using frequencies and percentages for each variable. Continuous data were examined by the mean and standard deviation (SD) or median and interquartile range (IQR), where appropriate frequencies and percentages were used for categorical data. Data distribution was examined for normality, homoscedasticity, and linearity using histograms and Q-Q plots. Most of the study variables were normally distributed. Demographic baseline data and clinical variables of the intervention and control groups were compared using student t-test or Wilcoxon rank-sum test for continuous variables, and Chi-square or Fischer exact test was used for proportional differences.

The current study was designed to investigate changes in participant's fatigue levels, which was measured over time. A Linear Mixed models approach was used to model each study outcome to predict the relationship between the variables over time. Linear Mixed models used the Gaussian or normally distributed assumption. Unstructured correlation was used to fit the repeated measurements made over time on the same participant on the categorical variables. The interaction for time and study group

was tested in each model but was excluded when non-significant to produce a more parsimonious model. The variables, LVEF, class, smoking history, and CHF were included in the models as significantly different between the two study groups upon looking at baseline variables. Categorical variables for smoking history and LVEF class were condensed to the following: non-smoker and former or current smoker, and EF < 39%, EF 40 ≤ 55%, and EF 55≤ 70%, respectively.

The PROC MIXED procedure of the SAS statistical program was used to fit the Linear Mixed model to the continuous dependent variables (ICFS, FACT-An, SF-36, and 6MWT) of the longitudinal dataset. There are several advantages to using the Linear Mixed model over repeated measures Analysis of Variance (RM ANOVA) as the analysis allows for missing data at a single time point (Little & Rubin, 2002). The model also allows for time-varying covariates, whereas the RM ANOVA does not.

The primary outcome of fatigue trajectory over time was analyzed using a two-level Linear Mixed model (Cnaan, Laird & Slasor, 1997; Laird & Ware, 1982; Verbeke & Molenberghs, 2000). Repeated measures are located on level one, and the study groups are located on level two. The Linear Mixed model looked at the study group (invention and control) and time as independent variables, and ICFS total score as the dependent variable for all time points: baseline to 12 weeks. The ICFS subscales, Impact on Concentration and Impact on Daily Activities, and the ICFS Impact summary variables were modeled using generalized linear mixed models with a Gamma Distribution and an unstructured covariance. The interaction for time and study group was tested in each model but excluded when non-significant to produce a more parsimonious model.

The modeling of the secondary outcomes compared the two study groups among Time point 2 (discharge), Time point 3 (six weeks), and Time point 4 (12 weeks) for FACT-An and 6MWT. The research questions examined the effect of the intervention on outcomes which commenced at Time point 2 (discharge). Time point 1, the baseline, was included in the analysis for SF-36 and Hgb levels. The Linear Mixed model was used for these outcomes and accounted for covariates smoking history, LVEF, and CHF. Fixed effects modelling was used to fit the model parameters, and each study group means there is a group-specific fixed quantity. Parameter estimates reported were the least square means estimated from the Linear Mixed models.

Wilcoxon Rank Sums test was performed to compare the median adherence to medication between the two study groups. There was a limited outcome response for non-adherence; therefore, there was not enough power to perform multivariate analysis.

Dichotomous outcome variables (side effects of the study medication) were collapsed into three categories of upper gastrointestinal (GI) (nausea, vomiting, and heartburn); lower GI (abdominal pain, diarrhea, and constipation); and no reported side effects for further analysis and hypothesis testing were conducted for each variable in the model. The multivariate analysis was not performed due to too few side effects reported. Logistic regression was used in the study to assess the odds ratio of both upper and lower GI events.

3.11.1 Assumptions. The Linear Mixed model must meet the assumptions for linearity, homogeneity of variance, normality, and independence. The assumption of linearity is that the data follow a straight line, and the model residuals are plotted against the predictor variable to check for the best fit. Residuals are plotted in order to assess for

any trend which could indicate patterns or correlation. Homogeneity of variance assumes that the variance of residuals is equal across groups. The residuals are plotted against the fitted values to check for error variance. The Linear Mixed model assumes the residuals of the model are normally distributed, and the QQ plots were used to test this assumption. A random sample was chosen from the population. The dependent variables were normally distributed in the population.

3.11.2 Handling of missing data. Missing data are common in clinical trials, mainly longitudinal studies from self-reported questionnaires (Eekhout et al., 2014) (deVet, Terwee, Mokkink & Knol, 2011), such as the ICFS (Paddison et al., 2006). Missing data can range from skipped single items, scale scores, to complete questionnaires, and can reduce statistical power resulting in biased estimates thereby causing invalid results (Kang, 2013). In this longitudinal study, attrition and non-response on the self-reported questionnaires resulted in missing data. The missing data are missing at random (MAR). The mechanism of MAR is the probability of a value being missing is related to other observed variables such as patient characteristics or treatment allocation (Eekhout et al., 2014). Linear mixed models are commonly used for the analysis of repeated measures providing unbiased estimates by only analyzing the observed data. Therefore, imputation of the missing data is not required (Biering, Hjollund & Frydenberg, 2015). The Linear Mixed model is a preferred method and was chosen to analyze the missing repeated measures of outcome data in this study.

Various techniques are available to handle missing data in an item and total scores but have no advantages over Linear Mixed models. A standard method, complete case analysis, works under the assumption that the data are missing completely at random

(MCAR) (Eekhout et al., 2014). This analysis decreases sample size and therefore reduces power (Eekhout et al., 2014). Listwise deletion is a simple method of addressing missing data but removes all cases with even a single piece of data missing. This method will reduce the sample size and power. Mean imputation is a method by which a mean score of the non-missing data is imputed for the missing score (Eekhout et al., 2014). This method preserves the sample size but reduces the variability in the data (Eekhout et al., 2014). Multiple Imputation is an advanced method that replaces the missing items with a set of different plausible imputed values (Eekhout et al., 2014). Missing data from repeated outcome measures results in unbalanced data and can be handled properly with multiple imputations but may not lead to improved inference; however, Linear Mixed model deals with the imbalance (Biering et al., 2015).

3.12 Threat to Validity

In the study, design, data collection, and analysis incorporated several approaches to prevent threats to validity. These approaches comprised internal validity, external validity, and reliability. Steps were taken to improve validity and minimize bias throughout the study. The study design was a two-arm parallel experimental design that included random assignment of the participants to the different groups being compared, blinding of the investigator and participants, and the addition of a control group. The random assignment was illustrated by the CONSORT flow diagram described earlier in this chapter and illustrated in the next chapter. Also, prior research demonstrates the reliability and validity of the instruments employed in the study to be adequate.

3.12.1 Internal validity. Internal validity is described as the quality of the study and whether the results are from the effect of the intervention and not due to chance or

another factor (Spieth et al., 2016). The study design was used to answer research questions and address threats to internal validity. The RCT attributed a cause and effect relationship to the intervention instead of by chance. The experimental design allowed each participant an equal chance of being assigned to each group, minimizing a threat to validity (Bickman & Reich, 2015; Spieth, 2016). The main threat to internal validity was a systematic bias in selection and participant assignment (Bickman & Reich, 2015; Spieth, 2016). Approaches to control for systematic bias included a randomization scheme generated by the statistician, and the randomization list was kept by a pharmacy that ensured concealment.

3.13 Sources of bias

To ensure the accuracy of the result outcomes, the design of this study was to assure equipoise; that is, the participants were randomly assigned to the treatment or control group and decreased selection and treatment bias. This placebo-controlled study achieved equipoise as there is no standard of care for the treatment of POF, and participants could benefit from the treatment with minimal risk.

Double blinding (preventing the investigator and the participant from knowing the group assignment) was performed to avoid performance bias. An external pharmacy produced a placebo similar to the study drug in efforts to reduce bias. Detection bias was reduced by the investigator being blinded. Stratification and block randomization was performed apriori to prevent a balance of cofounders in the groups.

Individuals with CAD requiring CABG surgery were chosen as the target population for the study. A representative sample of hospitalized patients who had elective CABG surgery was selected as representative of the target population, which

could minimize selection bias. Volunteer bias is present when individuals enroll in an intervention or placebo study as they generally experience positive outcomes by participating. This bias can be referred to as the Hawthorne effect (McCambridge, Witton & Elbourne, 2014). A random sampling of the target population was conducted to prevent volunteer bias.

Attrition is common in RCTs, especially longitudinal studies due to protocol violations or participant withdrawals. Participants in this longitudinal study who dropped out before study completion did so due to the effects of the medication, symptoms resolved, or a change in health. Attrition bias was avoided by using the intention to treat (ITT) approach in this study to prevent differences in the groups due to attrition. The group assignments remained equal, even with participant dropout. All randomized participants were included in the final analysis in the groups they were allocated to. Participants were excluded from the study if they did not meet entry criteria before randomization or were randomized and did not take any of the medication. Also, participants were excluded from the final analysis for protocol violations, including increased frequency of study medication during the trial. Data collected from questionnaires contained missing data. Missing data can decrease the statistical power, cause bias in the estimates of the parameters, and reduce the representativeness of the sample (Kang, 2013).

3.13.1 External validity. Threats to external validity occur when investigators make incorrect inferences of the results, and there are issues with the accuracy of the findings. Random selection techniques can minimize threats to external validity, allowing results to be generalized to the population of the sample studied. Participants were chosen

for the study by chance, and each person in the target population had equal opportunity to be included in the sample. Random selection improves external validity, and the results can be translated into research evidence. The sample may not be representative of the population having CABG due to sample size.

3.13.2 Reliability. The instruments used in the study provided both consistent and accurate measurements. The investigator collected all measurements at each time point to prevent measurement error.

3.14 Conclusion

This chapter outlined the study methodology and methods, sampling, inclusion/exclusion criteria, consent process, outcomes examined, rigor, and data collection. The full-scale study was a double-blind controlled trial that examined the relationship between fatigue, QOL, exercise capacity, and anemia using an oral iron supplement and placebo. A combination of self-rating instruments and objective measures were used to gather data on 104 primary CABG patients. Data were collected at baseline, discharge, at six weeks, and following completion of the intervention therapy. The primary study endpoint was a comparison of fatigue scores between the two study groups measured at six weeks and 12 weeks. Secondary study endpoints included QOL, anemia, functional capacity, side effects of iron, adherence, and Hgb (see Table 2). The primary safety endpoints comprised medication adherence and adverse events. Data were analyzed using descriptive, parametric, and non-parametric statistical methods.

The next chapter will discuss the results of the trial in relation to each corresponding question. The similarities and differences in participants at discharge and

12 weeks postoperatively for fatigue levels, functional capacity, QOL, anemia, and adherence are reported.

CHAPTER 4 RESULTS

This chapter is divided into three sections that describe the sample and the results of the data analysis, according to the research questions. The first section describes the total sample and compares the participants randomly allocated to both treatment arms. The socio-demographic and clinical characteristics are described in detail, and the baseline scores obtained using the study instruments are presented. The Consort flow diagram illustrates the progress of the participants throughout the RCT. The second section presents the results for the primary outcome variable for participants based on the ITT approach. Data were analyzed for the effect of oral iron on fatigue as measured by changes to the ICFS scores between discharge and twelve weeks. Section three presents the results of analyses for the secondary outcomes.

4.1 Setting

The study took place at a large, regional referral site for cardiac surgery; this is affiliated with a university medical school in Atlantic Canada.

4.2 Description of the Sample

The study sample was drawn from a population of patients referred for elective CABG surgery, which was performed at the site. Participants who were enrolled in the study were randomly allocated to either a placebo arm or a treatment arm for the study. Six hundred and eleven patients were screened for eligibility, in either the pre-admission clinic or on the inpatient unit.

Of the 611 eligible patients, 491 participants (49%) were excluded because they did not meet the study inclusion criteria; if they met inclusion criteria but declined to participate (46%), or for other reasons (5%). Other reasons for exclusion involved 23

participants who were either: enrolled in another study, received medical treatment instead of surgery, or had CABG surgery performed at another site. Of the participants screened, 121 (20%) agreed to participate (see Figure 2).

One hundred and twenty-one eligible participants were provided with information about the study, agreed that they had been fully informed of the risks and benefits, and consented in writing (See Informed Consent form, Appendix C) to participate (Manti & Licari, 2018; Nijhawan et al., 2013). The participants completed baseline assessments. Enrolment of participants took place between July 2015 and February 2018 (30 months). Of these participants, n = 121 initial, 12 were not randomized at discharge because they either withdrew consent or subsequently did not meet eligibility criteria. Of the participants that did not meet inclusion criteria following enrolment, two had a Hgb > 120 g/L at discharge, one was started on oral iron supplements postoperatively before discharge, and nine individuals decided to withdraw consent before randomization. One hundred and nine (109) participants were subsequently randomized at hospital discharge, which was slightly larger than the targeted sample size of 100 participants. This additional enrolment compensated for anticipated "lost to followup" and patient withdrawal. Five participants withdrew consent the day after discharge and returned all of their study medication and were removed from the final data analysis. According to the ITT criteria, participants can be excluded from the study analysis if individuals do not meet inclusion/exclusion criteria or do not take any of the study medication (Gupta, 2011).

Of the 104 participants included in the final analysis, 54 participants were randomized to the intervention group, and 50 were randomized to the control (placebo)

group. There was an additional loss of participants after randomization. Across both study groups, twenty-nine participants (15 participants in the control group and 14 participants in the intervention group) withdrew consent to participate over the course of the study. Twenty-six percent attrition occurred in the intervention group, and 30% attrition occurred in the control group. Reasons for withdrawal included reported side effects that participants attributed to the study medication or premature discontinuation of the study medication. Five persons were withdrawn for protocol violations, and seven participants were "lost to follow-up" (five voicemail messages were left, but telephone calls were not returned). This number of participants (41) represents a dropout rate of 39% of the sample.

Sixty participants returned completed questionnaires for at least one-time point following randomization. Five participants did not answer questionnaires but completed bloodwork at least one-time point following randomization. Data from questionnaires and blood work were collected from all four-time points. Randomization or time point two was considered a baseline for analysis because that is when the participants started the drug. The study was stopped due to time constraints and on advice from the thesis committee and program advisor to meet program deadlines.

The first patient was enrolled on July 25, 2015, and the last patient appointment for follow up was on Feb 21, 2018. The final analysis was conducted on 104 participants, applying ITT criteria. All patients randomly assigned to intervention or control groups received the treatment that they were assigned. A diagram representing the trial layout by the CONSORT statement (Schulz, Altman & Moher, CONSORT Group, 2010) is presented in Figure 2 in the results chapter.

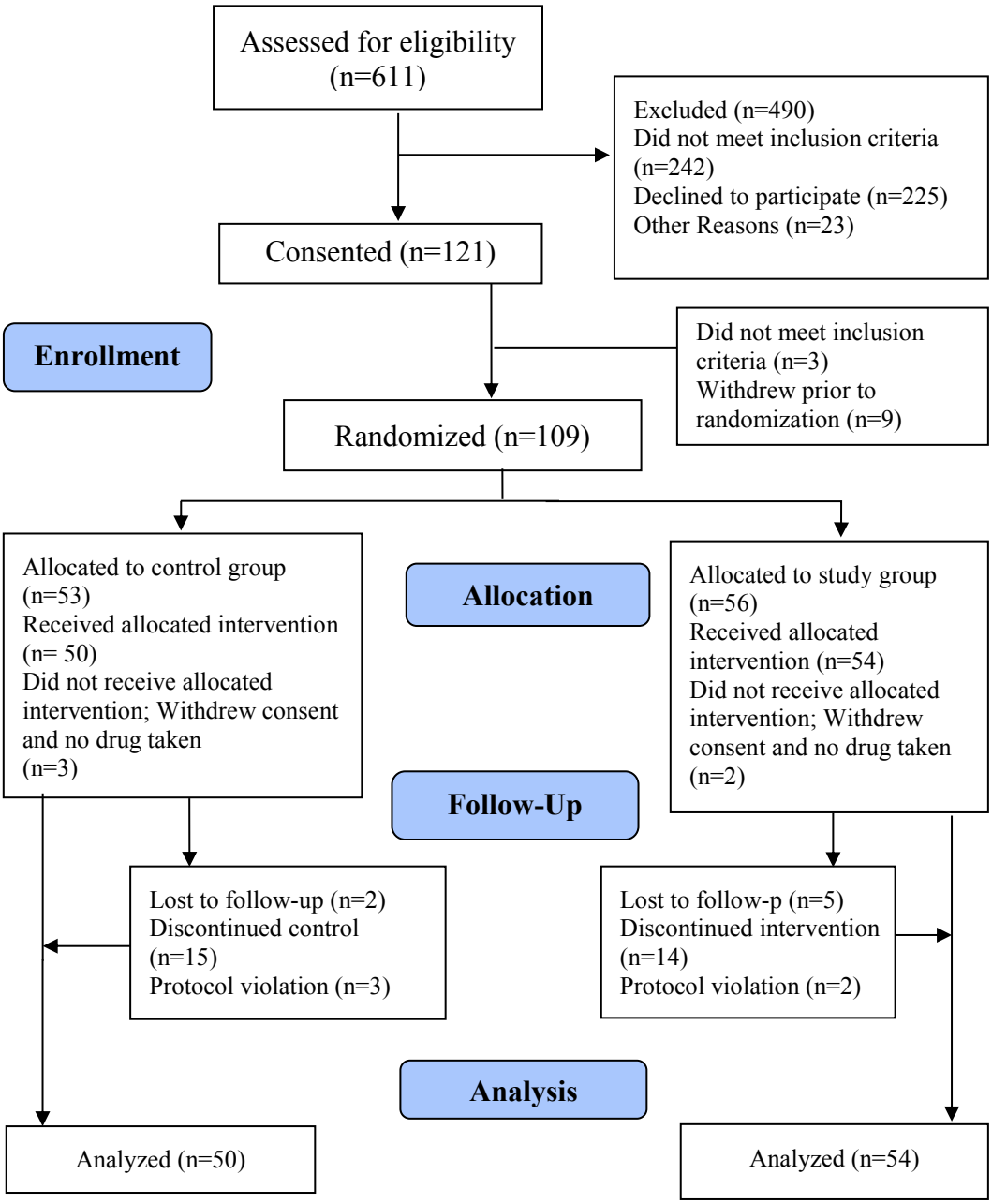

Figure 2
CONSORT 2010 Flow process of the phases of the study, the Consolidated Standards for Reporting of Trials (CONSORT) statement (Schultz, Altman & Moher, 2010).

4.3 Descriptive analysis

Descriptive analysis was applied to examine and summarize data reflecting the

characteristics of the study sample as a whole, and between the intervention and control groups. Simple frequencies and measures of central tendency and dispersion are presented as mean and standard deviation, median (minimum and maximum), frequencies, and proportions (percentages). Baseline characteristics were compared by group using an Independent t-test and Chi-square analyses or Fisher exact test when appropriate (see Table 5 and 6). Data were examined for outliers, missing, and skewed data. Outliers and unusual values were checked against the raw data for data entry or coding errors. Corrections to the raw data were made for any detected errors. Linear mixed models were used to account for incomplete and missing outcome data. The criteria for the significance of results was set at $p < 0.05$ for the t-test analysis.

4.3.1 Baseline socio-demographic and clinical characteristics.

***4.3.1.1 Socio-demographic characteristics*.** The baseline socio-demographic characteristics of the sample are presented in Table 6. These include sex, age, height, weight, body mass index (BMI), marital status, place of residence, and employment status. There was a significant sex imbalance in the study sample (94 men). Each group had five women. More males than females are assessed as needing CABG surgery and referred for surgery (Wenger, 2012). The sample was predominantly male (90%), and the mean age of participants was 65 (SD = 8.84) years. Age ranged from 35 to 79 years, and mean body mass index (BMI) was 30.0 (SD = 5.36) kg/m^2. Seventy-six (73%) participants were married, nine (9%) were in a committed relationship, three (3%) were widowed, six (6%) were divorced, and ten (10%) were single. Fifty-one (49%) participants were employed; 51 (49%) were retired, and two (2%) were unemployed.

