# DIET AND EXERCISE FRAILTY INTERVENTION IN CARDIAC DEVICE PATIENTS

# THE USE OF DIETARY SUPPLEMENTATION AND SUPERVISED EXERCISE PROGRAM IN CARDIAC DEVICE PATIENTS WITH ATRIAL FIBRILLATION AND FRAILTY

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A Thesis submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree of Master of Science

McMaster University MASTER OF SCIENCE (2020) Hamilton, Ontario (Health Research Methodology)

**TITLE**: The use of dietary supplementation and supervised exercise program in cardiac device patients with atrial fibrillation and frailty

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**NUMBER OF PAGES:** 108

**LAY ABSTRACT (about 150 words):**

Frailty is a state of vulnerability in elderly that makes them susceptible to large declines in health from minor illnesses. Frail elderly are more likely to be admitted to the hospital, nursing homes and have higher chance of dying. Old age and frailty are not the same. Frailty is common in patients with a pacemakers and defibrillators. The purpose of this study is to test whether a supervised exercise program and a nutritional supplement will help improve frailty. We planned to recruit 24 patients into the randomized control trial and 100 patients in the registry and follow them for a period of one year. We aimed to understand how common is frailty in elderly with pacemakers and defibrillators and what factors contribute to developing frailty.

**ABSTRACT:**

**Background**

Frailty is an aging-associated vulnerability to poor health comes when challenged by physiologic stressors. Frailty is a common problem amongst the elderly and is associated with increased mortality and health care resource utilization. Frailty is common in recipients of cardiac devices. What is not known is whether interventions will improve frailty and if this changes patient outcomes.

**Methods**

There are four chapters in this thesis. In chapter 1, a review of the current state of frailty research, methods of measurement, biomarkers, imaging modalities and interventions are presented. In chapter 2, a pilot randomized controlled trial is proposed to determine if a supervised exercise program and nutritional supplement improves physical frailty in cardiac device patients. Chapter 3 presents the results of the pilot study to date. In chapter 4, we discuss the challenges faced during the COVID-19 pandemic with respect to recruitment and conducting the trial and changes to the protocol that could have improved the study and adapted to the current state of research.

**Results**

There are two conceptual models of frailty which include the frailty phenotype and frailty index. Frailty instruments are abundant and there is no gold standard measurement. Frailty biomarkers, imaging techniques in their current state are complementary measures and are not yet ready for clinical practice. The DEFINIT P trial is single centre RCT involving 24 cardiac device patients randomized to 12 month supervised exercise

program and nutritional supplement. Recruitment was halted due to COVID-19 pandemic.

**Conclusions**

Frailty is common in cardiac device recipients. A gold standard frailty instrument is not yet established though efforts are currently underway. The DEFINIT P study is feasible with respect to recruitment and consent targets but whether the adherence target to the exercise intervention and nutritional supplement is achieved remains unknown due to stopping the pilot trial as a result of the COVID 19 pandemic.

**ACKNOWLEDGEMENTS:**

I would like to thank my research thesis supervisor Dr. Jeff Healey who saw potential in my work and kindly agreed to take me on as a research fellow. Throughout the compilation of this work, he has been an invaluable supporter who provided me with actionable advice and constant feedback on not only academic matters but also professional development.

I also would like to thank Dr. Richard Whitlock for being part of my committee and providing me with the vision of what can be achieved during my time at McMaster University. Thank you for you feedback and support.

To Dr. Darryl Leong, thank you so much for taking me on and trusting me with such an important and practice changing research in frailty. Thank you for your feedback and teaching.

I would like to thank Dr. Shamir Mehta for reviewing my thesis and being a great academic mentor. I have learned a tremendous amount information from you, and I hope we can continue our collaboration on future projects.

I also want to thank my colleagues at Population Health Research Institute and McMaster University's Health Research Methodology. The relationships we have cultivated over my time here are precious and lifelong.

Lastly, I want to thank my parents who sacrificed so much of their youth to escape a war torn nation of Afghanistan and provide me with every opportunity to pursue my academic career. All that I am and have achieved is credit to them for always believing in me and encouraging me to aim high.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| **BMI** | Body mass index |
| **CABG** | Coronary artery bypass grafting |
| **CI** | Confidence interval |
| **CRT** | Cardiac resynchronization therapy |
| **CT** | Computed tomography |
| **DXA** | Dual-energy X-ray absorptiometry (DXA) |
| **eCRF** | Electronic case report forms |
| **EFS** | Edmonton Frail Scale |
| **HR** | Hazard ratio |
| **ICD** | Implantable cardiac defibrillator |
| **MOCA** | Montreal Cognitive Assessment |
| **MRI** | Magnetic resonance imaging |
| **NYHA** | New York Heart Association |
| **RCT** | Randomized controlled trial |
| **PAQ** | Physical Activity Questionnaire |
| **PCI** | Percutaneous coronary intervention |
| **PHQ** | Patient Health Questionnaire |
| **PHRI** | Population Health Research Institute |
| **REFS** | Reported Edmonton Frail Scale |

## DECLARATION OF ACADEMIC ACHIEVEMENT

Dr. Zardasht Oqab was involved in protocol writing and design changes of the study. He was responsible for development of Case Report Forms, training of study coordinator, data collection, statistical analysis and writing of all the chapters in this thesis.

Dr. Jeff Healey was the primary thesis supervisor. He was involved in conception and design of the study as well as review of results and analysis.

Dr. Richard Whitlock was provided valuable feedback on writing and reviewed all aspects of this thesis.

Dr. Darryl Leong was involved in conception and design of the study. He also advised on statistical analysis and provided valuable feedback throughout thesis writing.

Dr. Stuart Connolly was involved in review of the thesis and provided valuable feedback.

## OVERVIEW OF THESIS

This thesis is composed of four chapters. Each chapter is briefly described below.

**Chapter 1:** Provides background on the current state of frailty research. Frailty definitions and the conceptual models of frailty are discussed. Frailty instruments are broadly composed of questionnaires, physical performance tests or a combination of the two. Biomarkers and imaging are novel methods which are under study but are not ready for clinical practice. Physical activity and nutritional supplements are two ways that frailty can be improved.

**Chapter 2:** In chapter 2, I discuss the design and rationale of the DEFINIT P study which is a pilot randomized controlled trial of a supervised exercise program along with nutritional supplementation in elderly cardiac device patients.

**Chapter 3:** In this chapter, results of the pilot study are presented. The prevalence of frailty in cardiac device patients along with demographic and comorbidities associated with frailty are presented.

**Chapter 4:** This chapter focuses on challenges faced as a result of the COVID-19 pandemic with respect to recruitment and conducting the trial. Changes to the protocol are proposed that aims to improve the study and adapt it to the current state of conducting research.

# CHAPTER 1

# THE STATE OF FRAILTY RESEARCH, INSTRUMENTS, BIOMARKERS, IMAGING AND INTERVENTIONS

**What is frailty?**

Over the past two decades, clinicians have increasingly recognized frailty as a major health care concern with ever growing research publications however a gold standard definition has yet to be established. Geriatricians define frailty as a biologic syndrome of decreased reserve to stressors, resulting from cumulative declines across multiple physiologic systems leading to a decline in homeostatic reserve and resiliency.(1-3) Frail patients do not exhibit the same symptoms, clinical outcomes or share specific disease presentations.(1) This is one of the major challenges to establishing a universal definition of frailty syndrome as it is a multidimensional concept with variety of interacting domains. A systematic review of clinical definitions of frailty found the most common identifying factors for frailty were physical functioning, gait speed and cognition.(4) Yet, not every measurement instrument includes all these domains. Additionally, which frailty domains to include in the definition and which to use as a clinical outcome is also debated. For example, disability and functional decline is used in the definition of frailty but they can also represent a clinical outcome.(4) There is also no consensus on tools used to measure the specific domains of frailty.

Frailty is associated with adverse outcomes such as increased falls, hospitalizations, worsening disability, nursing home admissions and mortality.(5-9) Frailty in community-dwelling adults increases with age, affecting 11% of elderly over the age of 65 years and 25% over the age of 85 years.(10) Frailty is

an important healthcare concern as the Canadian population is aging with one in four adults projected to be aged 65 years or older by the year 2036 and the average life expectancy is also projected to increase by 2 years in women and 2.9 years in men.(11) Though prevalence of frailty is more common in the elderly, frailty is not synonymous with chronological age. Despite the absence of a universally accepted definition, frailty poses a significant health care threat due to higher burden of health care utilization by the elderly and ultimately increased health care costs. There are two conceptual models of frailty that can help define this syndrome further and identify frail patients who are at high risk of morbidity and mortality using validated assessment tools.

**The Fried Frailty Phenotype Model**

The frailty phenotype is one of the widely accepted conceptual models of frailty. Fried et al. used prospective, observational data from the Cardiovascular Health Study which enrolled 4735 participants over the age of 65 years between 1989-90 and 582 African American participants between 1992-93.(1) All eligible participants underwent annual examinations and outcomes were monitored for a follow up period of up to 7 years. The age of participants ranged between 65 to 101 years and 58% were female. The result of this analysis identified five domains with high predictive validity to identify adverse health outcomes including falls, hospitalization, worsening disability and death. These five domains included: unintentional weight loss of >10lbs over 1 year, self-reported

exhaustion, weakness (grip strength), slow walking speed, and low physical activity. Frailty was defined as the presence of three or more of the criteria. Participants who had one or two of the criteria were prefrail and absence of all criteria were considered robust. In the phenotypic model, there is no emphasis on number or type of co-morbidities, medication history or cognition. At its core, it is a model of identifying physical frailty. In this model, all the domains are given equal weight which in practice may not be the case.(12)

There are a number of methodological issues with this study. In prospective, observational studies characteristics that might predict outcomes are measured at baseline and participants are followed over time for particular outcomes of interest. In the Fried et al study, baseline characteristics such as health habits, weight loss, physician diagnosis of comorbidities, hearing and visual impairment, physician activity level were all based on self-report data, a method prone to error. Given that this is an elderly vulnerable population, recall bias may have played a role in data collection. The study was conducted in US centres with disproportionally Caucasian patients which can affect the generalizability of the results. Another limitation of the study is that the Cardiovascular Health Study was a prospective, longitudinal study of coronary heart disease and stroke in elderly over the age of 65 years and was not designed to study frailty.(13) This was an analysis after the completion of the study and not truly a prospectively designed frailty study. This is not a significant

limitation since the measurements obtained were relevant, appropriate and available for informing the frailty phenotype. Nevertheless, this was an important study because it operationalized the definition of frailty and provided an instrument to not only screen patients but also the ability to monitor for progression or improvement of frailty. An alternative to Fried's phenotype is the frailty index model.

**The Frailty Index Model**

The frailty index is a mathematical model that takes into account accumulation of age associated functional deficits such as comorbid illness, poor health attitudes, signs of disease, laboratory findings and self-reported disabilities.(14) The prevalence of chronic disease, disability and frailty increase with age but the rate of accumulation and types of deficits can vary between people. The frailty index is a proportion of all deficits present over the total number of deficits measured thus disregarding the inherent value of any one particular deficit. The frailty index score ranges between 0 and 1 with higher numbers denoting increased frailty status. A cut-off value of 0.25 has been used in several studies to define frailty. Theoretically, the frailty index can be constructed using any number of deficits as long as the criteria for inclusion are met. In order to consider a deficit for the index: 1) it must increase with age; 2) it must be health-related; 3) it must be present in at least 1% of the study

population; 4) it must not be present in 80% of the study population before age 80; 5) it must not be missing in more than 5% of the study population.(15)

One of the advantages of the frailty index is the ability to construct it using various available health data which can include prior large clinical trials, electronic health records or health care databases. The model has been built and validated using comprehensive geriatric assessments and was shown to predict adverse clinical outcomes with worsening frailty status.(16) Additionally, a frailty index using electronic primary care records has been studied in 931,541 patients. The frailty index had robust predictive validity for clinical outcomes including mortality, hospitalization and nursing home admissions (*c* statistic estimates for these outcomes at 12 months were 0.72, 0.74 and 0.66, respectively).(17)

**How is frailty measured?**

***Frailty instruments***

There is no gold standard instrument for measuring frailty. One of the major reasons for this is that a universally accepted definition of frailty is not yet established though international efforts have increased in recent years.(18) A universal definition would lead to identifying a gold standard instrument against which all other instruments can be compared, and their validity and reliability could be established. There are over 20 instruments proposed to measure frailty and many others are in development.(19) They can range from questionnaires,

physical performance assessments such as grip strength, walking speed and others combine both methods. Table 1 provides a description of available frailty instruments in clinical practice.

Another reason for the multitude of instruments is that frailty populations are heterogenous. For example, a patient with severe arthritis in the hands would not be able to use a dynamometer for grip strength assessment thus increasing the need to choose an instrument which does not have physical performance testing. Alternatively, a patient with recent stroke who may have aphasia may not be able to answer questionnaires and will require physical performance testing to determine frailty. Language barriers would also limit the use of questionnaires in all populations though translated versions of the instruments are available in other languages. Ultimately, it may turn out that reliably diagnosing frailty may require a combination of physical performance testing and questionnaires. Furthermore, certain populations will require more personalized instruments or establishment of other objective assessment tools such as advanced imaging and biomarkers.

### *Frailty Biomarkers*

The interest in identifying biomarkers associated with frailty has been increasing. There a number of processes associated with frailty which can include changes in the inflammatory markers, hormone levels, metabolism, serum markers and musculoskeletal changes (Figure 1). One of the challenges

facing researchers is differentiating normal aging processes with pathological accelerated aging associated with frailty (Figure 2). Furthermore, as mentioned previously frailty is a dynamic process affecting not only physical domains but also emotional and psychosocial therefore changes in the serum levels of biomarkers make up only a single dimension of frailty. As such alone they would be weak predictors of frailty progression and in identifying clinically important outcomes associated with frailty.(20) Nevertheless, it is intriguing that if the framework of the frailty index model was applied in identifying a combination of biomarkers that could identify those at highest risk of frailty, it would change the landscape of management of this population. It would allow clinicians to use labs as a diagnostic tools, provide a method to stage and classify frailty and use it as method to monitor response to treatment and prognostication.(21) The current state of biomarker research is far from this reality. Caveats to using biomarkers include high costs, specialized lab techniques, unproven role in predicting clinical outcomes, lack of consensus on type of biomarkers, timing of their use and which populations can benefit most. Nonetheless, a combination of labs and clinical instruments are feasible in improving the diagnostic accuracy of frailty and can inform clinical decisions regarding care of elderly patients.

### *Frailty Imaging*

Imaging techniques have been proposed to indirectly assess the presence of frailty. Sarcopenia which is defined as loss of muscle mass, strength and

performance is one of the key domains of frailty. This domain can be measured by the use of gait speed test or grip strength using a dynamometer. However, these tests are partly effort dependent and certain populations may not be able to perform them due to physical limitations as such radiological methods of sarcopenia have been studied as a surrogate marker of frailty. Dual-energy X-ray absorptiometry (DXA) is an imaging modality that can assess fat mass, lean body mass and bone mineral content. DXA values of $<7.23 kg/m^2$ for men and $<5.67 kg/m^2$ in women have been shown in several studies to denote sarcopenic patients.(22-24) The use of appendicular lean mass (sum of lean tissues in arms and legs) adjusted for BMI or height can discriminate physiological muscle mass loss from aging from pathological loss of muscle.(25)

Computed tomography (CT) is considered a gold standard of body composition measurement by the International Sarcopenia Working group. A single slice measurement of cross-sectional area at the level of L3 has been used in multiple studies. At this level there are several muscles that can be visualized including the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques and the rectus abdominis. A skeletal muscle index (skeletal muscle cross sectional area normalized for height) of <=43.75 cm2 in men and <=41.10cm in women have been established as cut offs for sarcopenia.(26, 27) Other studies have looked at psoas muscle alone,(28) paravertebral muscles at level of T12,(29) pectoralis major and minor, serratus

anterior, external and internal intercostals, teres major, infraspinatus, rhomboid major, trapezius and subscapularis at T5.(30) Each of these studies attempt to quantify muscle mass in these individuals and compare to physiological muscle mass studies in order to identify sarcopenia. Diagnosing sarcopenia by CT scans is especially useful in patients with cancer because of routine use of CT scans for diagnosis and monitoring for treatment effects are readily available. In a meta-analysis of patients with non-small cell lung cancer, sarcopenia diagnosed by CT scans was found to be an independent predictor of worse survival in patients undergoing surgery for non-small cell lung cancer (Hazard ratio 2.85, 95% confidence interval 1.67 to 4.86).(31) Patients undergoing colorectal cancer who had low skeletal muscle index had higher rates of postoperative infections and delayed recovery.(32) The disadvantages of this modality is the high radiation exposure, technical expertise required and may not always be readily available.

Magnetic resonance imaging (MRI) is another gold standard modality of measuring muscle quantity and mass.(33, 34) MRI has defined quantitative measures of sub-clinical muscle differences and therefore has the potential to detect sarcopenia.(35) In one study, quantitative MRI measurements correlated well with frailty index, grip strength and muscle power.(36) One of the disadvantages of this modality is the length of time for image acquisition makes it impractical for most clinical applications. Although, a single MRI cross sectional area acquisition at 50% of femur length yields good estimation of muscle and fat

volume which can be used to diagnose sarcopenia.(37) It takes <2 minutes to acquire the image. Cross sectional area at 50% of femur length has been shown to correlate well with muscle volume for all muscle groups therefore makes it an idea target of image acquisition.(38) However, thus far cut offs for sarcopenia has not be well defined in literature. This modality is also expensive and requires specialized expertise as well as equipment and therefore its use has been limited to research studies for the time being.

**Frailty Interventions**

Improving frailty and preventing progression in at risk populations can be achieved using various interventions. Since frailty is a complex syndrome, interventions that focus on targeting multiple domains show the most promise at improving frailty. Nonpharmacological treatments including physical activity, nutritional supplements or combination of both have been studied. The health benefits of physical activity in general population is well established with lower risks of mortality from all causes, mortality and morbidity from cardiovascular causes, lower risk of stroke, diabetes, osteoporosis, falls and dementia.(39-45) Acute exercise has also been shown to improve long term memory function and long-term exercise optimizes the molecular machinery responsible for memory processing.(46) Therefore, exercise has the potential to target multiple domains of frailty and is an attractive, potentially low cost intervention in this population.

The main challenge to exercise would be compliance particularly in a population that also suffers from exhaustion, depression and multiple co-morbid conditions that may prevent them from participating in exercise programs.

**Chapter Summary:**

Frailty is a biologic syndrome of decreased reserve to stressors, resulting from cumulative declines across multiple physiologic systems leading to a decline in homeostatic reserve and resiliency. There are two widely accepted conceptual models of frailty which include the frailty phenotype and frailty index. Frailty is associated with poor health outcomes including increased risk of mortality, hospitalizations, falls and nursing home admissions. Frailty is diagnosed using validated questionnaires, physical performance tests or a combination of the two. Biomarkers and imaging are novel methods which are under study but are not practical at this time. Physical activity and nutritional supplements are two ways that frailty can be improved. Whether this improvement will lead to improved clinical outcomes is not yet known. In the next chapter, I will propose a pilot randomized controlled trial of a supervised exercise program along with nutritional supplementation in elderly cardiac device patients. An in-depth review of different types of exercise programs and nutritional supplements will also be presented.