Ninety-nine (95%) participants resided in the province where the site was located, and 30% lived in the municipality, while 65% lived in a rural area. Five percent of participants lived outside the province but within the referral catchment area. The study groups (intervention and control) were compared for group differences on categorical variables using the Chi-square statistic and Fisher Exact test where appropriate. An independent t-test was used to compare means for continuous variables. Randomization produced a balanced sample for each arm of the study. There were no significant differences between groups for socio-demographic variables (Table 7).

Table 7. *Socio-Demographics Characteristics of Study Participants by Group*

Variable	**Control Group (n=50)**	**Intervention Group (n=54)**	***p*-value**
Sex, n (%)			0.90
Males	45 (90%)	49 (91%)	
Females	5 (10%)	5 (9%)	
Age (Yrs.) median (min, max)	64.5 (35, 83)	66.0 (40, 82)	
BMI, median (min, max)	29.0 (21.7, 46.7)	28.8 (20, 48)	
Marital Status, n (%)			0.40
Single	4 (8%)	6 (11%)	
Divorced	4 (8%)	2 (4%)	
In a Commited Relationship	4 (8%)	5 (9%)	
Married	38 (76%)	38 (70%)	
Widowed	0 (0%)	3 (6%)	
Employment Status, n (%)			0.39
Employed	25 (50%)	26 (48%)	
Unemployed	0 (0%)	2 (4%)	
Retired	25 (50%)	26 (48%)	
Residence, n (%)			0.37
Rural	35 (70%)	33 (61%)	
Urban	14 (28%)	17 (31%)	
Outside Province	1 (2%)	4 (7%)	

Note. BMI= body mass index, *p values < 0.05 are significant between groups

4.3.1.2 Clinical characteristics. Table 8 illustrates the data analyses of clinical characteristics. Study group differences were compared on 37 categorical variables using the Chi-square test or Fisher exact test and two continuous variables using the independent t-test. In this study, participants presented with a diagnosis of CAD requiring elective coronary revascularization. The majority of patients (52%) had a three-vessel CABG procedure. The average length of postoperative stay was 7.83 (SD = 3.7) days. The clinical variables included congestive heart failure (CHF); cardiac valve disease; MI; arrhythmia; musculoskeletal disease; hypertension; diabetes mellitus; hyperlipidemia; kidney disease; respiratory disease; gastric reflux (GERD); history of alcohol use; other comorbidities previous surgery; transfusion of red blood cell components; CABG procedure; American Association of Anesthetists (ASA) class of surgical risk; smoking history and LVEF. Categorical variables for smoking class and LVEF class were condensed, as illustrated in Table 8.

At baseline, the majority of participants (outpatient and inpatient) (41%) had angina - causing restricted activity, and they were unable to complete the 6MWT preoperatively. The average LVEF was 66%, ranging from 55-70%. The majority of participants (81%) had an ASA 3 classification. A history of hyperlipidemia was identified in 95% of participants, and hypertension was reported in 89% of the study sample individuals. Diabetes was present in 42% of participants. All patients were discharged from hospital on aspirin; 97% of participants were prescribed a beta-blocker, and 98% were prescribed antihyperlipidemic drugs. Other reported medical conditions among the sample were gout, obstructive sleep apnea, kidney stones, and benign prostatic hyperplasia (see Table 8).

Table 8. *Clinical Characteristics of Study Participants by Group*

Variable	**Control Group (n=50)**	**Intervention Group (n=54)**	***p*-value**
Congestive Heart Failure, n (%)			0.04*
Yes	1 (2%)	7 (13%)	
Valve Disease n (%)			0.14
Yes	2 (4%)	0 (0%)	
Myocardial Infarction, n (%)			0.79
Yes	20 (40%)	23 (43%)	
Arrhythmia, n (%)			0.28
Yes	2 (4%)	5 (9%)	
Musculoskeletal Disease n (%)			0.75
Yes	17 (34%)	20 (37%)	
Hypertension n (%)			0.65
Yes	44 (88.0)	49 (91%)	
Diabetes Mellitus			0.13
Yes	25 (50%)	19 (35%)	
Hyperlipidemia, n (%)			0.71
Yes	48 (96%)	51 (94%)	
Kidney Disease			0.17
Yes	2 (4%)	6 (11%)	
Respiratory Disease, n (%)			0.48
Yes	10 (20%)	8 (15%)	
GERD/ Reflux, n (%)			0.34
Yes	25 (50%)	22 (41%)	
No Previous Median Sternotomy n (%)			0.17
Yes	0 (0%)	2 (4%)	
Alcohol Use, n (%)			0.59
Yes	9 (18%)	12 (22%)	
Other Co-Morbidities, n (%)			0.36
Yes	28 (56%)	35 (65%)	

Note. * $p < 0.05$ is significant between groups

Variable	Control Group (n=50)	Intervention Group (n=54)	*p*- value
EF Class, n (%)			0.02*
1: ≤ 39%	5 (10%)	17 (31%)	
2: 40-54%	6 (12%)	7 (13%)	
3: 55-70%	39 (78%)	30 (56%)	
Smoke Class, n (%)			0.02*
Non-smoker	21 (42%)	35 (65%)	
Former or Current Smoker	29 (58%)	19 (35%)	
ASA Physical Score n (%)			0.07
Class 1	1 (2.0)	0 (0.0)	
Class 2	7 (14.0)	1 (1.9)	
Class 3	36 (72.0)	48 (88.9)	
Class 4	6 (12%)	5 (9.3)	
Echo	28 (56.0)	34 (63.0)	0.55
Length of Postop Stay, Day 0= Surgery Day M (SD)	7.8 (3.7)	7.9 (3.9)	0.94
Length of Surgery (Min) M (SD)	236 (46.2)	230 (52.0)	
Operative Procedure			0.24
1 or 2 Vessel Disease	20 (37.0)	15 (30.0)	
3-Vessel Disease, Inc. Proximal LAD	24 (44.4)	30 (60.0)	
4 or More Vessel Disease	10 (18.5)	5 (10.0)	
RBC Transfusion, Intraoperative (Units)			0.63
0 Units	52 (96.3)	49 (98.0)	
1 Units	1 (1.9)	1 (2.0)	
2 Units	1 (1.9)	0 (0.0)	

Note. * $p < 0.05$ is significant between groups

Postoperative Medications of Study Participants (N=104) by Group

Variable	Control Group (n= 50)	Intervention Group (n=54)	*p*-value
Beta-Blockers	51 (94.4)	49 (98.0)	0.62
AntiHyperlipidemic	54 (100.0)	47 (94.0)	0.10
Diuretics	47 (87.0)	43 (86.0)	1.0
Aspirin	54 (100.0)	50(100.0)	
Proton Pump Inhibitor	25 (46.3)	18 (36.0)	0.32
Antidiabetics	18 (33.3)	23 (46.0)	0.23
Antiplatelet Drugs	15 (27.8)	9 (18.0)	0.26
Antibiotics	7 (13.0)	8 (16.0)	0.78
Calcium Channel Blocker	4 (7.4)	3 (6.0)	1.0
Narcotics	12 (22.2)	11 (22.0)	1.0
ACE Inhibitors	17 (31.5)	17 (34.0)	0.84
Sedatives	0 (0.0)	1 (1.9)	0.39
Antiarrhythmic	12 (22.2)	13 (26.0)	0.82
Anticoagulants	6 (11.1)	5 (10.0)	1.0
Nitrates	2 (3.7)	2 (4.0)	0.0
Antihypertensive	40 (74.1)	30 (60.0)	0.15
Anti-inflammatory	1 (1.9)	2 (4.0)	0.61
Other	51 (94.4)	49 (98.0)	0.62

Note. * $p < 0.05$ is significant between groups

Postoperative Complications of Study Participants by Group, Mean (SD)

Variable	Control Group (n=50)	Intervention Group (n=54)	*p*-value
Postop Infection	1 (1.9)	4 (8.0)	0.19
Atrial Fibrillation	17 (31.5)	13 (26.0)	0.67
Edema	2 (3.7)	3 (6.0)	0.67
Bleeding	1 (1.9)	2 (4.0)	0.61
Other Complications	22 (40.7)	26 (52.0)	0.33
Postoperative RBC Transfusion			0.25
0 Units	48 (89.0)	42 (84.0)	
1 Unit	5 (9.3)	3 (6.0)	
2 Units	0 (0.0)	3 (6.0)	
3 Units	1 (1.9)	2 (4.0)	

Note. Mean SD=Standard Deviation, *p-value < 0.05 is significant between groups

Atrial fibrillation is a common postoperative complication following CABG surgery, and this arrhythmia was observed in 30 (29%) participants. Three participants (2.9%) experienced postoperative bleeding, and 4.8% experienced ongoing peripheral edema, while infections occurred in five (4.8%) patients. Forty-eight (46%) participants had minor postoperative complications that did not delay discharge.

Mean Hgb was 97.6 g/L (12.20) for males and 92.5 g/L (12.50) for females at discharge. Anemia (< 120 g/L) was present in all participants at discharge, with 80% of participants having an Hgb < 110 g/L. A red blood cell transfusion was required for blood loss in 3% of the patients, and 2% were transfused platelets and 2% plasma intraoperatively, and transfusion of red blood cells (13.5%), platelets (2%), and plasma (2%) was required during the postoperative period.

There were no significant differences between the two groups for baseline clinical characteristics except for CHF, smoking history, and LVEF. These categorical variables were added as covariates in the data analysis.

4.4 Preliminary Analysis

Data were coded and entered manually into a password-protected, hospital computer by the investigator and checked by the study monitor. A study monitor was appointed by the investigator to assure good clinical practice and adherence to research guidelines. A hospital computer was chosen for data collection to protect the confidentiality of the data and provide a regular backup of the data. Analysis of the data was performed according to an ITT approach (Gupta, 2011) using the statistical package SAS STAT software 14.3 Version 9.4. Data were collected through participant assessment, self-reported questionnaires, walk test, and laboratory testing. Data were analyzed to answer the three research questions.

4.4.1 Recoding of variables. Several of the dependent variables from the self-reported questionnaires were recoded to create new variables and to produce new values or codes to represent the individual subscales for analysis. This recoding is described in detail below

4.4.2 ICFS. The Identity Consequence Fatigue Scale is a 31-item scale designed and assessed to measure POF and return to normal daily activities. The first 18 items in the ICFS use a six-point Likert scale for responses where 5 = all of the time; 4 = very often; 3 = fairly often; 2 = some of the time; 1 = almost never; 0 = not at all. For items 19 and 20, the Likert scores are on a five-point scale where 4 = I strongly disagree; 3 = I disagree; 2 = neutral and 1 = I agree. The remaining 11 items are on a five-point Likert scale, including questions 21-31 where 4 = as often as usual; 3 = nearly often as usual; 2 = sometimes but less than usual; 1 = only occasionally and 0 = not at all. The scale assessed the impact on daily activities. Direct scoring was given to items 1, 2, 4, 6, 8, 10,

12, 13, 15-17, and 18. Reversed scoring was assigned to items 3, 5, 7, 9, 11, 14, 19, 20, and questions 21-31. Higher fatigue scores represented a higher level of fatigue.

ICFS variables IFC1 to IFC31 were recoded into five subscales of the fatigue concept. First, reverse coding of items: IFC3, IFC5, IFC7, IFC11, IFC14, IFC19 to IFC31 for each time point was carried out following the scoring instructions (Paddison et al., 2006). Next, the reverse coded and coded items were combined to create five specific subscales of fatigue. The third step was to generate standardized subscale scores for subscales (feelings of fatigue, feelings of vigor, impact on energy, impact on concentration, and impact on daily activities). Lastly, a total score was calculated by averaging the five subscales, and scoring of the subscales and total scores was conducted using SAS software. All five subscales of the ICFS were normally distributed, as illustrated in Table 9.

Table 9. *Five Subscales for the 31 item ICFS Questionnaire, Recoded Variables*

ICFS Variable	Subscales of recoded variables	Skew	Kurtosis
IFC1, IFC4, IFC6, IFC10, IFC12	Feelings of Fatigue	0.004	-0.53
IFC3_r, IFC5_r, IFC_r, IFC14_r	Feelings of Vigor	-0.41	-0.55
IFC9_r, IFC15-IFC18	Impact on Energy	-0.49	-0.33
IFC2, IFC8, IFC11_r, IFC13, IFC19_r, IFC20_r	Impact of Concentration	0.55	-0.05
IFC 21 to IFC31	Impact on Daily Activities	5.5	35.30

The mean total and subscales scores of the fatigue symptom at baseline were assessed by the ICFS, as presented in Table 10. The total score is the average of the five subscales.

Table 10. *Mean ICFS Subscales and Total Score at Baseline*

ICFS Variable	n (%)	Actual Range	Min and Max of Actual Range	Mean	SD
Feelings of Fatigue	77 (74%)	100	0-100	47.69	24.02
Feelings of Vigor	76 (73%)	80	20-100	68.42	21.68
Impact on Energy	74 (71%)	96	3-100	56.22	23.46
Impact of Concentration	77 (74%)	98	0-96	32.05	21.90
Impact on Daily Activities	76 (73%)	1238	13-1250	100.79	162.10
Total ICFS Score	77 (74%)	255	16-271	60.98	32.53

Note. ICFS=Identity Consequence Fatigue Scale

4.4.3 FACT-An. The FACT-An was designed to assess QOL with a focus on anemia and fatigue (Cella, 1997). The questionnaire consists of a general component (FACT-G) composed of 28 questions and the FACT-An Anemia subscale, which includes the FACT-Fatigue (FACT F) subscale measuring 13 fatigue specific items and seven anemia related items (Cella, 1997). The original 48 items were recoded to create five distinct subscales for FACT-An. Cella (1997) developed a guideline to identify the subscales and recode the variables. Items GP1-GP7, GE1, GE3-GE6, HI7, HI12, AN1-AN4, AN6, AN8-AN10, B1, AN11-AN16 were reverse coded into (4 = 0), (3 = 1), (2 = 2), (1 = 3), (0 = 4) according to the scoring instructions. The recoded and reverse coded items were combined into five specific subscales. The five subscales included physical well-being, social/family well-being; emotional well-being; functional well-being; and anemia/fatigue. Each subscale was calculated by summation of all the questions in each subscale. A score was created between a range of 0 to 100, where 0

equals poorer QOL, and 100 indicates higher QOL. All subscales were normally distributed, as described in Table 11.

Table 11. *Five Subscales for the 48 items of the FACT-An Questionnaire, Recoded Variables*

FACT-An Variable	Subscales of Recoded Variables	Skew	Kurtosis
GP1-GP7	Physical Well-Being	-0.97	0.63
GS1-GS7	Social/Family Well-Being	-0.78	-0.16
GE1-GE6	Emotional Well-Being	-0.85	0.23
GF1-GF7	Functional Well-Being	0.08	-0.10
HI7 HI12 An1-An10 B1 An11 An12 BL4 An13-An16	Anemia Subscale	-0.10	-0.81

4.4.4 SF-36 Questionnaire. The SF-36 was developed to assess the individual subscales of HRQOL (Ware & Sherbourne, 1992). The eight subscales included physical functioning, role limitations due to physical health problems; role limitations due to personal or emotional problems; emotional well-being, social functioning; energy/fatigue; and general health perceptions (Ware & Sherbourne, 1992).

4.4.4.1 Recoding of SF-36 Questionnaire. First, the original responses of the SF-36 were recoded according to the published scoring key so that the highest score reflects a more favorable health state (Ware & Sherbourne, 1992). Second, the items were recoded to score 0 to 100, so that 0 is the lowest possible score and 100 the highest possible score (Hays, Sherbourne & Mazel, 1993). The items were then averaged into eight specific subscales. The eight subscales included physical functioning, role limitations due to physical health problems, role limitations due to personal or emotional

problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions.

The items SF1, SF2, SF20, SF22, SF34, SF36 were recoded as responses (1 = 100) (2 = 75) (3 = 50) (4 = 25) (5 = 0). Items SF3-SF12 were recoded as (1 = 0) (2 = 50) (3 = 100). Items SF13-SF19 were recoded as (1 = 0) (2 = 100), and SF21, SF23, SF26, SF27, SF30 were recoded as (1 = 100) (2 = 80) (3 = 60) (4 = 40) (5 = 20) (6 = 0). Questions SF24, SF25, SF28, SF29, SF31 were recoded as (1 = 0) (2 = 20) (3 = 40) (4 = 60) (5 = 80) (6 = 100) and SF32, SF33, SF35 were recoded as (1 = 0) (2 = 25) (3 = 50) (4 = 75) (5 = 100). The next step was to average the items in their same scales to determine a range for each of the eight subscale scores.

All subscales were checked for normality by skewness, and all subscales were normally distributed except for role limitation due to physical health problems and emotional wellbeing, which was highly skewed (see Table 12).

Table 12. *Eight Subscales for the 36 items of the SF36 Questionnaire, Recoded Variables*

SF36 Variables	**Subscales of recoded variables**	**Skew**	**Kurtosis**
3-12	Physical Functioning	-0.09	-1.07
13-16	Role Limitation Due to Physical Health Problems	1.05	0.57
17-19	Role Limitation Due to Emotional Problems	-0.42	-1.69
23 27 29 31	Vitality, Energy/ Fatigue	-0.04	-0.98
24-26 28 30	Emotional Wellbeing	-1.26	1.27
20 32	Social Functioning	-0.50	-0.74
21 22	Bodily Pain	-0.19	-0.82
1 33-36	General Health Perceptions	-0.45	-0.89

4.5 Baseline Outcome Measures

The purpose of this quantitative study was to 1) examine the effect of oral iron in reducing POF measured by the ICFS over 12 weeks, 2) determine how effective oral iron was on improving fatigue, functional capacity, QOL, and anemia and 3) assess the degree patients adhere to taking oral iron. The research questions for this study directed the analyses of these results.

4.5.1 Primary outcome.

4.5.2 Research question 1. Is oral iron effective in reducing POF as measured by the ICFS over 12 weeks?

4.5.2.1 Analyses of the Identity Consequence Fatigue Scale (ICFS). The impact of fatigue was measured using a self-reported ICFS questionnaire at all four study time points. The 31 items were recoded and labeled into new variables for the analysis. The five subscales were averaged to provide percentages as scores. Normality was assessed using histograms, Q-Q probability plots, skewness, and kurtosis. All of the subscales of the ICFS were normally skewed except for Impact on Daily Activities, which was highly skewed. There was a linear relationship between the dependent variables of ICFS as assessed by scatterplot. In the current study, the ICFS subscales were analyzed and demonstrated a relatively high degree of reliability, with a Cronbach's alpha coefficient of 0.90.

The SAS statistical program was used to fit the Linear Mixed models to the continuous dependent variables of the longitudinal dataset. This model allows for both fixed and random effects to be analyzed. All models displayed in the tables below are Linear Mixed models using the Gaussian or normally distributed assumption. An

unstructured covariance structure (where the relationships are all different) was used to fit the repeated measurements made over time on the same subject. The first simple analysis looked at the study group and time as independent variables and ICFS total score as the dependent variables. The repeated observations were analyzed to see if there was a change in mean response over time and if the trends between study groups were similar (between subjects and within the subject's effects). The interaction for time and study group was tested in each model to determine if the null hypothesis (change over time is the same for each group) would be rejected. The interaction was excluded when statistically non-significant ($p = 0.65$) to produce a more parsimonious model. The study group and time interaction variable results of a non-significant p-value are inconclusive and failed to reject the null hypothesis.

The test of fixed effects showed that the effect of the intervention between groups on the ICFS total score was not significant ($p = 0.91$) and failed to reject the null hypothesis (Table 13). However, the effect of time on fatigue levels using the mean ICFS total scores was statistically significant ($p < 0.001$).

Table 13. *Type 3 Tests of Fixed Effects of the effect of Study Drug between groups and overtime*

Effect	**Num DF**	**Den DF**	**F-Value**	***p*-value**
Time point	3	87	48.16	<0.0001*
Study group	1	87	0.01	0.91

Note. Study group= intervention and control, Num DF=Numerator Degrees of Freedom, Den DF= Denominator Degrees of Freedom, *p values < 0.05 are significant between groups

The trends of mean fatigue levels for the study groups shows that there is no significant difference in the fatigue scores between the intervention (oral iron) group and

the control (placebo) groups. The least-squares mean estimate for the control group was 52.243 (SE = 2.7117) and intervention group 52.681 (SE = 2.6867), as shown in Table 14. The results showed a statistically significant difference in the means at each time point (p = 0.0001) for each group using the ICFS total mean scores; therefore, the null hypothesis for time was rejected.