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## Table 1: Contemporary frailty instruments for clinical use

| Tool | Type | Components examined | Frailty scoring system | Psychometric properties | Time to complete, min | Tool administered by |
|---|---|---|---|---|---|---|
| Clinical Frailty Scale | Judgment based | Visual chart of nine pictures covering the frailty spectrum, with corresponding explanation text. | Nine grades of frailty from 1 (very fit) to 9 (terminally ill). A score of 5 or more indicates frailty. | Predictive validity and reliability[36] | < 5 | Physicians or practice nurses |
| Gait Speed | Performance based | Patient is asked to walk from one place to another at usual speed. Distance considered ranges from 2.4 to 6 m. | A walking speed of < 0.8 m/s identifies patients at high risk of frailty. | Diagnostic test accuracy[34] | < 5 | Physicians or practice nurses |
| Timed-up-and-go test | Performance based | The test measures the time taken to stand up from a chair, walk a distance of 3 m, turn, walk back and sit down. | A time of > 10 s identifies patients at risk of frailty. | Diagnostic test accuracy[37] | < 5 | Physicians or practice nurses |
| FRAIL | Questionnaire | Five items with yes/no answers:<br>• Fatigue<br>• Resistance (ability to climb up one flight of stairs)<br>• Ambulation (ability to walk one block)<br>• Illness (> 5 comorbidities)<br>• Loss of weight (> 5%) | Frailty: three or more components present<br>Prefrailty: one to two components present<br>Robust: zero components present | Convergent and predictive validity[38] | < 5 | Physicians, practice nurses, or patients or their family members |
| Groningen Frailty Indicator | Questionnaire | Fifteen-item clinician-administered questionnaire concerning four domains: physical, social, psychological and cognitive. | Frailty: scores > 4 | Construct validity[39] | 15 | Physicians or practice nurses |
| PRISMA-7 | Questionnaire | Seven-item self-completed questionnaire with yes or no answers that covers ADL limitations, age (> 85 yr) and sex | Frailty: three or more components present | Diagnostic test accuracy[34] | < 5 | Self-administered |
| Tilburg Frailty Indicator | Questionnaire | Contains two parts: 10 questions on determinants of frailty and diseases (Part A) and 15 questions on components of frailty in three domains (i.e., physical, psychologic and social frailty) (Part B) | A score of 5 or more indicates frailty. | Reliability, construct, predictive and concurrent types of validity[40] | < 15 | Self-administered |
| Frailty phenotype | Mixed (questionnaire and performance based) | Five items with yes or no answers:<br>• Weight loss over the past year (≥ 4.5 kg unintentionally)<br>• Slow walking speed<br>• Low grip strength<br>• Exhaustion (two self-reported questions)<br>• Low physical activity | Frailty: three or more components present<br>Prefrailty: one or two components present<br>Robust: no components present | Concurrent and predictive validity[10] | 15–20 | Physicians or practice nurses |

## Table 1 continued: Contemporary frailty instruments for clinical use

| Tool | Type | Components examined | Frailty scoring system | Psychometric properties | Time to complete, min | Tool administered by |
|---|---|---|---|---|---|---|
| SHARE Frailty Instrument (SHARE-FI) | Mixed (questionnaire and performance based) | Includes five variables: exhaustion, weight loss, weakness (as assessed by handgrip strength using a dynamometer), slowness and low activity | Web-based calculator distinguishes three categories: nonfrail, prefrail and frail | Construct and predictive validity[41] | < 10 | Nonphysicians (e.g., nurses, allied health professionals) |
| Study of Osteoporotic Fractures | Mixed (Questionnaire and performance based) | Three items with yes or no answers:<br>• Weight loss (> 5% intentional/unintentional)<br>• Exhaustion (Do you feel full of energy?)<br>• Inability to rise from a chair five times without using arms | Frailty: one or more components present<br>Prefrailty: one component present<br>Robust: No components present | Predictive validity[42] | < 5 | Physicians or practice nurses |
| Electronic Frailty Index | Data set | As per the Frailty Index below, with variables obtained from primary care electronic medical records | Severe frailty: a score of > 0.36<br>Frailty: a score of 0.24–0.36<br>Mild frailty: a score of 0.12–0.24<br>Fit: a score of ≤ 0.12 | Predictive validity[43] | < 5 (if automated) | Automatically computed from the electronic medical records* |
| Frailty Index | Data set | Any 30 or more health deficits (variables) that increase in prevalence with age but do not plateau with age. Variables should be multidimensional, including ADLs/IADLs, comorbidities, mood, cognition and nutritional status. | Frailty is measured on a continuum, although > 0.25 is often selected to define frailty.[44] | Criterion and construct validity[45] | 20–30 | Mostly administered by researchers; further use in clinical practice needs to be explored |
| Edmonton Frail Scale | Multidimensional | Nine items: cognition, health (two items), admission to hospital, social support, nutrition, mood, function and continence | Frailty: score > 7 | Construct validity and reliability[46] | < 10 | Physicians or practice nurses |

Note: ADL = activities of daily living, IADL = instrumental activities of daily living, PRISMA-7 = Program of Research to Integrate the Services for the Maintenance of Autonomy, SHARE = Survey of Health, Aging and Retirement in Europe.
*The Electronic Frailty Index is easy to use once it is automated in the electronic medical records; however, if done manually, it requires time and training.

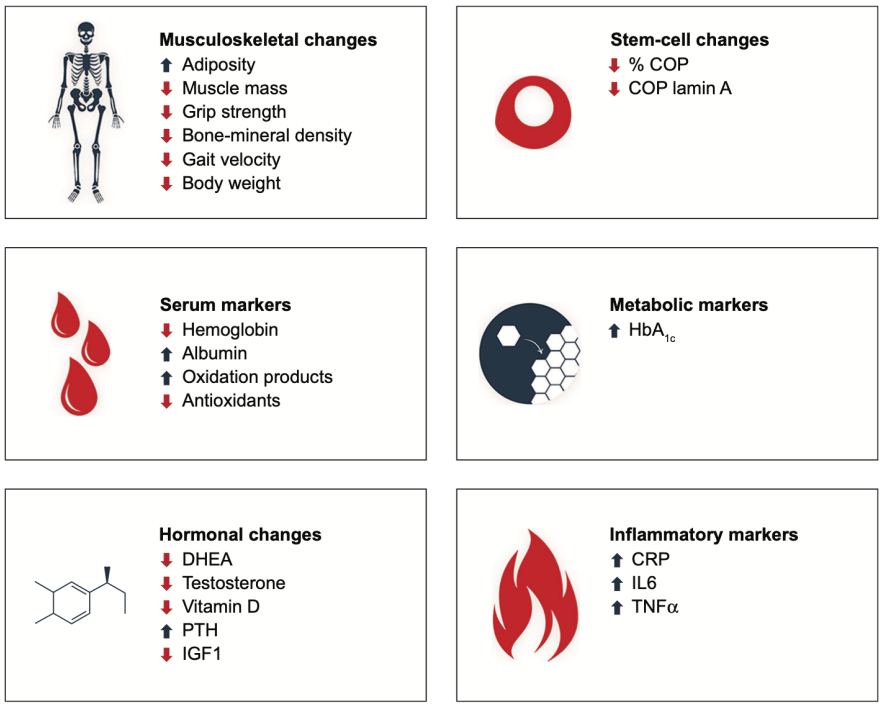


**Figure 1: Biomarkers of frailty(20)**

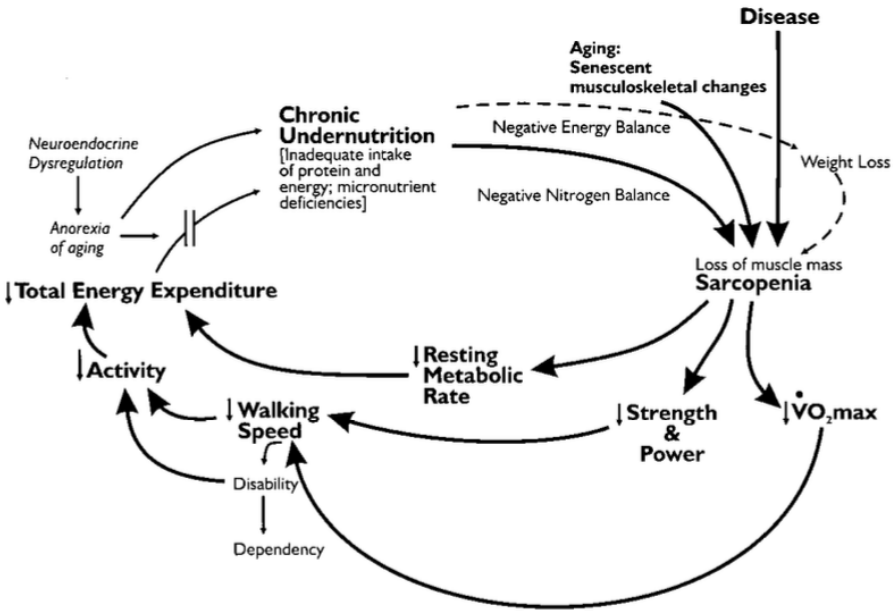


**Figure 2: A cycle of frailty(1)**

# CHAPTER 2

# DESIGN AND RATIONALE OF THE DEFINIT-P TRIAL: A PILOT RANDOMIZED CONTROLLED TRIAL OF DIET AND EXERCISE INTERVENTION IN FRAIL CARDIAC DEVICE PATIENTS

## ABSTRACT

### Introduction

Frailty is common in cardiac device recipients and is associated with poor clinical outcomes. Supervised exercise programs and nutritional supplementation have shown promise at improving frailty. The use of these interventions in an elderly cardiac device population is not known.

### Methods

DEFINIT-P is a prospective, randomized, single centre, parallel group, open label pilot trial. A total of 124 patients are planned for recruitment, of which 24 will be randomized to a supervised exercise program or a single education session on diet and exercise. All participants will receive an over the counter nutritional supplement containing whey protein, creatine and branched chain amino acids. The remainder of the 100 patients will be enrolled into a frailty registry. The primary outcomes of the trial are the rate of identification of eligible patients, proportion of patients consenting to participate, rate of adherence to the intervention and obstacles to and facilitators of adherence to intervention.

### Conclusions

The DEFINIT P trial is a single center pilot randomized controlled trial that will help determine the feasibility of a larger trial of whether supervised exercise program and nutritional supplementation improves physical frailty and clinical outcomes in cardiac device patients. (ClinicalTrials.gov Identifier: NCT04052672)

## Background

Physical frailty is defined as an aging-associated vulnerability to poor health outcomes when challenged by physiologic stressors(47). Frailty and its precursor pre-frailty are common in the general adult population and both confer a poor prognosis. We examined unpublished data from nearly 200,000 adults from the general population with median age of 50 years from countries of all income levels and found that frailty affects 1 in 20 individuals and prefrailty 1 in 5. Pre-frailty and frailty were associated with adjusted hazard ratios (95% confidence interval (CI)) for death of 1.34 (1.25-1.44) and 2.15 (1.95-2.37), respectively. Frailty is even more frequent in older populations and those affected by chronic cardiovascular disease. In an individual-level pooled analysis of 140,000 participants (mean age 69 years) enrolled in six large clinical trials coordinated by the Population Health Research Institute who had or were at high risk of developing atherosclerotic cardiovascular disease, we found that pre-frailty affected 40% of patients, and frailty another 40%. Pre-frailty and frailty were respectively associated with adjusted hazard ratios for death of 1.27 (1.15-1.40) and 3.87 (3.64-4.11). Thus, it is clear in different populations, with and without cardiovascular disease, that pre-frailty and to a greater extent frailty are associated with poor outcomes.

The implantation of cardiac devices (pacemakers and defibrillators) is increasing rapidly. Frailty has recently been recognized as especially frequent among recipients of cardiac devices (pacemakers and implantable defibrillators) (48, 49). In Canada, the number of pacemakers alone increased from 14,375 in 2006 to 16,532 in 2012 (50). In the US, pacemaker implantation increased by 56% between 1993 and 2009, during which there were nearly 3 million recipients (51). The available data suggest similar patterns among other high-income countries; in Western Australia, the overall pacemaker prevalence rate is nearly 500 per 100,000, rising to >2000 per 100,000 adults aged >75 years (52). Frailty in the cardiac device population has been relatively under-studied, however. There is a paucity of information on how the effects of frailty might be mitigated in cardiac device recipients. Cardiac device recipients typically have risk factors for frailty including older age and co-morbidities such as hypertension, diabetes, atrial fibrillation, heart failure, and coronary disease. In a recent cross-sectional study of 219 implantable cardiac device recipients by Kramer et al. (mean age 68 years), 47.5% of participants were pre-frail and 12.8% were frail (48). Mylnarska et al. found that among 171 pacemaker recipients (mean age 74 years), 25% were frail, as compared with 10% of a control group (49). The results from these studies would suggest that frailty and pre-frailty are common in the cardiac device population.

Though the prevalence of frailty is high amongst cardiac device recipients, interventions such as exercise and nutritional supplementations show promising results in improving physical frailty. A systematic review of randomized trials of exercise interventions among heart failure patients with implantable defibrillators or biventricular pacemakers found that exercise increased peak VO2 by 2.6mL/kg/min (53). Importantly, the maximum duration of follow-up in these trials was 3 months, so whether these benefits are longer-lasting is unknown. Thus, while short-term gains in aerobic capacity can be demonstrated in cardiac device recipients (mostly heart failure patients), we do not know whether: 1) this translates to a clinically relevant reduction in frailty, or 2) this improves clinical outcomes, or 3) this level of exercise is sustainable. In fact, there is a paucity of information on whether exercise can be performed by patients with pacemakers for bradycardia indications to an extent that yields clinical benefit. One of the largest trials of an exercise intervention outside cardiac device patients was the LIFE trial (54). In this study, 1635 sedentary adults from the general population aged 70-89 years were recruited by mail outs. Participants were randomized to a health education program (control) or a physical activity group (intervention). The intervention included walking, and strength and flexibility training with a goal of 150 minutes/week of exercise. The intervention was administered in a supervised setting over 6 months, including a gradual transition from a center-based program to a home-based program. Over an average follow-up of 2.7 years, 58.6% of the

intervention group needed at least one medical leave, and after excluding these, the attendance rate at the scheduled supervised sessions was 63%. The intervention led to a significant reduction in the inability to walk 400m (hazard ratio 0.82, 95% CI 0.69-0.98)(54).

There are a number of nutritional interventions that have been studied with respect to frailty. Creatine plays an important role in rapid energy provision during muscle contraction(55). In older adults, short term creatine monophosphate supplementation increased body mass, enhanced fatigue resistance, increased muscle strength and improved the performances of activities of daily living, irrespective of whether combined with resistance training or not (56-58). Vitamin D deficiency is common in frail elderly. A systematic review on the effects of vitamin D supplementation in elderly showed a small positive impact on muscle strength(59). Whey protein is another important supplement which has been shown when taken short-term, can lead to significant improvements in handgrip strength in community-dwelling frail elderly(60). A study involving frail elderly over the age of 80 enrolled in a hospital rehabilitation program found that whey protein supplementation improved functional outcomes, strength and knee extensor force(61). A multi-ingredient supplement (whey protein, creatine, alpha lipoic acid, co-enzyme Q10 and vitamin E) increased strength and lean mass in older men(62). Therefore, nutritional supplements may be an important strategy,

especially when combined with resistance training, in improving functional outcomes and thus frailty.

The DEFINIT P trial (ClinicalTrials.gov Identifier: NCT04052672) was designed to study the feasibility of a larger clinical trial involving supervised exercise program and nutritional supplement to improve physical frailty and clinical outcomes in an elderly cardiac device population.

## METHODS

### *Design and oversight*

DEFINIT-P is a prospective, randomized, single center, parallel group, open label pilot trial. A total of 24 patients will be recruited and randomized to a supervised exercised program or a single 1 hour education session on diet and exercise which at present is equivalent to standard-of-care for cardiac device recipients. A flow chart depicting the trial design is shown in Figure 1. The Steering Committee will comprise study principal investigators, and additional scientists with clinical and methodological expertise. The Steering Committee will be responsible for producing and conducting a scientifically sound study design and ensuring accurate reporting of the study. The pilot study is coordinated by the Population Health Research Institute in Hamilton, Ontario, Canada. The authors are solely responsible for the design and conduct of this study, all statistical analysis, writing and editing papers as well as its final contents. The

protocol was approved by the institutional review board at Hamilton Health Sciences, Hamilton, Ontario, Canada. Written informed consents were obtained from all participants.

### *Study objectives*

The primary objective of this pilot study is to evaluate the feasibility of a larger trial that will address the question of whether a supervised exercise program and a nutritional supplement in elderly cardiac device patients, who are pre-frail or frail, reduces physical frailty.

### *Eligibility criteria*

The eligibility criteria are shown in Table 1. Adults who are diagnosed as pre-frail or frail and are recipients of a permanent pacemaker, implantable cardiac defibrillators (ICD) or cardiac resynchronization therapy (CRT) devices will be eligible for enrollment. Patients with a cardiac device who are non-frail will be eligible to participate in the registry. Patients who are eligible for the randomized control trial who do not wish to have follow up visits will also be eligible for the registry. Patients will be excluded if they are less than 55 years of age or unwilling to provide informed consent. Patients will be eligible for the registry but not eligible for the randomized control trial if they are non-frail, have existing referral for cardiac rehabilitation, severe heart failure (New York Association class

IV), dementia as identified by Montreal Cognitive Assessment score <2, unstable angina or any other medical condition that will prevent exercise participation.

### *Frailty Assessment*

Frailty was measured using Fried Frailty Criteria (Appendix A) which is operationally defined by the presence of number of phenotypic criteria including: unintentional weight loss, exhaustion, grip strength, walking speed and low physical activity. We used the Physical Activity Questionnaire to determine physical activity levels instead of the Minnesota Leisure Time Activity questionnaire.

*Frailty definitions

| | |
|---|---|
| Fried Frailty Criteria(47) | **Weight loss:** unintentional weight loss of at least 4kg in the last year.<br>**Exhaustion:** Response of "a moderate amount of the time (3-4) days" or "most of the time" to the CES-D scale item: "I felt that everything I did was an effort" during the past week.<br>**Physical activity levels:** will be calculated using the Physical Activity Questionnaire<br>**Walk time:** Time in seconds to complete 15 feet walk at usual pace. Stratified by gender and height.<br>**Grip Strength:** Low grip strength as measured by a dynamometer. Stratified by gender and BMI quartiles. |
| Non-frail | Zero criteria met |
| Pre-frail | Meets 1 or 2 criteria |
| Frail | ≥3 criteria are met |

### Outcomes

The primary outcomes are: (1) rate of identification of eligible patients, 2) the proportion of eligible patients consenting to participate and randomized, (3) the

rate of adherence to the trial interventions, (4) the obstacles to and facilitators of adherence to the intervention. A reasonable criteria for success of this pilot trial would be to aim for adherence to the trial interventions of ≥60%. The secondary outcomes of this pilot trial are identification of frailty biomarkers, physical activity levels as measured by the cardiac device, clinical cardiovascular outcomes (myocardial infarction, stroke, heart failure hospitalization, atrial fibrillation, ventricular tachyarrhythmia), cardiac device complications (inappropriate defibrillator shocks, lead dislodgement) and injury from a fall or fracture. Objective measures of physical activity will be downloaded from the participant's cardiac device (cardiac devices contain several mechanisms to allow measurement of activity levels, including piezoelectric motion sensors that allow continuous quantification of movement, and estimation of minute ventilation from the body's bioimpedance). Additionally, health-related quality of life based on the EQ-5D scale from baseline visit, to 3 months, 6 months and 12 months will be performed.

***Screening and randomization***

Screening will occur in the Cardiac Device Clinic at the Hamilton General Hospital, where all cardiac device patients are followed within two weeks of their device implantation. We anticipate identifying very close to 100% of eligible patients. Consecutive patients with a cardiac device (permanent pacemaker or

implantable cardiac defibrillator) will be recruited. During the screening phase, we will collect demographic information, anthropometric measurements, vital signs, social history including smoking and alcohol use, past medical history, current medications, frailty measurement, physical function tests, Physical Activity Questionnaire (PAQ), Patient Health Questionnaire (PHQ) 9, EQ5D for RCT patients and a blood specimen will be drawn for the biobank.

Participants consenting to involvement in the exercise intervention part of the study will be randomized by the Interactive Web Randomization System (IWRS) to either the exercise intervention group or the control group in a 1:1 ratio. The IWRS is a 24-hour computerized randomization internet system maintained by the coordinating centre at the PHRI, which is part of Hamilton Health Sciences and McMaster University in Hamilton, Ontario, Canada. Randomization will be stratified by cardiac device type. All participants will be receiving the nutritional supplement and will not be randomized.