Table 14. *Least Squares Means of Intervention and Control Groups of the ICFS using a Linear Mixed Model over time (Time point 1-4)*

Effect	**Intervention Control Group**	**Visit**	**Estimate**	**Standard Error (SE)**	***p*-Value**
Control group	0		52.2430	2.7177	
Intervention group	1		52.6812	2.6867	
Time point		1	60.9833	3.6600	<0.0001*
Time point		2	76.1199	3.3432	<0.0001*
Time point		3	41.4407	2.5363	<0.0001*
Time point		4	31.3044	2.4935	<0.0001*

Note. 0=Control, 1=Intervention, *p values < 0.05 are significant between groups

In Figure 3, the graph displays a substantial parallel decrease in the trends of the mean responses at time point 3 after randomization and a further reduction at time point 4. The intervention group had a slightly higher fatigue level compared to the control group at time point 1 (preoperatively). However, the mean levels of fatigue increased following surgery similarly in each group (no statistically significant difference).

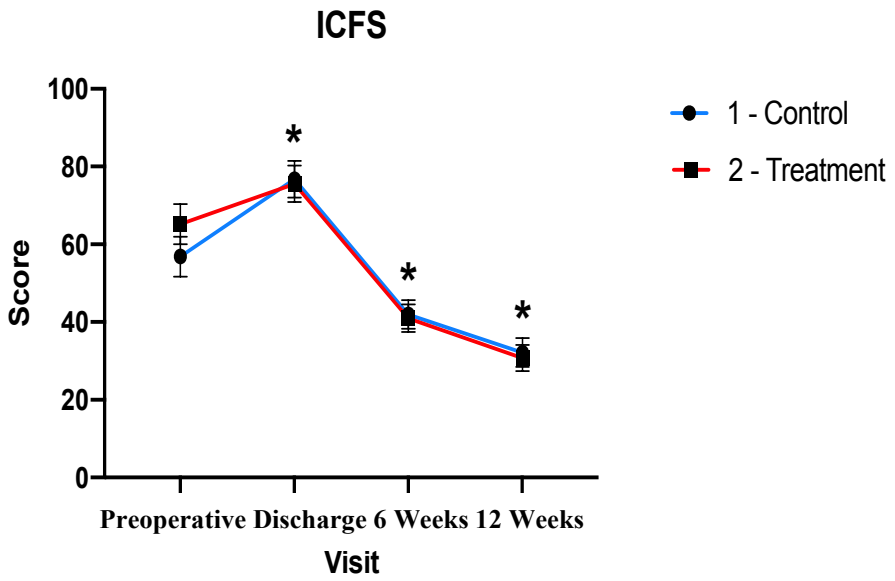

Figure 3. Total ICFS mean score by visits (time points 1-4) of control and intervention groups. *Note*. $p < 0.05$. Both study groups improved > 25% in POF at 12 weeks (1 –control 53.3%; 2 – intervention 53.9% of time point 2) exceeding the study goal (25% reduction in POF).

Figure 4 illustrates the means and standard deviation of the study groups over time. There were no statistically significant differences between the means of the study groups. However, there was a statistically significant difference in fatigue in both groups over time. The results of this study demonstrated a fatigue level at 12 weeks that was less than levels preoperatively.

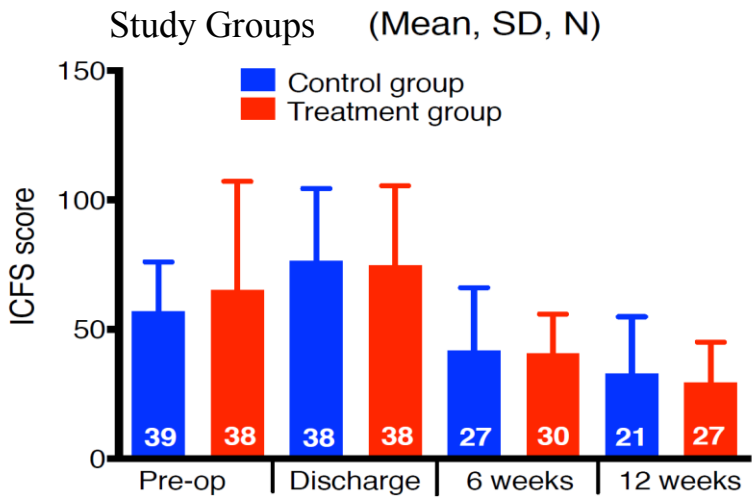

Figure 4. Total ICFS mean scores by visits (time points 1-4) of control and intervention groups. *Note*. SD=Standard Deviation, N = number of participants

There were no statistically significant differences between study groups. However, there were significant differences ($p < 0.0001$) between all pairs of measures across time points, as shown in Table 15.

Table 15. *Differences of Intervention and Control Groups of the ICFS Total Scores over time*

Effect	**Intervention Control Group**	**Visit**	**Intervention Control Group**	**Visit**	**Estimate**	**Standard Error**	***p*-value**
Study group	0		1		-0.4382	3.7811	0.91
Time point		2		3	34.6791	3.9067	<0.0001*
Time point		2		4	44.8154	3.8308	<0.0001*
Time point		2		1	15.1366	4.3845	0.0009*
Time point		3		4	10.1363	2.2913	<0.0001*
Time point		3		1	-19.5426	4.1710	<0.0001*
Time point		4		1	-29.6789	4.1761	<0.0001*

Note. Study Group 0= Control, 1= Intervention, *p values < 0.05 are significant between groups

Left ventricular ejection fraction class, smoking history, and CHF were included as covariates in the models because the values were statistically significantly different between the two study groups at baseline. The effects of the covariates were analyzed as fixed effects to see if these variables influenced a change in the mean response over time. The results are presented in Table 16. The effect of the covariates between study groups was not significant ($p = 0.99$). The results showed a statistically significant change ($p < 0.0001$) in the mean response of fatigue levels over time. The study group, covariates (LVEF, smoking class, and CHF) and time point interaction items were all statistically non-significant. The trends in the mean response over time are the same across the study group for covariates.

Table 16. *Type 3 Tests of Fixed Effects*

Effect	**Num DF**	**Den DF**	**F-Value**	***p*-value**
Time point	3	76	38.51	<0.0001*
Study group	1	76	0.00	0.99
LVEF class	2	76	0.30	0.74
Smoke History	1	76	0.29	0.59
CHF	1	76	0.05	0.83
Study group and time point	3	76	0.50	0.68

Note. Study group= intervention and control, Num DF=Numerator Degrees of Freedom, Den DF= Denominator Degrees of Freedom, *p values < 0.05 are significant between groups, LVEF=Left ventricular ejection fraction (1: ≤ 39% 2: 40-54% 3: 55 - 70%), CHF=Congestive Heart Failure, Smoking history= Former or Current smoker, Non-smoker

The table shows that there was no significant difference between groups for the study drug on the subscales of the ICFS over time points two to four. All of the results for the study group and covariates showed no significant differences with the mean subscales

or the ICFS summary scores. The global time point (time point two to four) was significant (p = 0.0001) for all subscales and summary scores. The perception and impact of fatigue changed over time within each group but did not differ significantly between groups (see Table 17).

Table 17. *Fixed effects for Predictors and Covariates on Primary Outcome Variables of the ICFS*

Outcome Variable	***p*-value**				
	Time point (global)	**Study group**	**LVEF Class**	**Smoke History**	**CHF**
Feelings of Fatigue	< 0.001*	0.40	0.34	0.29	0.30
Feelings of Vigor	< 0.001*	0.45	0.38	0.52	0.66
Impact on Energy	< 0.001*	0.63	0.54	0.90	0.53
Fatigue Experience Summary Score	< 0.001*	0.68	0.57	0.48	0.45
ǂ Impact on Concentration	< 0.001*	0.21	0.84	0.03	0.41
ǂ Impact on Daily Activities	< 0.001*	0.77	0.39	0.17	0.46
ǂ Fatigue Impact Summary Scores	< 0.001*	0.55	0.34	0.20	0.64

Note. Study Group = Intervention and Control Group, LVEF = Left ventricular Ejection Fraction, CHF = Congestive Heart Failure, * p values < 0.05 are significant between groups, Time point (global) = Time point 2-4,
ǂ = Variables were modeled using Generalized linear mixed models with a Gamma Distribution and an unstructured covariance

The difference in means for each subscale and summary scores between groups were non-significant statistically. The fatigue level means decreased in all subscales and summary scales from time point two to time point four (see Table 17). Decreased means scores indicate reduced fatigue levels.

Table 18. *Least Squares Means in each Group on the ICFS Subscale and Summary Scores over Time*

Outcome Variable	Least Square Means (Standard Error)				
	Control group	Intervention group	Time point 2	Time point 3	Time point 4
Feelings of Fatigue	35.34(4.92)	31.45(5.06)	52.55(4.87)	27.43(4.97)	20.21(4.96)
Feelings of Vigor	55.35(4.69)	58.36(4.81)	74.38(4.47)	52.79(5.15)	43.41(5.06)
Impact of Energy	47.83(5.06)	45.75(5.15)	65.29(4.99)	43.89(5.30)	31.17(5.29)
ǂImpact on Concentration	29.64(3.16)	24.49(2.66)	39.55(3.24)	24.63(2.14)	20.09(1.88)
ǂImpact on Daily Activities	67.10(6.17)	64.56(5.92)	136.02(12.26)	55.93(5.76)	37.48(4.19)
Fatigue Experience	39.88(4.04)	38.34(4.12)	55.12(3.89)	34.92(4.15)	27.28(3.98)
ǂFatigue Impact	57.96(4.37)	54.39(4.11)	101.49(7.14)	50.50(4.04)	34.53(2.99)

Note. = Variables were modeled using Generalized linear mixed models with a Gamma Distribution and an unstructured covariance

4.6 Secondary Outcomes

In this study, data obtained using the FACT-An, SF-36, Hgb biomarkers, 6MWT, a list of side effects for medication side effects events, and a pill count for medication adherence were analyzed for the secondary outcomes. Quality of life and mobility can be affected by POF and, therefore, affect recovery outcomes. Results for between-group comparisons, including covariates on the secondary outcomes, did not differ by intervention over time.

4.7 Research Question 2

If oral iron is effective, how effective is it in improving QOL?

4.7.1 Analysis of the short form 36 (SF-36). The SF-36 questionnaire measured health-related quality of life. The SF-36 instrument consists of 36 questions and eight domains which include physiological and psychosocial functioning; (bodily pain (BP); general health (GH); physical functioning (PF); role-physical (RP); vitality (VT); social functioning (SF); role emotional (RE); and mental health (MH). The possible scores for each domain range from 0 to 100, where 0 = poorer health and 100 = better health status. The subscales of the SF-36 were combined into two summary scores: a physical dimension represented by the Physical Component Summary (PCS) and a mental dimension represented by a Mental Component Summary (MCS). The Cronbach's alpha for the study was 0.95, which represents high reliability for the instrument.

4.7.2 Analysis of the SF-36 between study groups and between different time points. Research question #2 was answered by using linear mixed models to analyze repeated measures for predictors and covariates on outcome variables.

The table below illustrates that there was no statistically significant difference between study groups for the summary scores of the SF-36 over time points two to four, and therefore failed to reject the null hypothesis (see Table 18).

Table 19. *Fixed effects for Predictors and Covariates on Secondary Outcome Variables of the SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS).*

Outcome Variable	***p*-value**				
	Time point (global)	**Study group**	**LVEF Class**	**Smoke History**	**CHF**
PCS	< 0.001*	0.96	0.67	0.61	0.47
MCS	< 0.001*	0.92	0.20	0.32	0.39

Note. Study Group = Intervention and Control Group, PCS=Physical Component Summary (PCS), MCS=Mental Component Summary, LVEF = Left Ventricular Ejection Fraction, CHF = Congestive Heart Failure, * p values < 0.05 are significant between groups, Time point (global) = Time point 2-4

The differences in the least-square means of the intervention and the control group were non-statistically significant in each of the summary scores of the SF-36. However, the means for each summary score were statistically significantly different between time points two and four in both summary scores for the control and the intervention group. The least-square mean scores for the PCS increased over time, indicating a better health state, as displayed in Table 20.

Table 20. *Least Squares Means in each Group on the SF-36 Subscale scores over Time*

Outcome Variable	**Least Square Means (Standard Error)**				
	Control group	**Intervention group**	**Time point 2**	**Time point 3**	**Time point 4**
Physical Component Summary	40.95(1.75)	40.98(1.81)	33.41(1.62)	42.30(1.74)	47.19(1.95)
Mental Component Summary	48.49(1.78)	48.67(1.84)	44.43(1.64)	46.64(1.66)	38.15(4.15)

4.8 Research Question 2

Is oral iron effective in improving fatigue, QOL, and anemia?

The FACT-An instrument is a self-report questionnaire developed by Cella, (1997) consisting of 48 items that assess QOL, anemia, and fatigue. The instrument consists of the FACT – G (a core general questionnaire)containing 28 questions which measure general QOL, plus 13 fatigue-related questions, and seven non-fatigue related questions relevant to anemia (Cella, 1997). The scores of these 48 questions are rated on a five-point Likert scale with the following values: 4 = Very much; 3 = Quite a bit; 2 = Somewhat; 1 = A little bit; and 0 = Not at all. For data analysis, the individual item

scores were summed, then multiplied by the number of questions and divided by the number of items answered for each of the five subscales (physical well-being, functional well-being, emotional well-being, social well-being, and anemia/fatigue). The FACT- G summary scale consists of four subscales (physical well-being, functional well-being, emotional well-being, and social well-being). The sums of the five FACT-An subscales were added together to derive a total score. A Trial Outcome Index was calculated by summation of physical well-being, functional well-being, and the anemia/fatigue subscale. A higher score indicates a better QOL.

4.8.1 Analysis of the subscales scores of the functional assessment of cancer therapy –anemia (FACT-An) version 4. Research question 2 was answered by Linear Mixed modeling to analyze repeated measures for predictors and covariates on outcome variables (see Table 21). There was no statistically significant difference between groups for the study drug on any of the FACT-An subscales, summary scores, or total scores over time points two to four. The FACT-An had an alpha of 0.96 for the current study, which supports high internal consistency. The results failed to reject the null hypothesis.

There were, however, statistically significant differences in mean scores over time in all the subscales except social well-being subscale ($p = 0.0645$), summary scores, and trial outcome index scores for both study groups. Left ventricular ejection fraction participant scores were statistically significantly different over time for the emotional well-being subscale and QOL, as indicated by the FACT-G summary scores.

Table 21. *Fixed effects for Predictors and Covariates on Secondary Outcome Variables of the FACT-An*

Outcome Variable	*p*-value				
	Time point (global)	**Study group**	**LVEF Class**	**Smoke History**	**CHF**
Functional Well-Being	< 0.001*	0.38	0.11	0.81	0.57
Anemia/Fatigue Subscale	< 0.001*	0.051	0.43	0.64	0.93
Emotional Well-Being	< 0.001*	0.33	0.03*	0.85	0.44
Physical Well-Being	< 0.001*	0.17	0.07	0.44	0.59
Social Well-Being	0.06	0.72	0.20	0.51	0.26
FACT-G Summary Scale	<0.001*	0.55	0.04*	0.49	0.52
Total Fact An Score	< 0.001*	0.22	0.09	0.37	0.64
Trial Outcome Index	< 0.001*	0.13	0.17	0.44	0.68

Note. Study Group = Intervention and Control Group, LVEF = Ejection Fraction, CHF = Congestive Heart Failure, * p values <0.05 are significant between groups, Time point (global) = Time point 2-4

The means of the study groups (intervention and the control group) demonstrated no statistically significant difference for the study drug on each of the subscales, summary, and total scores of the FACT-An. However, there was a statistically significant difference in scores between time points two and four in all subscales except summary and total scores for both study groups, indicating improvement in QOL and health status (see Table 22).

Table 22. *Least Squares Means in each Group on the FACT-An Subscale and Summary Scores over Time*

Outcome Variable	Least Square Means (Standard Error)				
	Control group	Intervention group	Time point 2	Time point 3	Time point 4
FWB	16.62(1.49)	17.69(1.45)	13.08(1.43)	17.43(1.46)	20.97(1.42)
EWB	19.86(0.84)	20.73(0.85)	19.00(0.77)	20.61(0.79)	21.27(0.74)
PWB	18.80(1.35)	20.54(1.36)	14.29(1.32)	21.25(1.31)	23.47(1.29)
SWB	22.17(0.84)	21.85(0.86)	22.16(0.81)	21.42(0.77)	22.46(075)
ANS	50.08(3.38)	55.85(3.43)	38.24(3.43)	57.28(3.38)	63.37(3.39)
FACT-G	78.72(3.58)	80.75(3.58)	68.88(3.34)	81.25(3.49)	89.07(3.34)
TOTAL	129.08(6.69)	136.50(6.70)	107.14(6.39)	138.66(6.61)	152.57(6.47)
TOI	86.08(5.79)	93.97(5.83)	65.75(5.70)	96.20(5.74)	108.14(5.66)

Note. FWB = functional well-being, EWB = emotional well-being, PWB = physical well – being, SWB = social well-being, ANS = anemia/fatigue subscale, FACT-G = Functional Assessment of Cancer Therapy-General, TOTAL = sum of all subscales, TOI = sum of physical well-being, functional well-being and anemia/fatigue

4.9 Research Question 2

Is oral iron effective in improving functional capacity?

4.9.1 Analysis of the meters walked of the 6MWT. Thirty-six study participants out of 104 completed the walk test at time point 3 (six-week), and 25 out of 104 participants completed the walk test at time point 4 (12-weeks). The results in Table 23 show that there was no statistically significant difference between study groups for the 6MWT, and therefore, the null hypothesis failed to be rejected. Globally, there was a statistically significant difference for the 6MWT ($p = 0.001$) over time points two to four. It was noted, however, that participants with CHF reported statistically significant differences for the 6MWT ($p = 0.03$) over time.

Table 23. *Fixed effects for Predictors and Covariates on Secondary Outcome Variables of the 6MWT*

Outcome Variable	*p*-value				
	Time point (global)	**Study group**	**LVEF Class**	**Smoke History**	**CHF**
Six Minute Walk test (6MWT)	< 0.001*	0.21	0.25	0.99	0.03*

Note. Study Group = Intervention and Control Group, LVEF =Left Ventricular Ejection Fraction, CHF = Congestive Heart Failure, * p values < 0.05 are significant between groups, Time point (global) = Time point 2-4

Table 24 shows no statistically significant difference in the means for each study group for the 6 MWT; however, there was a statistically significant difference in the distance walked by participants across all time points.

Table 24. *Least Squares Means of Distance in Meters in each Group on the 6MWT scores over Time*

Outcome Variable	Least Square Means (Standard Error)				
	Control group	**Intervention group**	**Time point 2**	**Time point 3**	**Time point 4**
Six Minute Walk Test (6MWT)	261.19 (25.98)	285.98 (22.50)	141.58 (21.79)	315.19 (24.69)	363.99 (27.18)

Note. Six-minute walk test = meters walked in six minutes

4.10 Research Question 2

If oral iron is effective, how effective is it in improving anemia?

Anemia was measured using both serum Hgb biomarkers and the fatigue/anemia subscale FACT-An questionnaire. Linear mixed modeling was used to analyze repeated measures for predictors and covariates on Hgb levels. As discussed earlier in research question 2, FACT-An was also analyzed using Linear Mixed modeling for the outcome of anemia (see Table 21).

4.10.1 Analysis of the Hemoglobin Biomarkers.

Hemoglobin level was non-statistically significant for the study drug between study groups (p = 0.22) or covariates but was statistically significant (p = 0.001) from time point two to four (see Table 25). Since the p-value was less than 0.05, the null hypothesis failed to be rejected for this research question. Table 21 illustrates that there was no statistically significant difference between groups for the FACT-An subscale anemia/fatigue (p = 0.051).