***Study interventions***

**Exercise:** The exercise intervention will take place at the Hamilton Health Sciences Cardiac Health and Rehabilitation Centre. This is an outpatient rehabilitation service that offers exercise counselling and supervised exercise classes. Prior to starting an exercise program, each participant will undergo

cardiopulmonary exercise testing which is standard practice at our institution. This will provide a baseline fitness level and the results will be used to design an individualized program tailored to each participant's ability. Following the exercise test, participants will meet with the kinesiologist who will review their medical history, medications to plan the exercise program. If there are any concerning features during the test, results will be shared with the Primary Investigator for further review and management plan.

Current exercise guidelines suggest an exercise intensity that corresponds to 60-80% of peak functional capacity as determined by the cardiopulmonary exercise test. Given the population of interest is pre-frail or frail, we will aim for a 50-80% peak functional capacity. Participants will attend classes supervised by a kinesiologist. Each class is 1 hour in duration and consists of a combination of aerobic exercise in the form of walking, recumbent bike or stair climber, and strength and balance training for all major muscle groups.

During months 1 to 3, intervention participants will attend supervised sessions 3 times per week. Participants will continue to attend 2 times per week during the months 4 and 5 with additional home-based exercise undertaken to meet the exercise goal. After 5 months of supervised exercise, participants will be expected to continue exercise as a home-based program or at a private gym of

their choice for months 6-12. To ensure participants are comfortable with the home exercises, in the final month of the supervised program, the kinesiologist will gradually transition the participant to home-based exercises. A research assistant will contact participants at regular intervals to check progress, answer questions and record any concerns or issues that may arise. If exercises are not being followed or have become difficult, the program will be modified to meet the participants' fitness level. Participants will be provided with a log to record their exercise participation.

**Control:** The control group will undergo cardiopulmonary stress test to establish a baseline fitness level and to test for chronotropic incompetence. They will also receive general advice on health, exercise and nutrition, which will be administered at a single group session. At present, this is equivalent to standard-of-care for cardiac device recipients.

**Nutritional supplement:** All participants will be provided with a 12-month supply of the nutritional supplement. Participants will mix 1 scoop of the supplement in one cup of water or milk to dissolve it. The supplement provides an energetic value of 160 calories per serving. Participants will be asked to consume 7 servings of the study product per week throughout the 12-month intervention period. Participants will consume 1 serving daily immediately before breakfast

and will be instructed to consume the supplement as a single bolus within 5–10 minutes. Participants will be instructed to record product intake in a diary to check compliance. Refer to Appendix B for nutritional information of the supplement.

**Focus group interviews:** We will invite all participants in the randomized control trial to participate in focus group interviews (at 6 and 12 months) to provide insight into the obstacles to and facilitators of sustained exercise and adherence to the nutritional supplement. These interviews will be led by a facilitator with experience in focus group interview techniques. Interviews will be digitally recorded and transcribed for analysis.

**Blood sampling:** Approximately 20 mL blood will be drawn at baseline, 6 months and 12 months into evacuated tubes with heparin used for plasma collection and non-treated tubes will be used to collect serum. The sample will be centrifuged, aliquoted and stored in accordance with current laboratory standards.

**Intervention discontinuation:** Participants can choose to stop the exercise program at any time during the course of the pilot study. If a participant decides to stop attending the exercise program, the site investigator will discuss this decision with them. If the reason is due to inability to attend the program, then the site investigator will attempt to offer a reduced effort program or can design a

home-based exercise program if the patient chooses to continue to participate. Study Personnel will follow patients who make the decision to discontinue the exercise program or change to another option for exercise in the same way that they follow all other trial participants.

Participants can choose to stop the nutritional supplement at any time during the course of the pilot study. If a patient decides to stop the nutritional supplement, the site investigator will discuss this decision with the patient. If the reason is due to side effects or any intolerance, these will be documented. Study Personnel will follow patients who make the decision to discontinue the supplement in the same way that they follow all other trial participants.

All temporary interruptions and early permanent discontinuations will be documented along with the reason for interruptions/discontinuation. Appropriateness of restarting the exercise program or nutritional supplement will be reviewed at each subsequent follow-up. If the trial participant decides they want to resume the exercise program or nutritional supplement, the site investigator will re-initiate the study intervention(s) if they feel the study intervention(s) can be safely restarted and document the restart in the CRF.

Additionally, withdrawal of consent does not withdraw permission to collect vital status. Withdrawal of this consent must be made separately. In cases where subjects indicate they do not want to “continue”, investigators must determine whether this refers to discontinuation of study treatment (the most common expected scenario), unwillingness to attend follow-up visits, unwillingness to have telephone contact or unwillingness to have any contact with study personnel. In all cases, every effort must be made to continue to follow the participant at regular study visits. Survival status and outcome information must be determined for all subjects.

### *Follow-up*

At 3 months, a telephone follow-up will be performed to collect data on clinical outcome events (death, myocardial infarction, stroke, cardiac device complications, and hospitalizations), current medications, questionnaires; quality of life (EQ5D and PAQ) and adherence to the interventions if in the randomized control trial. Face-to-face follow-up visits will occur at 6 and 12 months. Table 2 portrays study procedures that contains information collected during each visit.

### *Definitions of study outcomes*

Study outcomes are defined in Table 3.

### *Event Adjudication*

The independent Safety Officer will be responsible for reviewing Serious Adverse Events (SAE) throughout the study period. All SAEs will be reviewed at 6 months and 12 months with the Operations Committee.

### *Statistical considerations*

**Sample size determination**: We aim to obtain consent from upto 150 participants to undergo baseline evaluation, including assessment of frailty. We expect 50% of these participants will be frail or pre-frail and eligible for randomization. Because this is a pilot trial, no power calculation for the randomized trial has been performed. We will be enrolling 24 participants into the pilot study.

**Statistical methods:** Descriptive statistics will be used to evaluate primary outcomes 1-3 (i.e. the rate of identification of eligible patients; the proportion of eligible patients consenting to participate, and randomized; and the rate of adherence to the trial interventions). Primary outcome 4 (the obstacles to and facilitators of adherence to the intervention) will be analyzed using a mixed methods approach, which will synthesize quantitative data from questionnaires on adherence, and qualitative data obtained from focus group interviews. Qualitative data on obstacles to and facilitators of exercise adherence will be

analyzed by the manual analysis of focus group interview transcripts to identify themes.

### *Data Handling and Record Keeping*

**Clinical CRFs and Source Documentation:** Study personnel at participating sites will complete e-CRFs by accessing a computerized program (i.e., OMNICOMM) via the internet and entering the required trial information directly into the e-CRFs for electronic submission to a server located at PHRI.

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation for all participants. Source documentation supporting the trial information reported on the e-CRF will be filed at the Investigator's site and made available for trial related monitoring, audits, IRB/IEC review, and regulatory inspections when required. In addition to this, copies of source documentation supporting outcome events and key study requirements will be blinded to identifying patient information and submitted to PHRI for central review. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

**Record Retention:** The Investigator must retain all study records/files, including nutritional supplement disposition records, copies of CRFs (or electronic files), and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures whichever is longer.

**Data Management Plan:** An internal Data Management Plan will be developed by the Population Health Research Institute to outline the detailed strategies for ensuring quality in data collection and reporting. This will include but is not limited to a description of the data management systems to be used, database design, set-up, testing and validation, database access and security, data validation strategies, reporting and communication strategies, handling of protocol deviations, database closeout and archiving.

***Participant information and consent***

All relevant information on the study will be summarized in a participant information sheet and informed consent form provided by the study centre or delegate. A sample subject information and informed consent form is provided as a document separate to this protocol.

Based on this participant information sheet, the investigator or designee will explain all relevant aspects of the study to each subject / legal representative or

proxy consenter (if the participant is under legal protection), prior to his entry into the study (i.e. before any examinations, study procedures, or any study-specific data are recorded on study-specific forms).

Each participant / legal representative or proxy consenter will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the participant / legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The participant / legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the participant's note/file of the medical institution. Any other handling and storage of the signed informed consent statement will be detailed in the informed consent form.

### *Patient Confidentiality*

All patient information will be stored on a high security computer system and kept strictly confidential. Subject confidentiality will be further ensured by utilizing subject identification code numbers to correspond to treatment data in the computerized files.

Individual subject medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited except for the following reason; medical information may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of the trial are to be available for inspection on request by the participating physicians, IRB/IEC, and Competent Authorities.

### *Patient Risk and Safety*

Potential risks of exercise in cardiac device recipients include shocks delivered by implantable defibrillators, arrhythmias and device lead dislodgement. One systematic review of exercise training in cardiac device patients found that the incidence of these adverse effects was low (1-2%)(53), while another meta-analysis found that the risk of defibrillator shocks among those undergoing an exercise program may eventually be lower than among controls (pooled odds ratio, 95% CI 0.47, 0.24-0.91)(63). Approximately 5 % of patients taking a protein

and/or creatine supplement will experience some abdominal bloating, cramping, gas and/or loose stools.

***Monitoring***

In accordance with applicable regulations, GCP, and PHRI's procedures, and PHRI project office staff will contact cardiac rehabilitation center prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy ethical requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

PHRI is responsible for the monitoring of the study. The purpose of monitoring is to verify that the data and study procedures have been conducted as described in this protocol and to ensure the validity of the study results. Study monitors will verify that:

1. Data are authentic, accurate and complete
2. Safety and rights of subjects are being protected
3. Study is conducted in accordance with the currently approved protocol
4. Any other study agreements are met. Monitoring will encompass a variety of methods at the central, and site levels; incorporate central data verification.

5. Signed informed consent will be verified to ensure that consent has been obtained.

**Discussion**

The DEFINIT-P trial will evaluate the feasibility of a larger trial on whether a supervised exercise program and a nutritional supplement taken for a year will improve physical frailty and whether the improvement translates to better clinical outcomes in elderly cardiac device recipients. The exercise intervention selected will be simple to implement with minimal equipment requirements and personalized to patients' abilities. The nutritional supplement is also available over the counter for use and can be continued upon the completion of the study. This will be first study to evaluate these interventions in an elderly cardiac device population.

The benefits of physical activity in general population is well established with lower risks of all-cause mortality, cardiovascular morbidity and mortality, stroke, diabetes, osteoporosis, falls and dementia.(39-42) The LIFE study was a multicenter randomized controlled trial comparing a supervised moderate-intensity physical activity program to health education in sedentary elderly population.(64) This study showed that the physical activity program reduced the risk of the primary outcome of first occurrence of major mobility disability (hazard ratio 0.82, 95% confidence interval 0.69 to 0.98; $p = 0.03$). More importantly, the

benefit of the intervention reduced the major mobility disability burden over an extended period of time (RR 0.75; 95% CI 0.64 to 0.89). In another study, Ng et al. randomised elderly to physical exercise, nutrition, cognitive training or combination treatment program for 6 months. This study showed improved frailty scores at 6 and 12 months in all groups with combination group reporting the greatest reduction, followed by physical therapy and finally cognitive therapy. Group based exercises have also been studied which incorporated balance and strength training exercises for 12 weeks and found improvement in gait speed, stand up test and Barthel index which were maintained at 36 weeks of retesting ($p < 0.05$).(65) Programs that showed improvement in frailty status focused on variety of exercise types targeting different muscle groups and mimicking day to day movements. We have aimed to have a variety of exercise types in the DEFINIT-P study which will have one hour supervised exercise sessions that incorporates aerobic, strength training and balance exercises.

Studies on nutritional supplementation alone such as increased protein intake have produced conflicting results. Certainly, it is well accepted that malnutrition in the elderly is associated with poor health outcomes including decreased functional status, muscle mass and greater risk of nursing home admission and mortality.(66) Borsheim et al supplemented a protein mix in elderly and found increased lean body mass, strength and physical function over a 16

week period.(67) This was supported by Bonnefoy et al designed a 2x2 factorial design involving protein supplement and exercise over a 9 month trial period.(68) Patients taking the nutritional supplement alone had increased muscle power by 57% at 3 months ($p=0.03$) and 2.7% at 9 months. In contrast, Carlsson et al did not find an increase in muscle mass or body weight with a 3 month supplementation of protein supplementation. Additionally, Fiatarone et al also did not find any improvement in muscle weakness or physical frailty when nutritional supplementation was used alone.(69) These studies have small sample size, short duration of supplementation, short follow up periods and have a high risk of selection bias. A randomized, double blind, placebo controlled trial of 65 patients studied the effects of a twice a day protein supplementations versus placebo and found no difference in any biochemical measure, skeletal muscle mass, or in hand and lower body muscle strength after 24 weeks.(70) It did show a significant improvement in overall physical performance which was tested by a composite score of gait, balance and chair rise test at 24 weeks ($p=0.02$). Arguably, when it comes to frailty, the improvement of physical performance is of greatest importance compared to mass alone. Creatine is another supplement that has been studied. In older adults, short term creatine monophosphate supplementation increased body mass, enhanced fatigue resistance, increased muscle strength and improved the performances of activities of daily living, irrespective of whether combined with resistance training or not. (56-58)

DEFINIT-P will study the effects of a combination of whey protein and creatine supplementation on improvement of physical frailty and will have both a long supplementation (1 year) and follow up periods.

The DEFINIT-P study will complement the existing studies and add to the gaps in literature in several ways. First, the supervised component of the exercise program is carried out by an exercise physiologist who can adjust the workouts to meet the abilities of patients. This will reduce the risk of intervention discontinuation. Frail elderly may have concerns about falling or other injuries which supervision and support can help overcome.(71) Second, we have combined strength training, balance training and aerobic exercises which have not been studied before. Targeting different aspects of physical performance will lead to greatest benefits from a physical activity program. Thirdly, if DEFINIT-P were shown to be feasible, it would lead to the largest to date randomized controlled trial that will have sufficient statistical power to detect reductions in other hard outcomes such as all-cause mortality or cardiovascular morbidity and mortality. Fourth, tracking physical activity levels using cardiac device data will be a novel method which can lead to new ways physicians can use the device data to improve the health of their patients. Lastly, safety of exercise intervention in these patients with respect to arrythmias or inappropriate shocks will be studied.

One of the biggest challenges to lifestyle modification interventions including diet and exercise is adherence. In one study involving home based exercise program in elderly frail population with 10 visits by a physiotherapist as well as dietitian recommended nutritional supplements, the adherence rate was poor between 25-49%.(72) Another exercise study that tested a 15 week group Tai Chi program for reducing risk of falls, had a drop out of 40% throughout the duration of the study.(73) The LIFE study which is what the DEFINIT-P study is modelled after reported over an average follow-up of 2.7 years, 58.6% of the intervention group needed at least one medical leave, and after excluding these, the attendance rate at the scheduled supervised sessions was 63%. Therefore, we would expect similar if not better attendance rate for the DEFINIT-P study which will enrol 12 patients into the exercise intervention arm. The supervised component of the exercise intervention is critical to adherence which ultimately leads to benefits observed with exercise. It would also be important to ascertain the barriers to exercise participation particularly in an elderly cardiac device population that have many comorbidities. The focus interviews which are conducted by a trained specialist will provide crucial data in terms of the challenges faced during the intervention period and allow for improvement of protocol for the larger study.

In summary, the DEFINIT-P trial will evaluate the feasibility of a larger trial on whether a supervised exercise program and a nutritional supplement taken for a year will improve physical frailty and whether the improvement translates to better clinical outcomes in elderly cardiac device recipients.

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**Figure 1: Study design and overview of the DEFINIT-P trial**

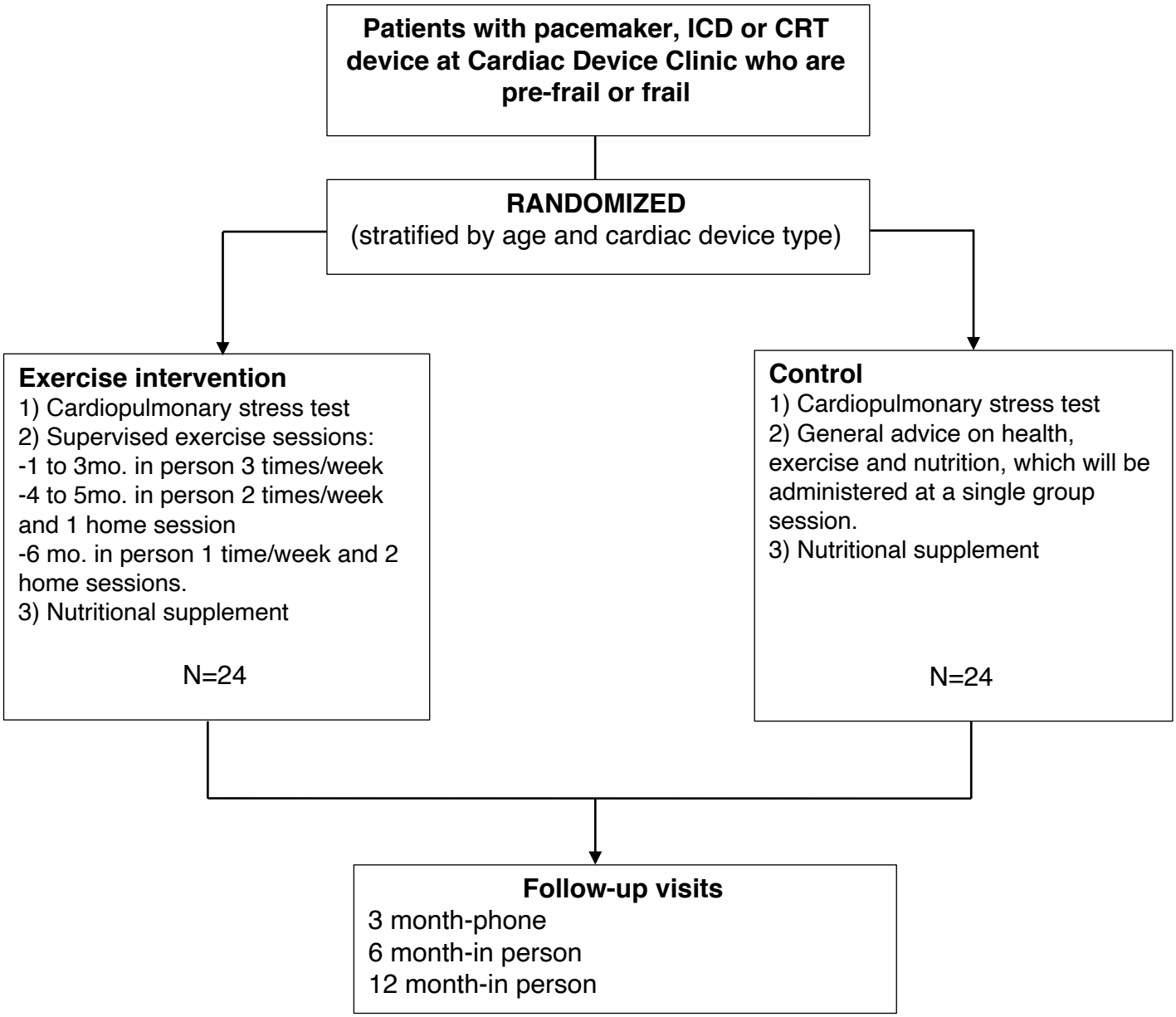

**Table 1: Eligibility criteria for the DEFINIT-P trial**

**Inclusion criteria**

1. Permanent pacemaker recipients **OR**
2. Implantable cardioverter defibrillator recipients

**AND** one of:

3. Pre-frail **OR**
4. Frail

**Exclusion Criteria**

Patients will be excluded if they fulfil any of following:

a) Age <55 years or
b) Unwilling to consent

Patients will be eligible for the registry but not eligible for the randomized control trial if they fulfill any of:

a) Are non-frail
b) Existing referral for cardiac rehabilitation
c) Severe heart failure (New York Heart Association class IV)
d) Dementia, as identified by a Montreal Cognitive Assessment score <21
e) Unstable angina
f) Any other medical condition that will prevent exercise participation