The FACT-An summary scores and total scores were also not statistically significant between groups or among the covariates. There were, however, significant differences for all three scores (FACT-An anemia/fatigue subscale, total score, trial outcome index score) over time.

Table 25. *Fixed effects for Predictors and Covariates on Secondary Outcome Variables of the Hgb Biomarkers*

Outcome Variable	*p*-value				
	Time point (global)	**Study group**	**LVEF Class**	**Smoke History**	**CHF**
Hemoglobin (Hgb)	< 0.001*	0.22	0.65	0.85	0.88

Note. Study Group = Intervention and Control Group, LVEF =Left Ventricular Ejection Fraction, CHF = Congestive Heart Failure, * p values < 0.05 are significant between groups, Time point (global) = Time point 2-4

Table 26 shows no statistically significant difference in the means for each study group; however, there was a statistically significant increase in the means of Hgb level over time.

Table 26. *Least Squares Means in each Group on the Hgb Biomarkers over Time*

Outcome Variable	Least Square Means (Standard Error)				
	Control group	Intervention group	Time point 2	Time point 3	Time point 4
Hemoglobin (Hgb)	122.31 (2.55)	119.21 (2.20)	97.64 (2.15)	128.06 (2.23)	137.03 (2.36)

4.11 Research Question 3

To what degree do patients taking oral iron adhere to the prescribed medication?

Medication adherence was assessed by the degree to which patients took their prescribed medication and the proportion (reported as a percentage) of the drug taken over a specific time frame (Osterberg & Blaschke, 2005). A pill count was calculated by the number of pills taken (number of pills dispensed minus the number of pills returned over the study period). The adherence rate is a percentage that is calculated by the number of pills taken divided by the number of pills prescribed (in days) multiplied by 100% (Haynes et al., 1980; van Onzenoort et al., 2011). The value for positive adherence rate was set at 80% for this study (Brown & Bussell, 2011; Haynes et al., 1980; Osterberg & Blaschke, 2005; Lee et al., 2007).

4.11.1 Analysis of Medication Adherence. A total of 68 participants took their prescribed study medication (34 in each arm of the study). Four of these 68 participants withdrew from the study prior to completion and returned the pill containers. Sixty-four participants completed the drug regimen for the entire study. Of the 64 participants completing the drug regimen, 25 returned the pill containers as directed. Thirty-nine (39) did not return the pill containers for counting. Of the sample of 64 participants who took their prescribed medication, 31 participants in the control group (placebo) consumed all

of their study medication. In the intervention group (intervention), 33 participants adhered to the medication regimen. Table 27 reports the results for medication adherence for the 68 participants that consumed their medication. There were no statistically significant differences between the study groups (p = 0.30) for medication adherence. Within the control group, 91% adhered, and 97% adhered to the intervention group to the study drug regimen. Participants who consumed their prescribed study drug were adherent > 80% of the time.

Table 27. *Adherence to Study Medication for each Study Group*

Outcome Variable	**Control Group n=34 N (%)**	**Intervention Group n=34 N (%)**	***p*-Value**
80% or greater Adherence to Medication			0.30
No	3 (9%)	1 (3%)	
Yes	31 (91%)	33 (97%)	

Note. Adherence was defined as taking 80% or greater of Medications, * p values < 0.05 are significant between the groups.

The participants that completed the study medication demonstrated a mean adherence rate of 99.97% (minimum-maximum of 98 - 100). Participants that did not complete the prescribed study medication (n = 4) withdrew from the study (see Table 28).

Table 28. *Self-reported Adherence for Participants who took the Study Medication*

Variable	**N**	**Mean**	**Median**	**Minimum**	**Maximum**
No	4	22.50	10.50	1.00	68.00
Yes	64	99.97	100.00	98.00	100.00

Note. Adherence was defined as taking 80% or greater of Medications

The Wilcoxon Rank Sums test was performed for medication adherence to determine whether there were significant differences in the median adherence to medication between the two groups (median 100; interquartile range (IQR) 0.0). There was no statistically significant difference between the study groups (p = 0.32). The mean for adherence for the control group is 93.76 (SD = 22.06), and for the intervention group, it was 97.06 (SD = 16.80). Participants that completed the prescribed study medication were adherent (Table 29).

Table 29. *Comparison of Medication Adherence for each group on the entire sample*

Intervention Control Group	**n**	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**
Control Group	50	93.76	22.06	100.00	1.00	100.00
Intervention Group	54	97.06	16.80	100.00	2.00	100.00

4.12 Side Effects of Oral Iron Supplements

Sixty-six participants (63%) of the total sample completed a list of study drug side effects for medication side effects during the study. Forty-one (62%) participants did not report any drug side effects. Twenty-five (38%) participants of the sample who returned the list of study drug side effects reported at least one side effect from the prescribed medication (placebo and intervention). The most commonly reported reason for stopping, or not adhering to the medication schedule, was gastrointestinal (GI) side effects. The most common side effect reported was constipation, which 13 participants (20%) experienced in the early postoperative period. This reported side effect frequently occurs postoperatively in the absence of iron therapy due to decreased bowel function after

surgery. Among the 66 participants, 11% reported nausea, 5% reported vomiting, 18% reported diarrhea, 5% reported abdominal pain, and 2% reported heartburn.

The reported side effects of the study medication were collapsed into three categories of upper gastrointestinal (GI) (nausea, vomiting, and heartburn); lower GI (abdominal pain, diarrhea, and constipation); and no reported side effects for further analysis. Table 30 illustrates the hypothesis testing for each variable in the model. The Chi-square test and p-values were not statistically significant between groups (p = 0.61) and covariates for lower GI side effects (see Table 30).

Table 30. *Type 3 Effects of Study Medication for Lower GI Side Effects by Study Group Intervention and Control) and Covariates*

Effect	**DF**	**Wald Chi-Square**	***p*-value**
Study group	1	0.2542	0.61
LVEF class	2	2.1828	0.348
Smoke history	1	2.6911	0.10
CHF	1	0.3605	0.55

Note. Study group = intervention group and control group, LVEF=Left ventricular ejection fraction, CHF=congestive heart failure, DF=degrees of freedom, * p values <0.05 are significant between-group

The odds of lower GI side effects for those in the intervention group were not statistically different from those in the control group OR 1.351 (95% CI 0.419 - 4.356) or for the covariates (Table 31).

Table 31. *Odds Ratio Estimates of Lower GI side effects of Study Medication by Study group Intervention and Control) and Covariates*

Effect	Point Estimate	95% Wald Confidence Limits	
Intervention vs Control Group	1.351	0.419	4.356
LVEF class 1: ≤ 39% vs. 3: 55-70%	0.444	0.070	2.828
LVEF class 2: 40-54% vs. 3: 55-70%	2.161	0.482	9.684
Former or Current smoker vs. Non smoker	0.348	0.099	1.228
CHF Yes vs. No	0.466	0.039	5.621

Note. LVEF = Left ventricular ejection fraction, CHF=congestive heart failure

Logistic regression was used to assess the probability of upper GI adverse effects related to the study medication as there was a limited number of participant-reported responses to apply a multivariate model. For this reason, only the study group (Intervention and Control) was included in the regression model. There was no statistically significant difference (p = 0.17) between groups as described in the results of Table 32.

Table 32. *Type 3 Odds Ratio of Upper GI Side Effects related to Study Medication between Study Groups (Intervention and Control)*

Effect	DF	Wald Chi-Square	*p*-value
Study group	1	1.8529	0.17

Note. Study group = Intervention and Control Group, DF = degrees of freedom, * p values < 0.05 are significant between-group

The odds of experiencing upper GI side effects for those in the intervention group were not statistically significantly different than those in the control group. The odds of experiencing any side effects from the intervention medication for those in the

intervention group was not statistically different from those in the control group OR = 3.214 (95% CI: 0.598 - 17.264) (Table 33).

Table 33. *Odds Ratio Estimates of Upper GI side effects of Study Medication by Study group (Intervention and Control) moreover, Covariates*

Effect	**Points Estimate**	**95% Wald Confidence Limits**	
Intervention vs. Control Group	3.214	0.598	17.264

Logistic regression was used to assess the probability of no reported GI adverse effects to the study medication because there was a limited number of participant-reported responses to apply a multivariate model. For this reason, only the study group was included in the regression model. There was no statistically significant difference (p = 0.34) between groups (see Table 34). There was also no difference detected in reported side effects from the study medication related to the covariates.

Table 34. *Type 3 Odds Ratio of No reported GI Side Effects related to Study Medication between Study Groups and Covariates*

Effect	**DF**	**Wald Chi-Square**	***p*-value**
Study Group	1	0.9209	0.34
LVEF Class	2	2.3575	0.31
Smoke History	1	3.2755	0.07
CHF	1	0.4991	0.489

Note. Study Group = Intervention and Control Group, LVEF = Left ventricular ejection fraction, CHF = congestive, heart failure, DF = degrees of freedom, * p values < 0.05 are significant between-group

The odds of experiencing any side effects from the intervention medication for those in the intervention group was not statistically significantly different from those in

the control group OR = 0.563 (95% CI: 0.174 -1.820). There were no statistically significant differences in the experience of side effects from the study medication related to the selected covariates (Table 35).

Table 35. *Odds Ratio Estimates of No reported GI side effects of Study Medication by Study group and Covariates*

Effect	Point Estimate	95% Wald Confidence Limits
Intervention vs. Control Group	0.563	0.174 1.820
LVEF Class 1: ≤ 39% vs 3: 55-70%	2.871	0.448 18.398
LVEF Class 2: 40 - 54% vs. 3: 55 - 70%	0.528	0.116 2.410
Former or Current smoker vs. Non smoker	3.186	0.908 11.176
CHF Yes vs. No	2.448	0.204 29.361

Note. LVEF = Left ventricular ejection fraction, CHF = congestive heart failure

4.13 Post-discharge Adverse Events

Following discharge, adverse events were reported for 74 participants and eight (11%) of those participants were readmitted to the hospital for reasons unrelated to the study medication. Approximately one year after randomization, there was one death due to metastatic cancer. The health records for these participants were reviewed by the research team and determined that the adverse event, hospital readmissions, and the death were unrelated to the study medication.

4.14 Summary

The results of this randomized controlled clinical study designed to test the effect of administering oral iron therapy to postoperative CABG patients for the purpose of treating POF have been presented in this chapter. The baseline sociodemographic and

clinical characteristics between the study groups were comparable except for three clinical features: LVEF class, CHF, and smoking history, indicating that the randomization resulted in similar groups. The overall study sample was under-represented by female participants. The data were analyzed according to the research questions, based on the outcomes of fatigue, functional capacity, QOL, anemia, and adherence. There were statistically significant differences over time for both study groups on the mean response of fatigue levels in the ICFS, all the subscales but social well-being subscale, summary scores, and trial outcome index scores in the FACT-An, the SF-36 summary scores, 6MWT, and the means of Hgb level. There were also statistically significant differences for the 6MWT in participants with CHF over time. Participants in the LVEF class demonstrated a statistically significant difference over time for emotional well-being subscale and QOL, as indicated by the FACT-G summary scores. No statistically significant differences were detected between study groups.

Chapter Five provides a discussion of the results, strengths, and limitations of the study and presents implications for future research, theory, and clinical practice.

CHAPTER 5 DISCUSSION

The purpose of this study was to address the research questions about the effectiveness of oral iron therapy on the change of the fatigue state in CABG surgery patients over 12 weeks following hospital discharge. Evaluation of the results failed to reject the null hypothesis in that there were no significant differences detected between study groups on any of the selected outcome variables for this study. At baseline, there were significant group differences for variables such as CHF, smoking, and LVEF. This final chapter contains a brief background review, a summary of the study results, reflections on the theory used, study design and sample, instruments, results about the literature, and study strengths and limitations. Finally, this chapter addresses implications for theory, future research, clinical practice, and conclusions.

5.1 Review of Study Background

Substantial research has been conducted on the adverse effects of postoperative symptoms on recovery and patient outcomes. Coronary artery bypass graft surgery is a standard procedure for improving blood flow to the heart in the treatment of CAD. Following CABG surgery, many patients experience symptoms, which can negatively impact patients and their recovery. One of the most frequent and distressing patient-reported symptoms following CABG surgery is fatigue. Early postoperatively, this symptom has a high incidence, reaching 95%, and, at one to two months after surgery, 50% of patients still complain of fatigue (Zimmerman et al., 2007; Barnason et al., 2008).

Previous studies describe POF as a non-specific symptom that has a significant negative impact on patient outcomes including QOL, functional capacity, social functioning and participation in daily activities (Christensen, & Kehlet, 1993; Rubin, et

al., 2004b; Whitehead, 2009; Zargar-Shoshtari, 2009; Nostdahl, Bernklev, Raeder, Sandvik & Fredheim, 2016). Postoperative fatigue has been defined as a collection of physical and psychological symptoms that delay return to normal activities (Zargar-Shoshtari & Hill, 2009). Fatigue is generally a subjective experience and may coexist with physical and mental factors and various complications after surgery (Kahokehr et al., 2012). The etiology of POF is thought to be multifactorial involving biological, psychological, and social factors (Hall & Salmon, 2002; Rubin et al., 2004a; Zargar-Shoshtari & Hill, 2009). Due to fatigue's subjective nature and multifactorial presentation, multidimensional instruments should be used for assessment. Thus, the rationale for using both a generic and a disease-specific questionnaire and a self-report measure in addition to Hgb biomarker. Fatigue is often under-assessed by physicians and health care providers. Moreover, clinicians and researchers are challenged in the proper assessment, better monitoring techniques, and treatment strategies for fatigue.

Despite the frequency with which CABG surgery is performed, limited research has been conducted to examine management and interventions aimed at decreasing POF. Thus, this study contributes to a gap in our knowledge of the phenomenon and how to assess and intervene in the negative experience and effects of POF in postoperative CABG patients.

The primary purpose of this investigation was to examine the effectiveness of oral iron therapy on the change of fatigue levels in CABG surgery patients over 12 weeks post-discharge. Possibly more clinically relevant is the determination of whether a single intervention, such as administration of oral iron, can improve primary and secondary patient outcomes.

5.2 Summary of Results

An analysis was conducted of the results at 12 weeks post-randomization for CABG participants who were randomly assigned to either an intervention group or control group. Despite statistically non-significant differences between study groups for the total ICFS mean scores at all time points ($p = 0.91$), at baseline, the intervention group tended to have worse ICFS mean fatigue scores than the control group. In the early postoperative period before discharge, POF increased in both groups. However, at both six weeks and 12 weeks assessments, the intervention group had better mean scores than the control group for POF. This may be an important finding, even though results failed to reach statistical significance, given the higher baseline starting POF score for the intervention group. Baseline values were controlled in the analysis. Both study groups had lower mean scores on the ICFS for POF at 12 weeks compared to a baseline; that is, the scores for both groups on the ICFS declined over the period of the study. The lower mean scores at 12 weeks could be due to recovery from the surgical intervention.

There was no evidence of a significant effect between the study groups; there was a difference in mean scores of the SF-36 and FACT-An and meters walked in the 6MWT at all time points. At hospital discharge, mobility was impaired for both the subscales of the SF-36 and FACT-An and the 6MWT. By the 12-week visit, mobility had better mean scores for both mobility subscales of the SF-36 and the FACT-An and the 6MWT. The 6MWT and the mobility subscale of both the SF-36 and the FACT-An reported similar results, which will be discussed in the study outcomes section.

Both the anemia/fatigue subscale means of the FACT-An, and the hemoglobin level reported no statistical difference between study groups; however, there were

statistically significant differences over time points. These results will be discussed in the study outcomes section.

The overall medication adherence average for both study groups was 94% based on pill count. Adherence in the intervention group was 97%, and in the control group, 91%. Medication adherence was defined as taking greater than 80% of the study medication (Brown & Bussell, 2011; Haynes et al., 1980; Osterberg & Blaschke, 2005; Lee et al., 2007). The results for the difference in adherence between study groups were not statistically significant. The study outcomes are fully discussed later in the chapter.

5.3 Theoretical basis for the study

The theory informing this study was that of Symptom Management, as outlined in Chapter two. Symptom Management Theory is a deductive theory comprising the dimensions of symptom experience, symptom management strategies, and symptom outcomes, and the nursing domains of person, health/illness, and environment (Dodd et al., 2001).

The SMT has been used to guide several qualitative and quantitative research designs related to the management of chronic diseases, cancer, HIV, palliative care (Humphreys et al., 2008; Newcomb, 2010), and CABG research (Barnason et al., 2008). The SMT demonstrated utility for this study evaluating the efficacy of oral iron on fatigue in post-operative CABG patients. The study focused on one symptom management strategy (oral iron) and symptom outcomes (fatigue, QOL, anemia). This theory postulates that symptoms are dynamic, change over time, and interact with sociodemographic and clinical characteristics (Dodd et al., 2001). A person's perception, evaluation, and response to the symptom captures the symptom experience and initiates

the symptom management process (Humphreys et al., 2014). The symptom experience begins with the patient identifying their perception of the fatigue symptom leading to symptom management and optimal outcomes (Dodd et al., 2001). The SMT, as currently conceptualized, lacks a communication component for symptom perception, influencing symptom management, and a feedback loop between outcomes and symptom experience (Newcomb, 2010). The benefits of this modification to the SMT are outlined later in the chapter.

The SMT assumes that an intervention or management strategy is required to manage a symptom (fatigue), therefore preventing adverse outcomes and hastening recovery (Dodd et al., 2001). Several studies confirm that interventions or management strategies based on SMT are associated with better symptom management outcomes (Dodd et al., 2001). Despite the modification suggested above, the SMT facilitated conceptualization of the study design and the use of oral iron to manage fatigue in the study population.

5.4 Design

An RCT is considered to be the gold standard and the most rigorous way to test the effectiveness of an intervention on selected study outcomes (Spieth et al., 2016). In this study, a commonly prescribed medication (oral iron) was compared with a placebo to assess the effectiveness of the intervention. An RCT is the most appropriate approach to provide the most robust possible evidence of effectiveness, including linking cause and effect (Spieth et al., 2016). The revised CONSORT statement for reporting RCTs was used to support the design plan (Moher et al., 2010; Schultz et al., 2010) and was rigorously adhered to for this study. As part of the CONSORT statement, the ITT

approach was adopted to maintain all randomized participants in their original randomized study group for data analysis (Gupta, 2011). This approach preserved the integrity of randomization for the participants that withdrew, protocol violations, and loss to follow-up after randomization, which were included in the final analysis.

5.5 Sample

5.5.1 Socio-demographic characteristics. For this study, a sample of patients requiring CABG surgery at one Maritime regional referral hospital was assumed to be representative of the population. The sample recruited was based on sample size calculations to detect statistically significant differences in outcomes across the two study groups (power) and consisted of 104 adult participants with n = 50 in the control group and n = 54 in the intervention group. Comparison of the socio-demographic characteristic of the study groups (placebo and intervention) indicate that randomization was successful in allocating similar participants to each arm of the study.

The sample consisted of a mix of socioeconomic groups but was heavily skewed to male participants (90%). This reflects a recognized under-representation of women as participants in cardiovascular research, and also in diagnosis and treatment of CAD (Abramov et al., 2000; Arif et al., 2016; Blasberg, Schwartz, & Balaram, 2011; Barnason et al., 2008; Maas & Appelman, 2010; ten Haaf et al., 2019). Historically, women have been underrepresented in clinical studies (Maas & Appelman, 2010). However, in recent years, there has been an increased interest in women with CAD as there are substantial sex differences in outcomes in CABG surgery patients (Abramov et al., 2000; Arif et al., 2016). Women present later in life for coronary artery revascularization, have smaller coronary arteries and smaller body size than men (Arif et al., 2016). Previous reports

have shown a significant decrease in mortality following CABG surgery compared to over time in women. Women are at a considerably higher risk of absolute mortality as compared to men because women are older than men at the time of surgery (Mannacio & Mannacio, 2018; Vaccarino et al., 2003). This situation reflects the sex-specific disease process of atherothrombosis (Mannacio & Mannacio, 2018; Vaccarino et al., 2003). This reduction in mortality can be attributed to improved surgical techniques, use of the internal mammary artery, and antithrombotic drugs (Mannacio & Mannacio, 2018).

Racial/cultural/ethnic demographic factors were not captured in the data collection. Segregating data collection by race and ethnicity is not a usual practice in Canada unless the research questions are explicitly directed to investigating these differences (Khan, Kobayashi, Lee & Vang, 2015). Race is considered to be a social rather than a biological construct and distinct from culture and ethnicity as a participant characteristic (Ford & Harawa, 2010). There are data gaps in the health of Canadians concerning race and ethnicity (Khan et al., 2015; Veenstra, 2009; Wu & Schimmele, 2005). Statistics Canada (2016) reports that approximately 80% of the population of Canada is identified as "Caucasian," while the other 20% is a diverse mix. Maritime Canada is particularly homogenous in its ethnic/cultural composition since most immigrants to Canada migrate to larger urban centres in central and western Canada with existing populations and resources for the integration of new Canadians (Statistics Canada, 2016). Despite this, Nova Scotia is unique in its demographic profile in that it includes several indigenous communities and African Nova Scotians, who are descendants of American slaves of African origin who came to Nova Scotia following the American Revolution (Black Loyalists) (Government of Canada, 2019). Future studies

should include a more diverse and inclusive sample. This diversity would facilitate sub-group analysis with the potential to detect differences in medication effectiveness for different sub-populations, which can be obscured within the analysis of the larger sample. For example, chronic anemia is common among indigenous Canadian populations (Christofides, Schauer & Zlotkin, 2005; National Institute of Nutrition, 2002; WHO, 2011) and more common among women (Verdon et al., 2003; Vaucher et al., 2012) than among men in the general population (WHO, 2011).

Data were gathered from all 104 study participants. Of the 104 participants at time point four, 46% of the participants completed the ICFS, 44% completed the FACT-An, 46% completed the SF-36, 82% had Hgb levels drawn, and 43% completed the 6MWT. Missing data may contribute to reducing study power (Kang, 2013; Papageorgiou, Grant, Takkenberg, & Mokhles, 2018). Mixed models for repeated measures were adopted to handle missing data as a mitigation strategy and need to be applied if the study is replicated.

5.5.2 Health-related characteristics. The analysis confirmed the similarity between groups for clinical characteristics except for three items: there were significant baseline differences in smoking history, LVEF, and CHF. Smoking is a known modifiable risk factor for CAD (Messner & Bernhard, 2014). Forty-seven percent of the study participants were current or former smokers. Smoking combined with hypertension, low LVEF, and high cholesterol increase the risk of progression of CAD and mortality from myocardial infarction. Though the majority of participants in the study had a normal LVEF, the average was 66%, ranging from 55 - 70%.

Congestive heart failure is a chronic disease, and fatigue is one of the cardinal symptoms of CHF related to decreased blood perfusion leading to reduced oxygen-carrying capacity (Borges et al., 2018). In the current study, a small number (n = 1 in the control group and n = 7 in the intervention group) of participants had a diagnosis of CHF. Co-morbidities such as CHF, smoking history, and LVEF were accounted for in the study design and reflect the SMT description of fatigue as multi-factorial. Future studies with a larger sample might be able to use statistical methods (factor analysis) that could uncover any differences in the weighting of co-morbidities as factors contributing to the experience of fatigue.

5.6 Study Instruments

The selection of study instruments was based on previous studies reporting self-perceived fatigue, physical function, anemia, and QOL and on reported psychometric properties of each instrument (Cella, 1997; Paddison et al., 2006; Ware & Sherbourne, 1992; Zargar-Shoshtari et al., 2009). Both subjective and objective methods have been used to measure POF (which is a subjective experience): self-report questionnaires and performance-based measures. Objective measurement of functional capacity and anemia were assessed using the 6MWT (Balke, 1963) and Hgb biomarkers, respectively. The investigator tested all instruments used in this study for reliability by checking the Cronbach's alpha coefficient measure of internal consistency. A reliability coefficient of 0.70 or higher is acceptable for a self-reported questionnaire (Bland & Altman, 1997). All three self-report instruments (ICFS, FACT-An, and SF-36) reported a high level of internal consistency for this study with a Cronbach's alpha (0.90, 0.95, and 0.96), respectively. This means that an individual replicating this study should attain similar

results. The results of these analyses support the use of the ICFS, FACT-An, and SF-36 instruments for data collection for this study.

5.7 Assumptions Related to the Study

A major assumption for this study was that an RCT was the most appropriate design to answer the research questions. Well-constructed RCTs require several complicated steps and decisions using a few strong assumptions. Assumptions arise from the designing, implementing, and analyzing phases and need to be satisfied to help reduce bias (Krauss, 2018). In the design phase, the sample was randomly assigned to generate equally distributed groups. Inclusion and exclusion criteria were appropriately selected based on the sample population in efforts to answer the research questions and produce reliable results. The study included four-time points, which provided a sufficient number of observations for data analysis.

Another assumption underpinning this study is that the right questions were being asked. Future research on the experience of POF among CABG patients might want to explore non-pharmacological interventions or consider the role of convalescence in fatigue. At one time, patients and society expected lengthy periods of recovery and rehabilitation following major surgical procedures. Modern western culture has much shorter expectations for recovery, and patients may be anxious to reach full function and have unrealistic goals. Exploration of this phenomenon might shed light on the experience of POF in CABG patients.

5.8 Discussion of Study Outcome Measures

5.8.1 Outcomes for primary research question 1. Is oral iron effective in reducing POF as measured by the Identity Consequence Fatigue Scale (ICFS) over 12 weeks?

There was no statistically significant difference in total mean ICFS scores between-study groups (oral iron intervention and placebo) ($p = 0.91$) at any time point when linear mixed-effects modeling was conducted. These results indicate that oral iron was not effective in decreasing fatigue impact and fatigue experience scores at twelve weeks. However, there were within-group main effects demonstrated in all subscales and total ICFS mean scores at each time point ($p < 0.001$).

The effect on the study groups was not significant ($p = 0.98$) when the covariates: smoking history, LVEF, and CHF were added. The results showed a significant change ($p<0.0001$) in the mean fatigue response levels over time. A possible explanation is that fatigue is a known symptom of CHF related to reduced oxygen-carrying capacity (Borges et al., 2018). Low LVEF is also associated with fatigue (Perez-Moreno et al., 2014), and smoking is associated with the progression of CAD (Messner & Bernhard, 2014), which is associated with fatigue. Participants with these covariates may take longer than 12 weeks to recover postoperatively. Patients diagnosed with CHF may also have low LVEF and may experience chronic fatigue. The comorbidities were similar in both groups and may reflect a normal trajectory of recovery, and there were no group differences.

In the current study, subjective fatigue perception was evident preoperatively (mean 60.98) and continued to increase at discharge (mean 76.12). There was a marked decrease at the six-week assessment (mean 41.44), with a further reduction at 12 weeks

(31.30). Previous studies also identified the same trend in fatigue symptoms following CABG surgery (Barnason et al., 2008; Penckofer et al., 2005; Schulz et al., 2005). However, the authors used other symptom measurement tools to assess fatigue following CABG surgery. Zimmerman et al. (2002) reported 50% of patients (n = 35) experienced fatigue at eight weeks while King and Parrinello (1988) found similar results of persistent fatigue at two, four, and six weeks after CABG surgery. Other studies (n = 65) reported 74% of women experienced peak fatigue at 12 weeks after surgery (Schulz et al., 2005) and that fatigue persisted in 84% of CABG patients (n = 61) at 12 weeks (Penckofer et al., 2005).

There are a number of reasons why POF persists long term, which includes sleep deficit, anemia, medication-related, depression, and anxiety (Barnason et al., 2008; DeCherney et al., 2002; Kahokehr et al., 2012; Zargar-Shoshtari & Hill, 2009). These should all be explored further in future studies to determine if any of these are amenable to interventions to reduce the POF.

The results of the current study are consistent with a prospective study by Zargar-Shoshtari et al. (2009), where participants undergoing colonic surgery under a conventional plan were compared with participants in an Enhanced Recovery After Surgery (ERAS) program. Postoperative fatigue was increased in both groups early postoperatively. At 30 days following surgery, the ERAS participants reported a significant decrease in the ICFS total fatigue experience ($p = 0.04$) and the total fatigue impact ($p = 0.005$) reaching preoperative levels. At eight weeks, there was no difference between the two groups ($p = 0.28$).

The results of this study showed a reduction in fatigue levels at 12 weeks, which was less than preoperatively. This suggests the need for future studies to examine gains from the surgical procedure, such as a more active lifestyle.

5.8.2 Outcomes for secondary research questions. Question 2: Is oral iron effective in improving QOL, functional capacity, and anemia?

There was no statistically significant difference between groups for the study drug on the physical and mental summary scales of the SF-36 over time points two to four. The means of the intervention and control groups were similar in each of the subscales, summary, and total scores of the FACT-An. Quality of life and FACT-An anemia/fatigue subscale did improve in both groups over time, which was expected with cardiac revascularization and recovery. The between-group differences were not statistically significant for anemia on both measures of Hgb levels and mean FACT-An subscales between discharge and twelve weeks.

Functional capacity was evaluated using the 6MWT, and there was no significant difference between study groups on the 6MWT over time points two to four. However, participants with CHF had significant differences in mobility ($p = 0.03$). This result corresponded with CHF patients' experience of decreased muscular strength and endurance as part of their disease process — limiting functional capacity in the early postoperative period (Arena, Cahalin, Borghi-Silva & Phillips, 2014). Impaired mobility is common following CABG surgery and was confirmed in this study. During the early postoperative phase, CABG patients are on bedrest initially and experience systemic deconditioning effects, including muscle weakness (Winkelman, 2009). The consequence of these effects is immobility, affecting functional outcomes (Winkelman, 2009).

Previous studies reported similar results to this study, indicating a decrease in mobility at discharge, followed by a progressive increase in meters walked following discharge. Prior to discharge, deterioration in the distance walked following surgery could be due to systemic deconditioning effects, including muscle weakness, increased incisional pain, and prolonged respiratory issues, which could be caused by surgical trauma. Following discharge, participants may maintain activity by attending a cardiac rehabilitation program or a walking program. Physical activity levels increased, progressively from discharge to 12 weeks post-discharge on the PCS subscale measures of the SF-36, which were self-reported and may reflect social desirability rather than actual activity levels (Ware & Sherbourne, 1992). Over 50% of participants were married; therefore, the spouse could provide encouragement and companionship for physical activity.

Anemia was measured by both serum Hgb levels and using the anemia/fatigue subscale of the FACT-An. Hgb level was non-significant for the study drug between study groups ($p = 0.75$) or among covariates but was significant ($p < 0.001$) from time points two to four. There was no statistically significant difference between groups for the study drug for the subscale anemia/fatigue ($p = 0.051$) either. Results using the anemia/fatigue subscale may have achieved significance with a larger sample size permitting sub-group analysis.

The means for each study group were similar for the Hgb levels; however, there was a decrease in the means of Hgb level at discharge. This decrease in Hgb level could be related to surgical blood loss and hemodilution (dilution of a patient's circulating blood volume with intravenous fluids) (Partridge, Harari, Gossage, & Dhesi, 2013). The

surgical inflammatory response can cause a decrease in the GI iron uptake and a blunted erythropoietic response (Partridge et al., 2013). This inflammatory response can impact both iron metabolism and red cell production. These factors can further contribute to postoperative anemia.

Other studies have reported a similar lack of significance with postoperative oral iron therapy to increase Hgb levels and attribute the lack of response to increased surgical inflammation and a decreased absorption in the GI tract (Muñoz, Gomez-Ramirez & Campos, 2014; Muñoz et al., 2017). Once the inflammation subsides and healing is accomplished, iron metabolism and red cell production should improve. This may indicate a need for a longer post-operative time period for future investigations of oral iron therapy for POF in CABG patients.

The Anesthesia International guidelines (2017) and Seville consensus document (2013) strongly recommend that oral iron supplements should not be prescribed immediately postoperatively to treat postoperative anemia GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) 1B recommendation. (Leal-Noval et al., 2013; Muñoz et al., 2017). Several RCTs evaluated the effects of oral iron versus placebo on postoperative anemia in orthopedic and cardiac surgery patients and concluded there were no significant differences in red cell mass and iron stores between study groups (Crosby et al., 1994; Leal-Noval et al., 2013; Mundy et al., 2005; Parker, 2010). Therefore, for this study, participants were started on oral iron at discharge, which was approximately one week after surgery, and the surgery-induced inflammation should have resolved at that point. It is possible that the oral iron may have

been started too early, according to the above guidelines. The oral iron may need to be started at a later date, possibly as late as six weeks post-surgery.

5.9 Medication Adherence

Question 3: To what degree do patients taking oral iron adhere to the prescribed medication? In this study, two interesting results were found related to medication adherence. First, adherence among participants in both the control and intervention groups was high, compared to reports of adherence for iron therapy on the broader population (Arcangelo & Peterson, 2006; Swerdlow, 1992). However, it is essential to note that there were early dropouts in the intervention (37%) and control (47%) groups. Secondly, there was no significant difference between study groups in medication adherence or reported side effects. For the purposes of this study, adherence was defined as taking greater than 80% of the study medication (Brown & Bussell, 2011; Haynes et al., 1980; Osterberg & Blaschke, 2005; Lee et al., 2007). The adherence rate for those completing the study drug regimen was 91% in the control group, and 97% in the intervention group. Even though there was a high adherence rate for the participants that took the medication, there was no significant difference in adherence between the oral iron and the placebo groups ($p = 0.30$).

There are several possible reasons for adherence rates, which include once-daily dosing and the short duration of the study drug. Participants may also have been drawn from a population of patients who were greatly invested in their recovery from major cardiac surgery and thus more motivated to be adherent. Participants reported that the primary reason for non-adherence was due to GI side effects, but, interestingly, more GI side effects were reported by the control (placebo) group. Previous studies of oral iron

supplementation revealed a 25% nonadherence rate related to GI side effects and long-term iron use (Gereklioglu et al., 2016; Swerdlow, 1992; Vaucher et al., 2012). Additionally, the minimal presence of side effects in study participants may be attributed to the type of oral iron used, and the short duration of therapy. These two factors may also account for the high rate of adherence. Early attrition rates may be attributed to lingering GI upset following surgery.

The most common side effect experienced by participants in this study was constipation (20%), followed by diarrhea (18%). Notably, control group participants (32) reported experiencing heartburn that they attributed to the study medication, while only one participant from the intervention group experienced heartburn. Similarly, 50% more control participants experienced diarrhea compared to the intervention group (8 versus 4), respectively. This may illustrate how participants can attribute side effects to a study medication that can also be related to other factors. Postoperatively, CABG patients have trouble distinguishing between postoperative symptoms and the side effects of a new medication, which could result in medication non-adherence (Schultz et al., 2011). This illustrates the value of the inclusion of communication and feedback loops in the SMT to alert clinicians to the importance of patient education related to medication and postoperative recovery. Finally, it is important to note that 41 (62%) of the 64 participants who completed the list of study drug side effects did not report experiencing side effects. The oral iron (Feramax.com, 2019) that was used in this study is reported to have fewer GI side effects, and this may account for greater medication adherence. For this study, we investigated the impact of taking oral iron to address the subjective experience of POF. Results suggest that this is a low-risk therapy that resulted in a very

high level of adherence and no significant difference in side effects between the study and control groups.

5.10 Study Strengths

There are several strengths of this study, including originality, design, and advancing knowledge related to the use of oral iron in clinical practice. At the time of writing, no other published RCTs were uncovered in ongoing reviews of the literature that examined an oral iron intervention to decrease fatigue following CABG surgery.

The study was designed to directly compare two interventions (placebo and study medication) to establish superiority. The CONSORT 2010 statement was adhered to throughout the study and supported the design, conduct, and comprehensive reporting of results. Participants were successfully randomized to each of the two study groups, which balanced the risk factors and/or confounders between the treatment arms. This balance reduced the potential impact of selection bias on the study outcomes. The sample appears to be representative of the target population of CABG patients referred for surgery to the study hospital.

The study results indicated that the instruments chosen were appropriate because all of the outcome measures were aligned within the study–i.e., none of the measures produced results that were internally inconsistent with the overall results of the study. No single instrument produced results that were not aligned with results obtained from other measures. So overall study design was sound.

Another strength was the use of multidimensional POF instruments that had demonstrated strong psychometric properties in previous research and which had been used in studies that related to the research questions (Paddison et al., 2006; Nostdahl et

al., 2016). The secondary outcomes of fatigue, QOL, and anemia were measured with valid and reliable instruments with good reported psychometrics.

Finally, participants in the current study reported a high level of adherence to their study medication, which was supported by the end of study pill counts. Together, these factors indicate several strengths despite oral iron attrition rates.

5.11 Limitations of the Study

There were several limitations in the current study, including recruitment, retention, and generalizability. The sample was collected from a single hospital located in a regional catchment area. The sample may or may not be considered representative of the population of all CABG surgery patients. Further, the size of the sample, underrepresentation of women, and lack of diversity within it (although the sample was arguably representative of the Nova Scotia population from which it was derived) did not permit subgroup analysis that might have yielded information on which participants might have differentially benefited from the intervention. This affects the generalizability of the study to other populations of CABG patients. The results of the study can guide future studies on the phenomenon of POF in CABG patients and inform future studies with other surgical groups.

The inclusion criteria were amended during the study to comply with new evidence on the standard of care, thus increasing recruiting opportunities. Eligibility criteria were followed for the study, but recruitment may have been affected by surgeon bias. Potential bias by surgeons in explaining the study treatment options to potential participants can change attitudes toward enrolling in a study and on study retention. Exclusion criteria minimized some of the confounding variables but did not control for

all variables that may have contributed to fatigue. Furthermore, the participants' knowledge of the study may have influenced their expectations of the outcome.

At the time during which the study was being conducted, there was competition with other studies for participants, and this led to slower than desired recruitment. Despite the duration of the data collection period (July 2015 to February 2018), 121 participants were recruited based on the power calculation of 100. Though the IIT approach was utilized, missing data were a challenge during analysis. Replication of this study should aim for a larger, more diverse sample, and draw upon another surgical population to increase the enrollment of women and under-represented ethnic and cultural populations.

In this study, there was a low return rate of participants for the 6MWT, an objective measure that required participants to complete the walk test at the hospital. Patients were restricted from driving during the first six to eight weeks after surgery, which prevented some participants from returning for their follow-up visit and completing the 6MWT. In the study sample, the confidence interval was wide among the between-group differences, which precluded conclusions from being made. Alternately, self-administered questionnaires may have provided some information on determining functional capacity. Future studies may want to consider the relative value of including this measure.

A further limitation lies in the reliance on self-report methods to assess study outcomes. These are susceptible to social desirability, self-report bias, and participant burden. A few items in the scales may have been considered too personal (e.g., sexual and intimate experiences) for some participants. While paper-based questionnaires

allowed participants to complete them at home, on their own time, the paper format may have limited the return/ response rate (because of the requirement to mail back questionnaires) and contributed to the amount of missing data. A computer-based format may have provided participants with a faster and easier method of completing the surveys. Prompts to address missing data could be added, and this approach could even include a self-produced video of the 6MWT with appropriate instruction. It would not, however, address the problem of return visits for laboratory measures such as serum Hgb. The geographical distance from the study centre prevented some participants from returning for their follow-up visits, and this contributed to missing data. Had the study been funded, home visits would have been added to the inclusion criteria and enhanced data collection and reduced missing data.

Finally, 39% of participants withdrew following time point two, which impacted the ultimate sample size for analysis, the ability to detect group differences, and the generalizability of results to other surgical populations.

5.12 Implications for Theory

The study results support the use of the SMT to study POF in CABG patients and confirmed that the modifications related to communication and feedback loops, as recommended by Newcomb (2010), might enhance its relevance. The fatigue trajectory can vary along the treatment continuum, and the aspect of time is not specified in the SMT theory. In the symptom management strategy dimension, time refers to when the study drug was delivered (Dodd et al., 2001). It is logical to think symptom resolution will be the desired outcome; however, the theory was designed to acknowledge that not all symptoms can be completely alleviated, particularly in individuals with chronic

illnesses where clinicians and patients strive for the highest level possible of symptom relief. The SMT, therefore, accounts for variability over time in the recovery process (Dodd et al., 2001; Larson et al., 1994).