**Table 2: Study procedures**

| | Screening | | Baseline | 3-months* | 6-months | 12-months |
|---|---|---|---|---|---|---|
| Demographics | All | | | | | |
| Co-morbidities, Medications | All | | | RCT | RCT | RCT |
| **Cardiac Device Information** | | | All | | RCT | RCT |
| Montreal Cognitive Assessment | All | | | | | RCT |
| Vital signs, anthropometrics | All | | | | RCT | RCT |
| Frailty measurements | All | | | | RCT | RCT |
| PAQ | All | | | RCT | RCT | RCT |
| PHQ-9 | All | | | | | RCT |
| EQ5D | RCT | | | RCT | RCT | RCT |
| Cardiopulmonary exercise test | | | RCT | | | |
| Blood specimen | | | All | | RCT | RCT |
| Clinical outcome events | | | | RCT* | RCT | RCT |
| Adherence to the intervention if in the intervention group | | | | RCT* | RCT | RCT |

**Table 3: Definitions of outcomes**

| Term | Definition |
|---|---|
| **Serious AE (SAE)** | Any untoward medical occurrence that at any dose:<br>• results in death<br>• is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)<br>• requires inpatient hospitalization or causes prolongation of existing hospitalization (see section 7.1.2 for description of hospitalizations that are exempted from SAE reporting)<br>• results in persistent or significant disability/incapacity<br>• is a congenital anomaly/birth defect<br>• is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above. (Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) |
| **Atrial fibrillation** | A supraventricular arrhythmia with uncoordinated atrial activation and, consequently, ineffective atrial contraction. ECG characteristics include: 1) irregular atrial activity, 2) absence of distinct P waves, and irregular R-R intervals (when atrioventricular conduction is present). |
| **Ventricular tachycardia** | • Cardiac arrhythmia of ≥3 consecutive complexes originating in the ventricles at a rate >100 bpm (cycle length: <600 ms).<br>• Types of VT: |

| | |
|---|---|
| | ○ Sustained: VT >30 s or requiring termination due to hemodynamic compromise in <30 s. n Nonsustained/unsustained: ≥3 beats, terminating spontaneously.<br>○ Monomorphic: Stable single QRS morphology from beat to beat.<br>○ Polymorphic: Changing or multiform QRS morphology from beat to beat.<br>○ Bidirectional: VT with a beat-to-beat alternation in the QRS frontal plane axis, often seen in the setting of digitalis toxicity or catecholaminergic polymorphic VT |
| **Myocardial Infarction** | The MI definition is based on the Third Definition of MI and includes the following:<br>1. **Either** Cardiac ischemic symptoms (e.g. pain such as pressure, tightness or dyspnea) at rest or ischemic symptoms on minimal exertion, either of which lasts ≥ 20 minutes that the investigator determines is secondary to ischemia,<br>2. **OR** ECG or imaging changes consistent with MI in the absence of conduction abnormalities<br>3. New ECG changes indicative of trans-mural infarction<br>a. Q wave in leads V2 and V3 ≥ 0.02 sec or<br>b. QS complex in leads V2 and V3 or<br>c. Q wave ≥0.03 sec and ≥ 0.1 mV deep in leads I, II, aVL, aVF or V4-V6 in any two leads of a contiguous lead grouping [lateral - I and aVL; precordial V1-V6; infero-posterior - II, III, aVF] or<br>4. QS complex in leads I, II, aVL, aVF or V4-V6 in any two leads of a contiguous lead grouping [lateral - I and aVL; precordial - V1-V6; infero-posterior - II, III, aVF] or<br>a. R wave ≥ 0.04 sec in V1 and V2 and R/S ≥ 1 with a concordant positive T wave |

| | |
|---|---|
| | 5. New significant ST-segment- T-wave changes in two or more contiguous leads:<br>a. ST elevation at the J point ≥ 0.1 mV in all leads other than leads V2 and V3 where the following cut points apply: ≥ 0.2 mV in men ≥ 40 years; 0.25 mV in men < 40 years, or<br>b. ST depression horizontal or down sloping ≥ 0.05 mV, or<br>c. T wave inversion ≥ 0.1mV with prominent R wave or R/S ratio ≥ 1.<br>6. Development of new left bundle branch block (LBBB)<br>7. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality<br>8. Identification of an intracoronary thrombus by angiography<br><br>**And**<br><br>Elevation of cardiac biomarker values (Troponin preferably, CKMB, AST, LDH or myoglobin) with at least one value above the 99th percentile upper reference limit (URL) of the local laboratory.<br>NOTE: In the absence of a clinical MI, cardiac troponin may be elevated in several conditions such as heart failure, tachy/brady arrhythmia, aortic dissection, pulmonary embolism, severe respiratory failure, sepsis, renal failure, stroke, subarachnoid hemorrhage, severe anemia, contusion, myocarditis, strenuous exercise, etc. |
| **Stroke** | Stroke is defined as acute focal or global neurological dysfunction caused by brain or retinal vascular injury due to primary hemorrhage or infarction.<br>Symptoms or signs must persist >24 hours or when acute stroke is identified on brain imaging (i.e. if there is an acute/subacute stroke documented by CT or MRI) or at autopsy, the duration of symptoms/signs may be less than 24 hours. If death occurs within 24 hours, the neurological deficit must persist up to the |

| | |
|---|---|
| | time of death. Stroke can be a clinical diagnosis; while no neuroimaging is required for a diagnosis of stroke, neuroimaging makes the diagnosis more reliable. Stroke does not include diffuse brain ischemia due to anoxic-ischemic encephalopathy, or subdural hematoma.<br><br>Key data elements for the diagnosis of stroke (type-unspecified):<br>1. Was there abrupt onset of focal or global neurological deficit?<br>2. Did symptoms/sign persist for >24 hours?<br>a. If not, was there neuro-imaging evidence of acute brain infarction or hemorrhage?<br>3. Absence of an identified nonvascular cause?<br><br>Based on the clinical symptoms or signs, and computerized tomography (CT) or MRI imaging, strokes will be classified as:<br>1. Ischemic stroke<br>2. Hemorrhagic stroke<br>a. Primary intracerebral / intraparenchymal brain hemorrhage<br>b. Subarachnoid hemorrhage<br>b) Uncertain or unknown stroke |
| **Ischemic stroke** | Stroke with CT or MRI performed within 3 weeks that is either normal or shows infarct in the clinically expected area, or evidence of infarct in autopsy. Secondary hemorrhagic transformation of an ischemic stroke, even if severe, is categorized as ischemic stroke. |
| **Hemorrhagic stroke** | *Intraparenchymal brain hemorrhage*<br>Stroke with CT/MRI evidence of primary hemorrhage into the brain parenchyma including the brainstem and cerebellum (does not include hemorrhage secondary to ischemic stroke 'hemorrhagic transformation', post-traumatic bleeding into an area of contusion, hemorrhage into a tumour). Primary intraventricular hemorrhage should be included as intracerebral hemorrhage. |

| | |
|---|---|
| | *Subarachnoid hemorrhage*<br>CT or cerebrospinal fluid evidence of bleeding primarily in the subarachnoid space. Subarachnoid hemorrhage related to traumatic cerebral contusion or skull fracture not be counted as a stroke outcome (i.e. traumatic subarachnoid hemorrhages are not counted as strokes). Large or superficial intracerebral hemorrhages often are associated with minor amounts of subarachnoid hemorrhage, but these should be classified as intraparenchymal hemorrhages. |
| **Uncertain or unknown stroke** | Definite stroke that does not meet the above criteria for ischemic or hemorrhagic stroke (e.g. CT scan or MRI not done). The neurological deficit must have been present for 24 hours or more. |
| **Heart Failure** | The definition of heart failure has been adapted from clinical guidelines. Heart failure is defined as a clinical syndrome with at least one consistent sign (from tachycardia, tachypnea, pulmonary crepitation's, pleural effusion, raised jugular venous pressure, peripheral edema, or hepatomegaly) or symptom (from dyspnea, fatigue, dependent edema, symptoms of splanchnic congestion) of heart failure, plus either one positive diagnostic test (such as BNP > 400 or NT- pro BNP > ULN or chest X-ray showing pulmonary congestion, edema, pleural effusion, or cardiomegaly, or echocardiographic abnormality). |
| **Classification of Deaths** | Deaths will be classified as either vascular or non-vascular. All deaths will be assumed to be vascular in nature unless a non-vascular cause can be clearly provided.<br><br>Vascular death: includes cardiac deaths (e.g. cardiogenic shock, arrhythmia/sudden death, cardiac rupture) and other vascular deaths (e.g., stroke, pulmonary embolism, ruptured aortic aneurysm or dissection). All hemorrhagic deaths will be classified as cardiovascular deaths.<br><br>Non-vascular death: includes all deaths due to a clearly documented non-cardiac and non-vascular |

| | |
|---|---|
| | cause, such as respiratory failure (excluding cardiogenic pulmonary edema), infections/sepsis, neoplasm, and trauma (including suicide and homicide). |
| **Falls** | Fall defined as an event which results in a person coming to sudden, unintentional rest on the ground or other lower level, not as a result of a major intrinsic event (such as stroke) or overwhelming hazard. |
| **NYHA Class IV heart failure** | Defined as a physician decision to treat HF with IV diuretic, inotropic agent or vasodilator plus at least one of the following:<br>1) presence of pulmonary edema or pulmonary vascular congestion on chest radiograph thought to be due to HF; 2) râles reaching above the lower 1/3 of the lung fields thought to be due to HF; or 3) PCWP or LVEDP ≥18 mm Hg.<br><br>In the case of NYHA Class IV heart failure occurring as an outpatient, re-admission to an acute care facility is required in addition to the above criteria. Worsening HF is defined as requiring assisted ventilation (CPAP) or cardiogenic shock for those patients that already have HF. |