The results of this study support the SMT outlining fatigue as a complex and multifactorial construct, and the selection of a single factor for investigation may have impacted outcomes for this study. Only adding an iron intervention may have limited the efficacy of the intervention if potentiating interventions might have been required to achieve a statistically significant result (e.g., supervision of mobility or management of undesirable medication side effects). A multimodal intervention may be required to effectively improve POF. The results of the study will contribute to existing knowledge relating to the application of SMT in the management of postoperative symptoms. Future refinement of the SMT for research in surgical populations may increase the understanding of its usefulness.

5.13 Implications for Research

This research was conducted as a doctoral thesis project with limited funding, time, and resources. The study was limited to CABG patients admitted to a tertiary, regional referral centre in Maritime/eastern Canada. The sample reflects the relative homogeneity of the regional population and of persons referred for this type of surgery, which may affect generalizability to the wider population of CABG patients. Consequently, replication of this study among other surgical populations and other centres is recommended to validate this study's results. The application of SMT to future studies should include the recommended revisions to the theory for theory testing.

The current climate of postoperative recovery involves a shorter length of hospital stay and an expectation of the patient to achieve their return to independence in daily activities that may not be realistic. The burden of patient care has shifted from the hospital to the community setting, with earlier discharge and limited discharge education about potential complications, adverse symptoms, and cardiac management. Patients and family caregivers need ongoing healthcare support, especially people in rural areas where they may have limited access to ongoing support and supervision by health professionals (nursing, physiotherapy) during recovery. Telehealth and nurse telephone advice lines may provide opportunities for remote consultation, teaching, and support, or computer applications could provide patients in rural areas with improved access to nurses, providers, and hospitals. Patients could communicate with a healthcare provider in a timely manner and receive appropriate clinical services. Researchers examined a symptom management telehealth device to assess and provide strategies to manage POF and found a significant reduction in fatigue compared to standard care at six weeks (Barnason et al., 2009; Zimmerman & Barnason, 2007). These potential resources should be further researched to determine if they add value.

According to the recent review by Houston et al. (2018), no new RCTs examining the effect of oral iron with a primary outcome of fatigue scores have been reported. The participants in two studies of oral iron therapy for fatigue (Verdon et al., 2003; Vaucher et al., 2012) were all premenopausal women with iron deficiency. In this study, women were underrepresented in the sample and could not be compared. CABG patients tend to be drawn from and an older (postmenopausal) population. This surgical population also reported more co-morbidities than participants described in previous studies. This points

to a need for further research on the administration of oral (or parenteral) iron with a sample drawn from a wider population of women. Similarly, this study sample was drawn from a relatively homogenous population, and there is a need for research that specifically recruits a more diverse sample. This will support subgroup analysis to determine if there are population subgroups that would differentially benefit from post-operative oral iron therapy to manage fatigue.

Including additional time points to reflect early postoperative recovery (within one month) and late recovery (six months) might yield more information on when oral iron might be more or less effective. Further examination of the phases of recovery related to fatigue over one year might provide insight into the relative effectiveness of iron therapy for POF and determine the trajectory of fatigue.

Other research methodologies could add to our knowledge of POF and its management. Future research coupling a qualitative approach with a quantitative study (mixed methods) could support a more comprehensive approach to the investigation of POF and interventions. Qualitative research focusing on the description of the individual's fatigue experience during postoperative recovery and examining the caregiver's (nurse or significant other) perception of the patient's fatigue could provide further insight into the symptom and effectiveness of selected interventions. Taking into account other variables such as culture, ethnicity, sex, and age, as well as other surgical groups, could enhance future studies. As always, the nature and type of research questions posed will determine the ultimate design and methods for the conduct of future studies.

At this time, while there are newer instruments that have been developed to assess

POF (e.g., Nostdahl et al., 2016; Paddison et al., 2011), they have not been widely adopted in clinical research. Instruments used in this study may require refinement or revision based on these newer instruments. The development and testing of a simple, valid, and reliable fatigue screening tool to identify at-risk surgical patients would be useful. Screening using the tool could be conducted at the preadmission clinic or with new admissions to the hospital for patients awaiting surgery. These at-risk patients could receive further evaluation during hospital admission and treatment for POF. There is a need to investigate why POF screening tools have not been adopted in practice.

Finally, the conduct of a systematic review of the literature could lead to the development and implementation of a best practice guideline for the management of POF. Such a review could use principles derived from both the Cochrane and the Joanna Briggs Institute methodology to explore the full range of study methods and results in both published and gray literature. A well-researched and evidence-informed, inter-professional clinical practice guideline is a standardized way to ensure patients are receiving effective fatigue management, and guidelines facilitate improved understanding of fatigue among clinicians.

Taken together, results obtained from this study point to numerous indications and opportunities for further research to address this complex clinical problem. Learnings from this study can inform the topics, design, and approaches to future research on the phenomenon of POF and interventions to address a troublesome symptom that can negatively impact recovery.

5.14 Implications for Practice

Managing fatigue symptoms following surgery can be both challenging and burdensome for patients and clinicians. Prior research indicates that fatigue is prevalent following CABG surgery and that it is often overlooked for its impact on recovery. There is a need for nurses to have access to a fatigue screening tool, as suggested above, in implications for research. For example, Christensen et al. (1982) developed a visual analog scale (1-10) to assess POF. The visual analog scale is simple and takes little time to complete; however, the scale does not include multidimensions of the fatigue experience (Schwartz, Jandorf, & Krupp, 1993; Smets et al., 1995; Zargar-Shoshtari & Hill, 2009). This tool, in conjunction with knowledge gained over the intervening years, could be adapted for clinical use. Barriers and facilitators for adoption in practice should be identified and addressed by clinical leaders.

Development and adoption of clinical practice guidelines for health professionals (medicine, nursing, and other clinical team members, such as physiotherapy) to support evidence-informed assessment and management of POF are required. The guideline would include risk assessment and symptom recognition of fatigue after surgery, which could help patients cope with the symptoms and manage them during the recovery process.

Supporting clinicians to understand the presence of POF and related factors is required to mitigate the symptom. Clinical leaders can advocate for the adoption of screening tools and interventions, such as scheduled rest periods during hospital stays, noise level management, and other strategies to promote sleep. Nursing educators can support nurses to learn about how to assess and monitor changes in fatigue levels in early

recovery in hospital. Early POF management strategies are not usually addressed in written discharge instructions, and further patient education should be incorporated in discharge planning and teaching. As part of routine discharge planning, patients are educated by nursing and pharmacy personnel on how to manage post-operative symptoms and medication side effects. More education is required to encourage early and ongoing medication adherence and the importance of sleep and rest as well as exercise to promote recovery and sleep. This education could provide a better symptom experience for the patient post-discharge and potential reduction in hospital readmissions or clinic visits.

Incorporating post-operative recovery advice related to fatigue to the suite of services offered by 1-811 Nurse Advice telephone lines is another clinical practice opportunity. The addition of reading level appropriate patient education materials in the hospital setting and the use of personal computer applications to include health information and services should be considered. Engaging community pharmacists as part of the health team is desirable since they are the first contact with the patient or family member when picking up post-discharge prescriptions. Reviewing patient handouts for education/reading level appropriateness could be carried out with the provincial pharmacy association.

Postoperative adverse GI events, such as diarrhea and constipation, as found in this and other studies, need to be managed. Discharge materials highlighting preventive and management strategies for such adverse events are essential to optimal self-management and recovery.

5.15 Conclusions

Fatigue is a complex, multidimensional phenomenon that is common in the CABG population. This distressing symptom can negatively affect postoperative recovery. Postoperative fatigue has not been well researched compared to cancer-related fatigue and fatigue associated with other chronic diseases. This RCT represents a novel approach to explore the effects of administration of a single intervention (oral iron) on fatigue following CABG surgery over 12 weeks. Although the study results were not statistically significant for overall oral iron effect, nevertheless, the results contributed knowledge related to POF in CABG patients.

For example, the study built on existing knowledge related to POF and our understanding of the construct of fatigue and related theoretical constructs, which have implications for patients, nurses, and other health care professionals. The study results confirm a previously identified recommendation to modify the SMT to enhance its value for both research and practice by including a communication component among all dimensions as well as a feedback loop from outcomes to symptom experience. Increasing awareness of the fatigue construct may promote further research in the area of symptom management, and lead to incorporating strategies to decrease fatigue postoperatively, and improve QOL for patients at a critical time in their lives.

Adherence rates in this study were exceptional compared to the general literature. These rates were attributed to once-daily dosing, minimal side effects, and time-limited medication duration. These results add to the medication adherence body of knowledge.

Further studies are recommended using a larger sample size with greater representation from rural versus urban, women, and ethnically diverse patients. The

dissemination of these results will provide surgeons and nursing staff with knowledge related to the importance of fatigue recognition and screening at-risk patients to enhance recovery.

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APPENDIX A: HEALTH CANADA APPROVAL LETTER

2013/10/02 2:05:42 PM

Health Canada / Santé Canada

NATURAL HEALTH PRODUCTS DIRECTORATE

Notice of Authorization

Company Code. 32903
File No. 192928
Submission No. 192928

October 2, 2013

Dr. Blaine Kent
5th Floor Rm 5607 HI Site
1796 Summer St.
Halifax, NS
B3H 3A7

Dear Dr. Kent

Re: CLINICAL TRIAL APPLICATION for FeraMAX
Natural Health Products Regulations Section: 67

The Natural Health Products Directorate, is pleased to inform you that the information and material provided to support the above Clinical Trial Application , have been assessed and we have no objection to your proposed study. Please consider this as your notice of authorization to sell or import this natural health product for the purposes of this clinical trial in Canada.

Please note that you are responsible for ensuring the appropriate considerations are taken into account in order to comply with the requirements set out in the *Natural Health Products Regulations* (NHPR) and its associated guidance documents. For more information on the expectations and approaches relating to quality requirements and Good Manufacturing Practices for natural health products, please consult the *Quality of Natural Health Products Guide* and the *Good Manufacturing Practices* guidance document (http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/index-eng.php).

I would remind you of the necessity of complying with the *NHPR*, Part 4, in the sale of this product for clinical testing. In addition, the Regulations (Part 4) impose responsibilities, including commencement notice, record keeping and reaction reporting, on those conducting clinical trials. Please ensure that all systems are compliant in order to meet these responsibilities.

Please note that the mandatory reporting requirements of the NHPR for Serious Adverse Reaction (SARs) that have occurred in Canada will continue to be applied by the Therapeutic Products Directorate (TPD). However, we request that you submit all SAR case reports using the Council for International Organizations of Medical Sciences (CIOMS) I Form. This preferred form can be downloaded and printed

2936 RUE BASELINE RD
A.L. 3300B
OTTAWA, ONTARIO, K1A 0K9

at http://www.cioms.ch/index.php/cioms-form-i. The SAR report should be faxed to the following number: (613)941-2121.

You are also reminded that all clinical trials should be conducted in compliance with the Health Canada Guidance for Industry: Good Clinical Practice: Consolidated Guideline ICH Topic E6.

Should you have any questions concerning this letter, please contact the submission coordinator at nhpd-cta.dec-dpsn@hc-sc.gc.ca.

Yours sincerely,

Bruce Randall
A/ Director, Bureau of Product Review and Assessment
Natural Health Products Directorate
2936 Baseline Rd. (A.L. 3302C), Ottawa, ON K1A 0K9

Canada

APPENDIX B: REB APPROVAL LETTER

Capital Health

Capital Health Research Ethics Board
Centre for Clinical Research, Room 118
5790 University Avenue
Halifax, Nova Scotia, Canada B3H 1V7
Phone: 473-6436 Fax: 473-5620

February 10, 2014

Dr. Blaine Kent
Pain Management and Perioperative Medicine
5th Floor, Room 5607, Halifax Infirmary
1796 Summer Street
Halifax, NS B3H 3A7

Full Board Review
Full Approval Letter
(December 16, 2013 - December 16, 2014)

ATTENTION: Heather Mingo

Dear Dr. Kent:

RE: A Phase III Randomized Double Blind Placebo-Controlled Clinical Trial to Assess the Effects of Fermamax when Administered Orally Once a Day on Postoperative Fatigue Levels in Patients Following Elective Coronary Artery Bypass Graft Surgery

REB FILE #: CDHA-RS/2014-217

Thank you for your response dated February 7, 2014 received on **February 7, 2014** regarding your proposed study.

Document Name	*Version*	*Date*
Cover Letter	n/a	2014/02/07
Letter of Support from the Principal Investigator's Department/Division/Program/Service: ***Signed and dated by Dr Romesh Shukla***	n/a	2013/11/29
Ethics Approval Submission Form	n/a	2014/02/07
Consent Form	Version 2.0	2014/01/05
Research Team Contact Page	Version 2.0	2014/02/07
Advertisement	Version 2.0	2014/02/03
Protocol	Version 2.0	2014/02/07
Principal Investigator's CV – Blaine Kent	n/a	2014/02/07

I have reviewed these documents on behalf of the Research Ethics Board (REB) and note that all requested changes have been incorporated.

I am now pleased to confirm the Board's full approval for this research study, effective today. This includes approval / favourable opinion for the following study documents:

Document Name	***Version***	***Date***
Researchers Checklist for Submissions	n/a	2013/11/28
Letter of Support from the Principal Investigator's Department/Division/Program/Service: ***Signed and dated by Dr. Romesh Shukla***	n/a	2013/11/29
Letter of Support from Collaborating CDHA Department/Division/Program/Service: ***Signed and Dated by Dr. Greg Hirsch***	n/a	2013/06/25
Health Canada No Objection Letter • Notice of Authorization - Re: Clinical Trial Application for FeraMax Signed and Dated by Bruce Randall	n/a	2013/10/02
Ethics Approval Submission Form	n/a	2014/02/07
Consent Form	Version 2.0	2014/01/05
Research Team Contact Page	Version 2.0	2014/02/07
Advertisement	Version 2.0	2014/02/03
Supporting Materials • FACT-AN	4	2007/11/16
Supporting Materials - Identity-Consequences Fatigue Scale	1	2013/06/28
Supporting Materials - The SF-36 Health Survey	n/a	Copyright
Protocol	Version 2.0	2014/02/07
Product Information • FeraMAX	n/a	2012/11/22
Principal Investigator's License to Practice in Nova Scotia	n/a	Expiry Date: December 31, 2013
Principal Investigator's TCPS 2: Core Certificate	n/a	2012/01/11
Principal Investigator's CV	n/a	2014/02/07

Continuing Review

1. **The Board's approval for this study will expire one year after the date of full Board review (December 16, 2014).** To ensure continuing approval, submit a Request for Annual Approval to the Board 2-4 weeks prior to this date. If approval is not renewed prior to the anniversary date, the Board will close your file and you must cease all study activities immediately. To reactivate a study, you must submit a new Initial Submission (together with the usual fee) to the REB and await notice of reapproval.
2. Please be sure to notify the Board of any:

- Proposed changes to the initial submission (i.e., new or amended study documents or supporting materials),
- Additional information to be provided to study participants,
- Material designed for advertisement or publication with a view to attracting participants,
- Serious unexpected adverse reactions experienced by local participants,
- Unanticipated problems involving risks to participants or others,
- Sponsor-provided safety information (e.g., reports of serious unexpected adverse reactions, changes to the investigator's brochure / product monograph, DSMB reports)
- Additional compensation available to participants,
- Upcoming audits / inspections by a sponsor or regulatory authority,
- Premature termination / closure of the study (within 90 days of the event).

3. Approved studies may be subject to internal audit. Should your research be selected for audit, the Board will advise you and indicate any other requests at that time.

Important Instructions and Reminders

1. Submit all correspondence to Ethics Coordinator, Amanda Henneberry at the address listed at the top of this letter (do not send your response to the REB Chair or Co-Chair).
2. Be sure to reference the Board's assigned file number, CDHA-RS/2014-217, on all communications.
3. Highlight all changes on revised documents, and remember to update version numbers and/or dates.
4. Print and electronic advertisements are to be submitted to the Audio Visual Department for placement in the appropriate Capital Health template. Complete a Request for Graphic Services form (Form CD 0019, available on the Intranet) and fax to Audio Visual Services together with the REB approved advertising materials and confirmation of REB approval.

Best wishes for a successful study.

Yours very truly,

David Macdonald, MD, FRCPC
Co-Chair, Research Ethics Board

This statement is in lieu of Health Canada's Research Ethics Board Attestation:
The Research Ethics Board for the Capital District Health Authority operates in accordance with:
- *Food and Drug Regulations, Division 5 "Drugs for Clinical Trials Involving Human Subjects"*
- *Natural Health Products Regulations, Part 4 "Clinical Trials Involving Human Subjects"*
- *ICH Good Clinical Practice: Consolidated Guideline (ICH-E6)*
- *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*

/jm

APPENDIX C: CLINICAL TRIAL CONSENT FORM

CONSENT TO TAKE PART IN A RESEARCH STUDY
Participant Information

STUDY TITLE: A Phase III Randomized Double-Blind Placebo-Controlled Clinical Trial to Assess the Effects of FeraMax when Administered Orally Once a Day on Postoperative Fatigue Levels in Patients following Elective Coronary Artery Bypass Graft Surgery

CLINICAL STUDY REGISTRATION NUMBER: NCT01912261

PRINCIPAL Dr. Blaine Kent
INVESTIGATOR: 5th Floor Rm5607 A
Department of Anesthesia, Pain Management and Perioperative Medicine
Queen Elizabeth II Health Sciences Centre (QEIIHSC) Halifax Infirmary Site
1796 Summer St, Halifax, NS B3H3A7
Telephone: 1 902 222 9992

ASSOCIATE Heather E. Mingo, RN, Ph.D. (c)
INVESTIGATORS: 5th Floor Rm #5425
Department of Anesthesia, Pain Management and Perioperative Medicine
QEIIHSC Halifax Infirmary Site
1796 Summer St, Halifax, NS B3H3A7
1 902 473 3117

Myron Kwapisz, MD
Department of Anesthesia, Pain Management and Perioperative Medicine
QEIIHSC, Halifax Infirmary Site
5th Floor Rm5452B
1796 Summer St. Halifax, NS B3H3A7
Phone 902 473 7886

Dr. Jean Francois Legare
Dept. of Cardiovascular Surgery
QEIIHSC Halifax Infirmary Site
2nd Floor, 1796 Summer St, Halifax, NS B3H3A7
1 902 473-7597

STUDY SPONSOR: Dr. Blaine Kent

FUNDING AGENCY: BioSyent Inc., Dalhousie University

PART A.
Clinical Studies – General Information
1. INTRODUCTION

You have been invited to take part in a research study which is offered by Nova Scotia Authority (NSHA). 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.

Please read this carefully. Take as much time as you like. If you like, take it home to think about for a while. Mark anything you do not understand, or want to be explained better. After you have read it, please ask questions about anything that is not clear.

The researchers will:
Discuss the study with you
Answer your questions
Keep confidential any information which could identify you personally
Be available during the study to deal with problems and answer questions

We do not know if taking part in this study will help you. You may feel better. On the other ,hand, it might not help you at all. It might even make you feel worse. We cannot always predict these things. We will always give you the best possible care no matter what happens.

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

PART B.
2. WHAT IS THE PURPOSE OF THIS STUDY?

Normally surgery causes a stress to your body leading to inflammation. This inflammation can last a few days to weeks after surgery and can affect iron production of red blood cells in your body. This can result in feeling fatigued (tired), having low energy and being less active after surgery.

It is common practice for your doctor to prescribe oral iron supplementation therapy to treat your symptoms and increase the levels of iron and hemoglobin (low blood level) in your body. However, these prescribed therapies can have uncomfortable side effects that include nausea, upset stomach, diarrhea and constipation resulting in individuals stopping the oral iron early.

Oral iron supplement FeraMax® (now referred to as study product) may not have as many and less discomforting side effects and improve patients taking the study product as prescribed. The study product may increase the levels of iron and improve your blood level by producing more red blood cells sooner with less fatigue. However, it is unknown whether the study product influence red blood cell levels and fatigue-related activity. Thus the purpose of this study is to examine whether the study product would improve your recovery by making you less tired, increasing your blood level, improving exercise level.

3. WHAT IS BEING TESTED?

This product is not an experimental drug. It is an over the counter iron supplement to treat low iron and low blood level. You may have blood loss due to your surgery and we want to see if study product will improve patient fatigue and recovery.

4. WHY AM I BEING ASKED TO JOIN THE STUDY?

You are undergoing coronary artery bypass grafting surgery for the first time.

5. HOW LONG WILL I BE IN THE STUDY?

The study requires your participation for 12 weeks after you are discharged from the hospital.

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

This study is taking place at the QEII Health Science Centre. We plan to enroll 300 participants locally.

7. HOW IS THE STUDY BEING DONE?
This is a double-blinded placebo-controlled randomized single-center study. Randomization means that you will be assigned to either study product or placebo group. Your assignment will be by chance or like the flip of a coin. Blinding means that the research staff will not know which medication you are receiving. The medication and placebo are identical. The medication will be provided to you on your discharge day from the hospital. Placebo refers to a harmless pill that resembles the study product.
The study requires you to complete questionnaires, have blood tests done (7 ml of blood will be taken from your vein), perform a walking test and keep a symptom diary of your side effects of the medication. These tests will be performed when you are first seen in the preadmission clinic or on the nursing unit, on discharge from the hospital, six weeks and at 12 weeks when you complete your treatment. The tests will take about 1 hour to complete at each visit. The total amount of time that the entire study will take to complete will be 12 weeks.

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

If you want to be in this study and sign this 'consent' form, you will have to have some tests done to see if you can take part. This is called "screening". It is possible that the tests will show that you can't be in the study. There may be other tests done as part of usual care. Your research team will discuss these with you.

SCREENING
The research study screening tests that will be done are:
Review of your Health Record
Medical History
Laboratory tests

STUDY
We will do the following as part of the study:

In preadmission clinic or on the nursing unit, you will be asked to complete 3 questionnaires, have blood drawn and a walking test. The questionnaires tell us about tiredness, low blood level related symptoms and quality of life. For the walking test, we will measure how far you walk in 6 minutes. At discharge and at six weeks post discharge, we will repeat these tests and blood work again. After you finish the treatment, we will repeat the blood work, questionnaires, count any pill that were not taken and any side affects you had from the treatment.

FOLLOW UP
After surgery, your progress will be followed for 3 months after discharge. During your six week follow-up clinic visit and at the completion of your treatment we will have blood work drawn, complete the 3 questionnaires and walking test. The questionnaires and walking test are not part of standard of care. The blood work is part of standard of care at your last visit.

Of course you may ask not to have further tests done or to participate in any additional trial procedures at any time. Also, you do not have to follow any of these procedures following withdrawal from the research.

It is important that you tell the Principal Investigator about any drugs or medicines you are taking or wish to take. You must also tell the Principal Investigator about anything unusual that is happening with your health. This includes any medical problems that seem to be getting worse. If you have to see another doctor or have to go to a hospital, you must let the doctors know that you are in a research study. You should also tell your own doctor as quickly as possible, for your safety.

This table tells you what happens at each visit

Table Assessment

Assessments	Preoperative Baseline	Postoperative Discharge /Randomization	Post Testing Seven to Ten days post Discharge and Monthly Follow up	Six Week Follow-up	Study End 12 Weeks +/-1 week
Consent	X	X[2]			
Inclusion Criteria	X	X[2]			
Exclusion Criteria		X			
Study Enrollment	X				
Randomization		X			
Identity Consequence Fatigue Scale (ICFS)	X	X		X	X
Short Form-36 (SF-36)	X	X		X	X
Functional Assessment Cancer Therapy-Anemia (FACT-An)	X	X		X	X
6Minute Walk Test (6MWT)	X	X		X	X
Laboratory Tests	X[1]	X[1]		X[1]	X[1]
Medication Dispensed		X			
Collecting and reviewing Diary of Adverse Events					X
Follow up telephone calls Medication and diary reminders			X		
Serious Adverse Events collection			X		X

1. Standard of Care
2. Confirmation of Continued Eligibility

9. ARE THERE RISKS TO THE STUDY?

There are risks with this, or any study.

To give you the most complete information available, we have listed many *possible* risks, which may appear alarming. We do not want to alarm you but we do want to make sure that if you decide to try the study, you have had a chance to think about the risks carefully. Please also be aware that there may be risks in participating in this study that we do not know about yet.

The study product passes through the stomach to the bowel without any contact with the stomach. This product can minimize side effects (nausea, vomiting, abdominal pain, heartburn, diarrhea and constipation)

(FeraMax.com, 2013). A very serious allergic reaction to this product is rare. However, seek immediate medical attention if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, and trouble breathing.

Common risks (1 or more out of every 100 people but less than 1 out of every 10 people have experienced the following):

- Diarrhea
- Constipation
- Abdominal pain/Heartburn
- Nausea/Vomiting
- Allergic Reaction

You may notice none, some, or all of these side effects and they may be mild, moderate, or severe. Many side effects disappear after treatment is stopped. The Principal Investigator may prescribe medications to ease the discomfort you may experience if any of these side effects occur. If any severe reaction to the study product occurs, the Principal Investigator may interrupt or discontinue the study product treatment.

The Principal Investigator will be checking you closely to see if any of these side effects are occurring.

As the study product is experimental, there may be side effects that are not yet known. You must tell the Principal Investigator or a member of the research team about any new symptoms you experience.

BLOOD SAMPLE

You may experience some temporary discomfort when the blood sample is taken. There is a small risk of bruising, infection or swelling at the site where the needle is inserted, and some people may feel faint or dizzy.

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.

The study product may interfere with medications, both prescribed and over the counter that you are currently taking. Tell the Principle Investigator if you use any of the following products: antacids, methyldopa or other iron-containing products (e.g., multivitamins). Iron supplements can decrease the absorption of drugs such as antibiotics, bisphosphonates (e.g., alendronate), cefdinir, chloramphenicol, levothyroxine, levodopa, and quinolone, the doses of these medications should be taken as far as possible from your doses of iron. This product may interfere with certain laboratory tests (including testing for blood in stool), possibly causing false test results.

You should ask the Principal Investigator if the study product could interfere with your medications before consenting to be in this study. You should also consult with the Principal Investigator or members of the research team before taking any new medications. It is recommended that you do not use additional natural health products indicated for fatigue during the study.

10. ARE THERE OTHER CHOICES?

You do not have to be in this trial to get care for your problems. If you choose not to participate you will still receive the best possible care and if you require a blood transfusion for your low blood and fatigue you will be given one. Iron pills are not routinely ordered after surgery

New *drugs* become available for this sort of condition at different times and in different parts of the world. Like many other hospitals, we do not feel it is helpful to test more than one experimental treatment for the

same condition at the same time in the same person. This could even be dangerous so you will not receive two experimental therapies at the same time.
You are free to seek other opinions or choices in other hospitals or cities if you wish.

11. WHAT HAPPENS AT THE END OF THE STUDY?

After the study is completed, if needed, the study product is available over the counter and the participant is responsible for paying for the product.

12. WHAT ARE MY RESPONSIBILITIES?

As a study participant you will be expected to:

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

13. CAN I BE TAKEN OUT OF THE STUDY WITHOUT MY CONSENT?

Yes. You may be taken out of the study by Health Canada, Principal Investigator or the Research Ethics Board at any time, if:

- The treatment does not work for you (the fatigue (tiredness) gets worse);
- You do not follow the directions of the Principal Investigator;
- In the opinion of the Principal Investigator 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;
- You become pregnant

The NSHA Research Ethics Board, Health Canada or the Principal Investigator has the right to stop patient recruitment or cancel the study at any time.
You will be told about the reasons why you might need to come out of the study.

14. WHAT ABOUT NEW INFORMATION?

It is possible that new information may become available while you are in the study about some new treatment for your condition. 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.

15. WILL IT COST ME ANYTHING?

Compensation
You will not be paid to be in the study. There is no charge for the study product or for any tests. You may have to pay for other drugs (depending on your drug plan) such as those prescribed to treat or prevent side effects.

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 in the study. In no way does this waive your legal rights nor release the Principal Investigator, the research team, the study sponsor or involved institutions from their legal and professional responsibilities.

16. 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. No identifying information (such as your name or hospital number) will be sent outside of this health care facility. 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 investigator may be required by law to allow access to research records. A copy of this consent form will be put in your health record. Your family doctor will be told that you are taking part in this study.

When you sign this consent form, you give us permission to:

- Collect information from you
- Collect blood samples

Access to Records

The study doctor and members of the research team will see health and study records that identify you by name. Other people, during visits to this health care facility, may need to look at the health and study records that identify you by name. These people might include:

- The Research Ethics Board and people working for or with the Research Ethics Board
- Health Canada
- Sponsor Representative

Use of Your Study Information

The research team will collect and use only the information they need to judge the safety and usefulness of the product.

You also allow the collection, reporting and transfer of your anonymous personal health information and data from the study to:

- Regulatory authorities within and outside Canada

The sponsor and companies working for and with the sponsor will use the information collected about you during the study, only for scientific research and/or drug development purposes.

This information will include your:

- Age
- Male or female
- Medical conditions
- Medications
- The results of tests and procedures you had before surgery and during the study
- Information from the study interviews and questionnaires

Your name and contact information will be kept secure by the research team in the Perioperative Blood Management office. It will not be shared with others without your permission. Information will be kept for at least 25 years as required by law.

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.

Information collected and used by the research team will be stored at the Halifax Infirmary site, Halifax, NS. The sub investigators are the people responsible for keeping it secure.

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

Your Access to Records

You may ask the study doctor to see the information that has been collected about you. You may ask to make corrections to this information by talking with a member of the research team. Since the study is "blinded", you cannot see this information until the study ends. This is to prevent either you or your doctor from knowing, which study treatment you received until the results are reported.

17. WHAT IF I WANT TO QUIT THE STUDY?

If you choose to participate and later decide to change your mind, you can say no and stop your participation in the research at any time. Your health records may be examined in connection with this study or further analyses related to it. If you decide to withdraw from this study by providing notice to the study doctor, your health records will only be made available as described above.

However the above agencies, including the sponsor, will only look at and use study related records up to the date of your withdrawal from the study, except where it is necessary to ensure that the study is scientifically reliable and to report side effects associated with the study medication as required by regulatory authorities. A decision to stop participating in the study will not affect your health care.

18. DECLARATION OF FINANCIAL INTERESTS

BioSyent, Inc. has provided an industry grant and the product for this study. The amount of payment is sufficient to cover the costs of conducting the study.

19. WHAT ABOUT QUESTIONS OR PROBLEMS?

For further information about the study call **Dr. Kent.** Dr. Kent is in charge of this study at this hospital (*he* is the "Principal Investigator"). Dr. Kent's work telephone number is (902) 222-9992. If you can't reach the Principal Investigator, please refer to the sub investigator Heather Mingo. Her telephone number is (902) 473-3117.

If you experience any symptoms or possible side effects or other medical problems, please let the Principal Investigator know immediately.

If you can't reach the Principal Investigator, or it is after regular business hours, speak to the sub investigator. The after hour's number is **(902) 233-1344.**

Please call the Principal Investigator or research coordinator the next business day to tell them about the possible side effects or other medical problems you experienced.

The Principal Investigator is **Dr. Kent**.
Telephone: (902) 222-9992

The Sub investigator is **Heather Mingo**
Telephone: (902) 233-1344

Your Research Coordinator is **Heather Mingo**.
Telephone: (902) 473-3117

20. WHAT ARE MY RIGHTS?

After you have signed this consent form you will be given a copy.

If you have any questions about your rights as a research participant, contact the **Patient Representative** at **(902) 473-2133**.

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

PART C.

1. CONSENT FORM SIGNATURE PAGE

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

A Phase III Randomized Double Blind Placebo-Controlled Clinical Trial to Assess the Effects of FeraMax when Administered Orally Once a Day on Postoperative Fatigue Levels in Patients following Elective Coronary Artery Bypass Graft Surgery

I have been given the opportunity to discuss this study. All of my questions have been answered to my satisfaction.

I agree that my personal health and study information may be used as described in this consent 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*	
_____	_____	/	_____ /		
Witness to Participant's Signature	Name (Printed)	Year	Month	Day*	
_____	_____	/	_____ /	_	
Signature of Investigator	Name (Printed)	Year	Month	Day*	
_____	_____	_____ /	_____ /	_	
Signature of Person Conducting Consent Discussion	Name (Printed)	Year	Month	Day*	

I Will Be Given a Signed Copy of This Consent Form

Thank you for your time and patience!

APPENDIX D: CASE REPORT FORM

CASE REPORT FORM
HALIFAX SITE

General Instructions for the Investigator and Research Coordinator
When completing this SOURCE, please:

- Use black ballpoint pen
- Ensure that all writing is clear and legible, preferably in block letters
- Use English language
- Make corrections by drawing a line through the incorrect item, which must remain legible
- Date and initial all changes
- Do not use correcting fluids

Time
Always use the 24 hour clock format

Date:
Use the date format indicated for the date fields. If a date or part of a date is unknown, please fill in as much as possible and **put UNK for what is unknown.**
Missing Data
If some information has been impossible to obtain, please cross out the field/box and explain briefly next to the field/box why this information is missing and add your initials and date.

Laboratory Results
Hemoglobin results are required before randomization

Medications
Medical History
Signatures
The following CRF pages must be signed by the Investigator:
Inclusion and Exclusion Criteria (Investigator)
Serious Adverse Events (Principal Investigator)
End of Study/Premature Termination (Principal Investigator)

CHECKLIST FOR SCREENING DATE: ____/_____/__201_____
(DD) (MMM) (YYYY)

Informed Consent:
Signatures ☐
Copy to Subject ☐
Eligibility Criteria
Reviewed ☐
Medical/Surgical History ☐
Medications ☐
Completion of Screening Tools ☐
Preop ☐

Surgeon: _Dr _ _____

Comments:_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Signature:_____
Date:_____

SCREENING DATE: _____/____/___201_____
(DD) (MMM) (YYYY)

SUBJECT INCLUSION CRITERIA

	YES	NO
1. Subject is 19 years of age and older	☐	☐
2. Subject is willing and able to give informed consent	☐	☐
3. Non Urgent, first time, coronary artery bypass grafting.	☐	☐
4. American Society of Anesthesia (ASA) physical status I-IV	☐	☐
5. Able to read and write English to the degree necessary to participate in interviews	☐	☐

If the answer to any of the above questions is "no**", DO NOT** enroll the subject. If the answers are "yes", proceed to the exclusion criteria.

Signature:_____

Date:_____

SUBJECT EXCLUSION CRITERIA

	YES	NO	
1. Had prior median sternotomy surgery			
2. Previous history noncompliance with oral medications			
3. Allergy to iron			
4. History of hematological disorders that are deemed clinically significant as per investigator's clinical judgment			
5. Received Clopidogrel within two days prior to surgery, greater than 81mg of Acetylsalicylic acid 24 hours prior to surgery, or have received "new oral anticoagulants" (e.g., Apixaban, Rivaroxaban , and Dabigatran) within the recommended preoperative exclusion period			
8.History of iron metabolism disorders e.g., known iron overload, hemochromatosis, porphyria			
9. Chronic fatigue syndrome (a condition that is distinguished from other types of fatigue by fatigue lasting more than six months and has at least four other symptoms (e.g., sleep disturbances, headaches, joint pain, and concentration difficulties) that could contribute to increased fatigue (Afari & Buchwald, 2003)			
11. History of Fibromyalgia			
12. Current diagnosis of depressive disorder			
13. History of Hypothyroidism includes uncontrolled thyroid disease (abnormal TSH or T4 at screening visit) as per the Investigator's clinical judgment			

14. Any other unstable conditions as per the Investigator's clinical judgment			
Contraindications to the six minute walk test			
15. Resting heart rate > 120 beats/min 10 min after rest (relative contraindications)			
16. Systolic blood pressure >180mm +/- Diastolic blood pressure > 100mm Hg (relative contraindications)			
17.Resting Sp02 <85% on room air or on prescribed level of supplemental oxygen			
18. Physical disability preventing safe performance			
☐ Inclusion/Exclusion criteria have been reviewed. ☐ Subject appears to meet inclusion/exclusion criteria of the study at this point. Subject does not meet inclusion/exclusion criteria of this study at this time point.			
Signature Date			
19.Patient taking iron supplementation ≤ 60 days before surgery and in the postop period			
20. A Hemoglobin greater than or equal to 120g/L at discharge			
21. Received erythropoiesis-stimulating agents (e.g., epoetin alfa and darbepoetin alfa) postoperatively to discharge			
22. Serum Transferrin saturation more than 50% at discharge			

If the answer to any of the above questions is "yes**", DO NOT** enroll the subject.

Signature:_____ Date:_____

Demographic and Health Data Form

Introduction: This form is divided into two sections, the first section is related to patient demographics and the second section is about your health. There is no right or wrong answers. Please check (√) the correct box. If you don't understand a question, please ask the investigator to explain the question.

DATE: **_ _ / _ _ _ / 201_ _**

(DD) (MMM) (YYYY)

Section 1: Patient Demographics

	Comments/Notes
Diagnosis	
Surgical Procedure	
Age	
Gender	
Weight Kg	
Height cm	
BMI	
Marital Status	☐ Single ☐ Married ☐ Divorced ☐ Widow ☐ Common Law ☐ Separated
Occupation	
Other, Specify	

Signature:_____

Date:_____

Residence

☐ 1. Nova Scotia ☐ 2. Living in HRM

☐ 3. Living outside HRM ☐ 4. New Brunswick

☐ 5. Prince Edward Island ☐ 6. Newfoundland

☐ 7. Other----------

Section 2: Health Related History

SCREENING MEDICAL & SURGICAL HISTORY

DATE: _____/_____/_201_____

(DD) (MMM) (YYYY)

Co-Morbidities	No History	Yes	Currently on Medication? (yes/no)
Congestive Heart Failure			
Valve Disease			
Myocardial Infarction			
Arrhythmia			
Musculoskeletal			
Hypertension			
Diabetes Mellitus			
Hyperlipidemia			
Kidney Disease			
Respiratory			
Signature:_____ _____	Date:_____		
Co-Morbidities	No History	Yes	Currently on Medication? (yes/no)
GERD/ Reflex			
Previous Heart Surgery			
Smoking			
Alcohol			
Other			

ALLERGIES:

_____

_____

_____

Medications currently taking

☐ 1. Aspirin	☐ 2. Diuretics
☐ 3. Beta Blockers	☐ 4. Nitrates
☐ 5. Calcium Channel Blockers	☐ 6. ACE inhibitors
☐ 7. Antidiabetic drug	☐ 8. AntiHyperlipidemic drug
☐ 8. Anticoagulant Drug	☐ 9. Antiplatelet drug
☐ 10. Antibiotic	☐ 11. Proton Pump Inhibitor
☐ 12. Cholesterol	☐ 13 Narcotics
☐ 14. Sedatives	☐ 15.Antihypertensives
☐ 16. Ant inflammatory	☐ 17. Other

Signature:_____
Date:_____

LABORATORY ASSESSMENTS

PREOPERATIVE (Preadmission clinic or Floor) (Can be done within 6 weeks of screening date)

Blood Test	Result	Date of Results	Abnormal Values Yes/No	Significant Yes/No
WBC				
Hemoglobin				
Hematocrit				
MCV				
MCH				
RDW				
Platelets				
Retic Count %				
CRP				
Ferritin				
Iron				
TIBC				
Transferrin Saturation				

6MWT # of Laps _____ _____Meters

Borg Scale: Pre: Fatigue _____Dyspnea _____ Post: Fatigue _____

Dyspnea _____

Signature:_____
Date:_____

Preop

Ejection Fraction

☐ 1. ≤30% ☐ 2. > 31-49% ☐ 3. 50-65% ☐ 4. > 66%

Echo

☐ Yes ☐ No

ASA

☐ 1. Class I ☐ 2. Class II

☐ 3. Class III ☐ 4. Class IV

Operative Procedure

☐ 1. 1 or 2 vessel disease

☐ 2. 3-vessel disease, no proximal left anterior descending (LAD) involvement

☐ 3. 3-vessel disease and proximal LAD

☐ 4. Left main artery disease

Blood Transfusion Intraop

☐ 1. Red Blood Cells ----------number of units

☐ 2. Platelets ---------- number of units

☐ 3. Plasma ---------- number of units

Postoperative Complications

☐ 1. Infection ☐ 2. Atrial fibrillation ☐ 3. Edema ☐ 4. Bleeding

☐ 5. None ☐ 6. Other

_____

_____

Signature:_____Date:_____

Signature:_____Date:_____

DISCHARGE: Date: _____/_____/201_____ (dd/mmm/yyyy)

Length of Surgery _____min

Length of Stay _____days

Length of Stay Postop _____days

Blood Transfusion Postop

☐ 1. Red Blood Cells ----------number of units

☐ 2. Platelets ---------- number of units

☐ 3. Plasma ---------- number of units

Blood test	**Result**	**Results received**	**Abnormal Values Yes/No**	**Significant Yes/No**
WBC				
Hemoglobin				
Hematocrit				
MCV				
MCH				
RDW				
Platelets				
Retic Count %				
CRP				
Ferritin				
Blood test	**Result**	**Results received**	**Abnormal Values Yes/No**	**Significant Yes/No**
Iron				
TIBC				
Transferrin Saturation				

6MWT # of Laps _____ _____Meters

Borg Scale: Pre: Fatigue _____Dyspnea _____ Post: Fatigue _____

Dyspnea _____

Signature:_____Date:_____

Telephone Call: _____date (_____ /_____/_201___)

(DD/MMM/YYYY)

Adverse Events Yes/No Side Effects Yes/No

Completing Symptom Yes/No

_____-

_____

_____

_____

_____

Signature:_____ Date:_____

Six Week Follow-up

DATE: _____/_____/__201____ (DD/MMM/YYYY)

Adverse Events -

_____

6MWT # of Laps _____ _____Meters

Borg Scale: Pre: Fatigue _____Dyspnea _____ Post: Fatigue _____

Dyspnea _____

Blood test	Result	Results received	Abnormal Values Yes/No	Significant Yes/No
WBC				
Hemoglobin				
Hematocrit				
MCV				
MCH				
RDW				
Platelets				
Retic Count %				
CRP				
Ferritin				
Iron				
TIBC				
Transferrin Saturation				

Signature:_____ Date:_____

End of Study /12 Week Follow-up

DATE: _____/_____/__201___ (DD/MMM/YYYY)

Adverse Events

_____

Received Drug Diary _____ Y/N # of pills returned _____

6MWT # of Laps _____ _____ Meters

Borg Scale: Pre: Fatigue _____Dyspnea _____ Post: Fatigue _____

Dyspnea _____

Blood test	Result	Results received	Abnormal Values Yes/No	Significant Yes/No
WBC				
Hemoglobin				
Hematocrit				
MCV				
MCH				
RDW				
Platelets				
Retic Count %				
CRP				
Ferritin				
Iron				
TIBC				
Transferrin Saturation				

Signature:_____ Date:_____

Serious Adverse Events

Event_____

_____

_____

_____

_____

SAE completed and sent to Health Canada _____ (Yes/No)

Date occurred _____ (DD/MMM/YYYY)

Date sent _____(DD/MMM/YYYY)

Local SUAE completed and sent to REB _____

Date occurred _____ (DD/MMM/YYYY) Date sent _____ (DD/MMM/YYYY)

Comments

_____

_____

_____

_____

_____

_____

Signature:_____ Date:_____

Premature Termination _ _____ (Yes/ No)

Date occurred _____(DD/MMM/YYYY)

Reason for early termination

_____

_____

_____

_____

_____

Signature:_____ Date:_____

(DD/MMM/YYYY)

I have reviewed the data contained in this case report form and to the best of my knowledge the information is complete and accurate.

_____	_____	_____
Investigator's Name – Print Clearly	Investigator's Signature	Date

APPENDIX E: ICFS QUESTIONNAIRE

Pt Initials_____ Subject ID_____ Time PT____

Identity-Consequences Fatigue Scale

Please think about the **last two days** and tick the box that best describes how you have been feeling.

During the last two days …	Not at all ▼	Almost Never ▼	Some of the time ▼	Fairly Often ▼	Very Often ▼	All of the time ▼
1. I have been feeling drained	☐	☐	☐	☐	☐	☐
2. I have started things without difficulty but then quickly become tired	☐	☐	☐	☐	☐	☐
3. I have been feeling energetic	☐	☐	☐	☐	☐	☐
4. I have been feeling worn out	☐	☐	☐	☐	☐	☐
5. I have been feeling refreshed	☐	☐	☐	☐	☐	☐
6. My body has been feeling heavy all over	☐	☐	☐	☐	☐	☐
7. I have been feeling vigorous	☐	☐	☐	☐	☐	☐
8. It has been hard for me to get motivated to do my regular activities	☐	☐	☐	☐	☐	☐

Signature _____ Date _____

Pt Initials_____ Subject ID_____ Time PT____

Identity-Consequences Fatigue Scale

During the last two days …	Not at all ▼	Almost Never ▼	Some of the time ▼	Fairly Often ▼	Very Often ▼	All of the time ▼
9. I have been able to concentrate on things	☐	☐	☐	☐	☐	☐
10. I have been feeling fatigued	☐	☐	☐	☐	☐	☐
11. I have had the energy to do lots of things	☐	☐	☐	☐	☐	☐
12. Physically, I have felt tired	☐	☐	☐	☐	☐	☐
13. I have had to restrict how much I try and do in a day	☐	☐	☐	☐	☐	☐
14. I have been feeling lively	☐	☐	☐	☐	☐	☐

During the last two days, feelings of tiredness have meant …	Not at all ▼	Almost Never ▼	Some of the time ▼	Fairly Often ▼	Very Often ▼	All of the time ▼
15. I have had trouble paying attention	☐	☐	☐	☐	☐	☐
16. I have been forgetful	☐	☐	☐	☐	☐	☐
17. My thoughts have wandered easily	☐	☐	☐	☐	☐	☐
18. I have made more mistakes than usual	☐	☐	☐	☐	☐	☐

During the last two days, feelings of tiredness have meant …	I strongly agree ▼	I agree ▼	neutral ▼	I disagree ▼	I strongly disagree ▼
19. I have achieved very little with the day	☐	☐	☐	☐	☐
20. I have lacked the energy to do things I would normally do	☐	☐	☐	☐	☐

Signature _____ Date _____

Pt Initials_____ Subject ID_____ Time PT____

Identity-Consequences Fatigue Scale

The following questions ask how much **fatigue** interferes with the things you can do.

For activities you aren't doing, for reasons other than fatigue, tick the box labelled "N/A" (not applicable).

For example, if you are not the person who usually cooks in your household, tick the "N/A" box.

During the last two days, I have had enough energy to…	Not at all ▼	Only occasionally ▼	Sometimes, but less than usual ▼	Nearly as often as usual ▼	As often as usual ▼	N/A ▼
21. Read a newspaper/book or watch TV	☐	☐	☐	☐	☐	☐
22. Bath/wash	☐	☐	☐	☐	☐	☐
23. Dress	☐	☐	☐	☐	☐	☐
24. Do household chores	☐	☐	☐	☐	☐	☐
25. Cook	☐	☐	☐	☐	☐	☐
26. Work	☐	☐	☐	☐	☐	☐
27. Visit or socialize with family and friends	☐	☐	☐	☐	☐	☐
28. Engage in leisure or recreational activities	☐	☐	☐	☐	☐	☐
29. Shop or do errands	☐	☐	☐	☐	☐	☐
30. Walk	☐	☐	☐	☐	☐	☐
31. Exercise other than walk	☐	☐	☐	☐	☐	☐

Signature _____ Date _____

APPENDIX F: FACT-AN QUESTIONNAIRE

Pt Initials_____ Subject ID_____ Time PT____

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.* ☐					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-An (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

Pt Initials_____ Subject ID_____ Time PT____

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>EMOTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	<u>FUNCTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right	0	1	2	3	4

Signature _____ Date _____

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An9	I feel lightheaded (dizzy)	0	1	2	3	4
An10	I get headaches	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
An11	I have pain in my chest	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
An13	I am motivated to do my usual activities	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Signature _____ Date _____

APPENDIX G: FACT-AN SOFTWARE SCORING LICENSURE

FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY (FACIT) LICENSING AGREEMENT

The Functional Assessment of Chronic Illness Therapy system of Quality of Life questionnaires and all related subscales, translations, and adaptations ("FACIT System") are owned and copyrighted by David Cella, Ph.D. The ownership and copyright of the FACIT System - resides strictly with Dr. Cella. Dr. Cella has granted FACIT.org (Licensor) the right to license usage of the FACIT System to other parties. Licensor represents and warrants that it has the right to grant the License contemplated by this agreement. The terms of this license will grant permission Licensor provides to ***HEATHER MINGO*** **("Investigator")** *the licensing agreement outlined below.*

This letter serves notice that **HEATHER MINGO** is granted license to use the **English version** of the **FACT-AN** in **one not for profit study**:

This current license is only extended to HEATHER MINGO's research project subject to the following terms:

1) (HEATHER MINGO) agrees to provide Licensor with copies of any publications which come about as the result of collecting data with any FACIT questionnaire.

2) Due to the ongoing nature of cross-cultural linguistic research, Licensor reserves the right to make adaptations or revisions to wording in the FACIT, and/or related translations as necessary. If such changes occur, HEATHER MINGO will have the option of using either previous or updated versions according to its own research objectives.

3) (HEATHER MINGO) and associated vendors may not change the wording or phrasing of any FACIT document without previous permission from Licensor. If any changes are made to the wording or phrasing of any FACIT item without permission, the document cannot be considered the FACIT, and subsequent analyses and/or comparisons to other FACIT data will not be considered appropriate. Permission to use the name "FACIT" will not be granted for any unauthorized translations of the FACIT items. Any analyses or publications of unauthorized changes or translated versions may not use the FACIT name. Any unauthorized translation will be considered a violation of copyright protection.

4) In all publications and on every page of the FACIT used in data collection, Licensor requires the copyright information be listed precisely as it is listed on the questionnaire itself.

5) This license is for paper administration only and is not extended to electronic data capture. Electronic versions of the FACIT questionnaires are considered derivative works and are not covered under this license. Permission for use of an electronic version of the FACIT must be covered under separate agreement between the electronic data capture vendor and FACIT.org

6) In no cases may any FACIT questionnaire be placed on the internet without password protection. To do so is considered a violation of copyright.

7) Licensor reserves the right to withdraw this license if HEATHER MINGO engages in scientific or copyright misuse of the FACIT system of questionnaires.

8) There are no fees associated with this license.

9) This license is effective upon date issued by FACIT.org and expires at the completion of HEATHER MINGO's project.

10) HEATHER MINGO agrees to provide FACIT.org with a copy of any publication which results from this study.

Issued on: March 19, 2018

Shannon C Romo
Assistant Business Manager
FACIT.org
381 S. Cottage Hill Avenue
Elmhurst, IL 60126 USA
www.FACIT.org

APPENDIX H: 6MWT DATA SHEET

Affix label here

Six Minute Walk Test (6MWT) Worksheet

Contraindications to 6MWT
☐ No contraindications identified
☐ Resting Heart rate >120 beats/min after 10 minutes rest (relative contraindications
☐ Systolic blood pressure >180 mmHg +/- diastolic blood pressure >100 mmHg (relative contraindications)
☐ Resting SpO2 <85% on room air or on prescribed level of supplemental oxygen
☐ Physical disability preventing safe performance

Lap counter: __ _
Patient Initials: _____ Subject ID# _____
Walk # _____ Staff Initials: _____ Date: _____
Gender: M F Lap length_____meters
Medications taken before the test (dose and time): _____
Supplemental oxygen during the test: No Yes, flow _____ L/min, type _____

Baseline		**End of Test**	
Time	_____	___:_____	
Heart Rate	_____	_____	
Dyspnea	_____	_____	(Borg scale)
Fatigue	_____	_____	(Borg scale)
SpO2	____ %	____%	
B/P:	_____ / _____	_____ / _____	

Stopped or paused before 6 minutes? No Yes, reason:
_____
Other symptoms at end of exercise: angina, dizziness, hip, leg, or calf pain None
Number of laps: ____ Final partial lap: _____ meters
Total distance walked in 6 minutes: _____ meters
Predicted distance: _____ meters Percent predicted: _____%

Research Staff comments: Interpretation (including comparison with a preintervention 6MWT): _____

Signature_____ Date _____

APPENDIX I: SF-36 QUESTIONNAIRE

The SF-36™ Health Survey

Instructions for Completing the Questionnaire

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

EXAMPLE

This is for your review. Do not answer this question. The questionnaire begins with the section ***Your Health in General*** below.

For each question you will be asked to fill in a bubble in each line:

1. How strongly do you agree or disagree with each of the following statements?

	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
a) I enjoy listening to music.	○	●	○	○	○
b) I enjoy reading magazines.	●	○	○	○	○

Please begin answering the questions now.

Your Health in General

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

2. **Compared to one year ago**, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
○	○	○	○	○

Please turn the page and continue.

3. The following items are about activities you might do during a typical day. Does your **health now limit you** in these activities? If so, how much?

	Yes, Limited a lot	Yes, limited a little	No, not limited at all
a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○	○	○
b) **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
c) Lifting or carrying groceries	○	○	○
d) Climbing **several** flights of stairs	○	○	○
e) Climbing **one** flight of stairs	○	○	○
f) Bending, kneeling, or stooping	○	○	○
g) Walking **more than a mile**	○	○	○
h) Walking **several blocks**	○	○	○
i) Walking **one block**	○	○	○
j) Bathing or dressing yourself	○	○	○

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities	○	○
b) **Accomplished less** than you would like	○	○
c) Were limited in the **kind** of work or other activities	○	○
d) Had **difficulty** performing the work or other activities (for example, it took extra time)	○	○

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities	○	○
b) **Accomplished less** than you would like	○	○
c) Didn't do work or other activities as **carefully** as usual	○	○

Please turn the page to continue.

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
○	○	○	○	○

7. How much bodily pain have you had during the **past 4 weeks**?

None	Very mild	Mild	Moderate	Severe	Very severe
○	○	○	○	○	○

8. During the **past 4 weeks**, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

9. These questions are about how you feel and how things have been with you during the **past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a) did you feel full of pep?	○	○	○	○	○	○
b) have you been a very nervous person?	○	○	○	○	○	○
c) have you felt so down in the dumps nothing could cheer you up?	○	○	○	○	○	○
d) have you felt calm and peaceful?	○	○	○	○	○	○
e) did you have a lot of energy?	○	○	○	○	○	○
f) have you felt downhearted and blue?	○	○	○	○	○	○
g) did you feel worn out?	○	○	○	○	○	○
h) have you been a happy person?	○	○	○	○	○	○
i) did you feel tired?	○	○	○	○	○	○

10. During the **past 4 weeks**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
○	○	○	○	○

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a) I seem to get sick a little easier than other people	○	○	○	○	○
b) I am as healthy as anybody I know	○	○	○	○	○
c) I expect my health to get worse	○	○	○	○	○
d) My health is excellent	○	○	○	○	○

***THANK YOU* FOR COMPLETING THIS QUESTIONNAIRE!**

APPENDIX J: SF36 SOFTWARE LICENSURE

From: Pearlie Jenkins <pjenkins@qualitymetric.com>
Sent: Friday, May 9, 2014 17:03
To: blainekent@hotmail.com
Cc: Pearlie Jenkins; Andrew Harrison
Subject: QualityMetric Health Outcomes(tm) Scoring Software 4.5 Activation Key - Capital Health - QM022863

Dear Blaine Kent,

Thank you for purchasing QualityMetric Health Outcomes(tm) Scoring Software 4.5. Please use the Activation Key provided below to unlock the application for the licensed survey(s) and scoring features. This key will install a pre-determined quantity of scoring credits (as per the license agreement) which will be decremented each time a record is entered/scored. Once the credits are exhausted, you will need to contact OptumInsight Life Sciences to obtain more credits and resume scoring.

ACTIVATION KEY:
887E4-27484-5B5D3-D2349

LICENSED PRODUCTS AND SCORING FEATURES:
PRODUCT NAME: QualityMetric Health Outcomes(tm) Scoring Software 4.5
PURCHASE DATE: 01/28/14

SF36v2 Credit Count: 300
- SF36v2 MDE Enabled: Yes
- SF36v2 Utility Index: No
- SF36v2 RCI Score: No
- SF36v2 DQE Report: Yes

DOWNLOAD AND INSTALLATION:
You may download QualityMetric Health Outcomes(tm) Scoring Software 4.5 installer from the following location:
.tp://www.qualitymetric.com/download/SFScoringSoftwareV45Setup.msi

IMPORTANT NOTES - PLEASE READ
Important installation notes are provided below. More detailed instructions are included in the attached. If you

are prohibited from installing software or do not feel comfortable doing so, please consult your IT support and bring the items below to their attention:

1) Activation Keys are SINGLE-USE and can only be applied to one computer.
2) WINDOWS ADMINISTRATIVE ACCESS is required to install the software.
3) Subsequent use of the Scoring Software requires the ability to read/write to a specific path in the computer's registry (see documentation for more detail). [If the user is not an Administrator, this will need to be explicitly granted via REGEDIT]

4) You will be prompted to enter the activation key upon first launch. If you miss this opportunity, you can subsequently add keys via the "Tools" menu.

5) An active Internet connection is required for registration of Activation Keys. A workaround for offline activation is available in some cases.

SUPPORT:
- For installation help or system/software requirements, please consult the Installation Guide: http://www.qualitymetric.com/download/InstallationGuide_ScoringSoftwareV4.pdf
- For help on the use of the software, please review the User's Guide within the application itself (by clicking on Help -> Contents and Index).

- For additional technical support, please send an email to scoringsoftware@qualitymetric.com.
- For all other questions (such as licensure, billing, or scientific support), please contact your account representative.

APPENDIX K: RECRUITMENT POSTER

ORAL IRON (FeraMax®) RESEARCH STUDY

You are invited to take part in a study evaluating the effects of

FeraMax® on fatigue,

Conducted by Heather Mingo/ Dr Blaine Kent

at

Nova Scotia Health Authority, Halifax Infirmary site,

Halifax,

Department of Anesthesia

The study involves 4 one-hour visits over 3 months, having blood drawn, questionnaires, walk test and taking FeraMax® daily.

If you are at least 19 years old, having coronary artery bypass surgery and would like more information about participating, contact: Heather Mingo at 902 473

APPENDIX L: CONFLICT OF INTEREST

Oral iron FeraMAX® and placebo capsules used in this study were provided by BioSyent Inc. An unrestricted educational grant was also provided by BioSyent Inc.

APPENDIX M: PATIENT INSTRUCTION SHEET

A Phase III Randomized Double Blind Placebo-Controlled Clinical Trial to Assess the Effects of Feramax when Administered Orally Once a Day on Postoperative Fatigue Levels in Patients Following Elective Coronary Artery Bypass Graft Surgery

Patient Instruction for Taking Study Medication

Study Medication will be dispensed in bottles (84 capsules) at discharge.

Instructions

- Take one capsule daily with eight ounces of water, daily starting the day after discharge until day 84.
- Take medication at lunch time or dinner time,
- Do not to take over the counter or herbal medications.
- Important to continue taking the medication every day.
- Do not to take other forms of iron such as herbal remedies during the trial.
- Do not to take other natural health products indicated for fatigue during the trial.
- Record any signs and symptoms (i.e. nausea, vomiting, diarrhea, constipation and stomach pain)on the side effects diary Contact Heather Mingo 902 2331344 if you have questions
- You will be given a symptom diary for recording any side effects related to the medication while at home.
- Put the diaries in an opaque envelope labelled with instructions and returned on the study end visit.

APPENDIX N: STUDY DRUG SIDE EFFECTS LIST

Every day, please place a checkmark under the side effect(s) you experienced that day.
Start Date: _____

Day	Nausea	Vomiting	Diarrhea	Abdominal pain	Heartburn	Constipation	None	Comments	Complications
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
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44									

Day	Nausea	Vomiting	Diarrhea	Abdominal pain	Heartburn	Constipation	None	Comments	Complications
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