## Appendix A: Fried's Frailty Phenotype Criteria

*Criteria Used to Define Frailty*

- **Weight loss:** "In the last year, have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)?" If yes, then frail for weight loss criterion. At follow-up, weight loss was calculated as: (Weight in previous year – current measured weight)/(weight in previous year) = K. If K ≥ 0.05 and the subject does not report that he/she was trying to lose weight (i.e., unintentional weight loss of at least 5% of previous year's body weight), then frail for weight loss = Yes.
- **Exhaustion:** Using the CES–D Depression Scale, the following two statements are read. (a) I felt that everything I did was an effort; (b) I could not get going. The question is asked "How often in the last week did you feel this way?" 0 = rarely or none of the time (<1 day), 1 = some or a little of the time (1–2 days), 2 = a moderate amount of the time (3–4 days), or 3 = most of the time. Subjects answering "2" or "3" to either of these questions are categorized as frail by the exhaustion criterion.
- **Physical Activity:** Based on the short version of the Minnesota Leisure Time Activity questionnaire, asking about walking, chores (moderately strenuous), mowing the lawn, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golf, singles tennis, doubles tennis, racquetball, calisthenics, swimming. Kcals per week expended are calculated using standardized algorithm. This variable is stratified by gender.
  *Men*: Those with Kcals of physical activity per week <383 are frail.
  *Women*: Those with Kcals per week <270 are frail.
- **Walk Time**, stratified by gender and height (gender-specific cutoff a medium height).

| *Men* | *Cutoff for Time to Walk 15 feet criterion for frailty* |
|---|---|
| Height ≤ 173 cm | ≥7 seconds |
| Height > 173 cm | ≥6 seconds |
| *Women* | |
| Height ≤ 159 cm | ≥7 seconds |
| Height > 159 cm | ≥6 seconds |

- **Grip Strength**, stratified by gender and body mass index (BMI) quartiles:

| *Men* | *Cutoff for grip strength (Kg) criterion for frailty* |
|---|---|
| BMI ≤ 24 | ≤29 |
| BMI 24.1–26 | ≤30 |
| BMI 26.1–28 | ≤30 |
| BMI > 28 | ≤32 |
| *Women* | |
| BMI ≤ 23 | ≤17 |
| BMI 23.1–26 | ≤17.3 |
| BMI 26.1–29 | ≤18 |
| BMI > 29 | ≤21 |

## Appendix B: Nutritional Supplement

Serving Size: 1 Scoop (44g)
Servings Per Container Approx. 103

| Amount Per Serving | % Daily Value |
|---|---|
| Calories | 160 |
| Calories From Fat | 20 |
| Total Fat | 2.5 g 4%* |
| Saturated Fat | 1.5 g 8%* |
| Cholesterol | 70 mg 23% |
| Total Carbohydrate | 4 g 1%* |
| Sugars | 1 g † |
| Protein | 30 g 60%* |
| Calcium | 170 mg 17% |
| Iron | .87 mg 5% |
| Sodium | 140 mg 6% |
| **Nitro-Amino Matrix** | |
| L-Leucine | 3.2 g † |
| (as Whey Protein, L-Leucine) | |
| L-Isoleucine | 1.9 g † |
| (as Whey Protein, L-Isoeucine) | |
| L-Valine | 1.8 g † |
| (as Whey Protein, L-Valine) | |
| **Scientifically Studied Musclebuilder** | |
| Creatine Monohydrate | 3 g † |

* Percent Daily Values are based on a 2,000 calorie diet
† Daily Value not established

**Other Ingredients:**

Isolate Protein & Peptide Blend (Whey Protein Isolate, Whey Peptides, Whey Protein Isolate 97%), Whey Protein Concentrate , Cocoa (Processed With Alkali), Natural And Artificial Flavors, Soy or Sunflower Lecithin, Gum Blend (Cellulose , Xanthan, Carrageenan), Enzyplex (Papain, Amylase), Salt, Sucralose, Acesulfame-Potassium.

**Contains Milk And Soy Ingredients. Processed In A Facility That Also Processes Egg, Wheat, Tree Nut, Peanut, Fish and Shellfish Ingredients.**

# CHAPTER 3

# CLINICAL CHARACTERISTICS AND PREVALENCE OF FRAILTY IN CARDIAC DEVICE RECIPIENTS: INTERIM ANALYSIS OF DEFINIT-P STUDY

## ABSTRACT

### Background

Frailty is common in cardiac device patients. The aim of this pilot study, that will determine the feasibility of a larger multi-center randomized controlled trial (RCT), is to evaluate the efficacy of a supervised exercise program and nutritional supplement program in preventing or reversing progression of frailty in cardiac device recipients.

### Methods

Consecutive patients were recruited from an outpatient device clinic to be enrolled to either the RCT or the frailty registry. Patients were eligible for randomization if they had a cardiac device (permanent pacemaker, implantable cardiac defibrillator or cardiac resynchronization therapy) and were either prefrail or frail as measured by the Fried Frailty Criteria. Patients in the RCT were randomized to a 12 month supervised exercise program versus single education session on diet and exercise. All patients received a nutritional supplement containing whey protein powder and creatine.

### Results

Study was stopped early due to the limitations imposed by the COVID 19 pandemic. Over a 5 month period we recruited 14 patients into the RCT and 53 into the registry. The prevalence of frailty and pre-frailty was 48.5% and 51.5% were non-frail. The frail cohort was older with a mean age of 76.3 ±8.1 years

compared to 72.7 ±7.1 years in the non-frail cohort. Handgrip strength (OR 0.9, 95%CI 0.82 to 0.98, p=0.02) and 15 feet walk time (OR 2.49, 95% CI 1.06 to 5.83, p=0.04) showed a significant association with frailty. In terms of comorbidities, a history of diabetes and CABG were associated with frailty.

**Conclusion**

Frailty is common in recipients of cardiac devices. Individual frailty domains (handgrip strength, walk time and exhaustion) and history of CABG and diabetes were associated with frailty. We showed that our original estimate of 1 year to enroll all patients into the RCT and registry was feasible.

## INTRODUCTION

Frailty is common in cardiac device recipients. Frailty is a biologic syndrome of decreased reserve to stressors, resulting from cumulative declines across multiple physiologic systems leading to a decline in homeostatic reserve and resiliency.(1) Frailty is associated with adverse outcomes such as increased falls, hospitalizations, worsening disability, nursing home admissions and mortality.(6-9) The implantation of cardiac devices (pacemakers and defibrillators) is increasing rapidly. In Canada, the number of pacemakers alone increased from 14,375 in 2006 to 16,532 in 2012 [4]. In the US, pacemaker implantation increased by 56% between 1993 and 2009, during which there were nearly 3 million recipients [5].

Though frailty has been recognized in recent years as an important health outcome measure, there is a paucity in literature with respect to interventions aimed at improving or preventing frailty in cardiac device recipients. Nonpharmacological treatments including physical activity, nutritional supplements or combination of both have been studied. The health benefits of physical activity in general population is well established with lower risks of mortality from all causes, mortality and morbidity from cardiovascular causes, lower risk of stroke, diabetes, osteoporosis, falls and dementia.(39-45) Acute exercise has also been shown to improve long term memory function and long-term exercise optimizes the molecular machinery responsible for memory

processing.(46) However, whether improving frailty translates to improved health outcomes is not well known. The aim of this pilot study, that will determine the feasibility of a larger, multi-center randomized clinical trial, is to evaluate the efficacy of a supervised exercise program and nutritional supplement program in preventing or reversing progression of frailty in cardiac device recipients.

## METHODS

### *Study design*

The DEFINIT-P study was a prospective, single centre, parallel group, open label pilot randomized controlled trial. Consecutive patients with a cardiac device (permanent pacemaker, implantable cardiac defibrillator or cardiac resynchronization therapy) were recruited from an outpatient device clinic to be enrolled to either the RCT or the frailty registry. Approximately 24 patients will be enrolled into the RCT and followed for 12 months. We also planned to recruit 100 patients into the registry irrespective of whether they entered the RCT. The objective of this study was to test the feasibility of a larger trial and to identify obstacles to and facilitators of adherence to the intervention. The protocol was approved by institutional review of the local centre.

### *Patients*

Patients were eligible for randomization if they had a cardiac device (permanent pacemaker, implantable cardiac defibrillator or cardiac resynchronization therapy) and were either prefrail or frail. We excluded patients

who were less than 55 years of age or unwilling to consent. Patients were eligible for the registry but not the RCT if they were nonfrail, had existing referral for cardiac rehabilitation, severe heart failure, dementia as defined by a Montreal Cognitive Assessment (MOCA) score of <21, unstable angina or any other medical condition which prevented exercise participation.

### *Frailty measurement and definition*

Frailty was measured using Fried Frailty Criteria (Appendix A) which is operationally defined by the presence of number of phenotypic criteria including: unintentional weight loss, exhaustion, grip strength, walking speed and low physical activity.(1) We used the Physical Activity Questionnaire to determine physical activity levels instead of the Minnesota Leisure Time Activity questionnaire.

Frailty definitions

| | |
|---|---|
| Fried Frailty Criteria | **Weight loss:** unintentional weight loss of at least 4kg in the last year.<br>**Exhaustion:** Response of "a moderate amount of the time (3-4) days" or "most of the time" to: "I felt that everything I did was an effort" during the past week.<br>**Physical activity levels:** will be calculated using the Physical Activity Questionnaire.<br>**Walk time:** Time in seconds to complete 15 feet walk at usual pace. Stratified by gender and height.<br>**Grip Strength:** Low grip strength as measured by a dynamometer. Stratified by gender and BMI quartiles. |
| Non-frail | Zero criteria met |
| Pre-frail | Meets 1 or 2 criteria |
| Frail | ≥3 criteria are met |

### *Randomization and interventions*

Participants consenting to involvement in the RCT would be randomized by the Interactive Web Randomization System (IWRS) to either the exercise intervention group or the control group in a 1:1 ratio. The IWRS is a 24-hour computerized randomization internet system maintained by the coordinating centre at the Population Health Research Institute (PHRI), which is part of Hamilton Health Sciences and McMaster University in Hamilton, Ontario, Canada. Randomization would be stratified cardiac device type. All participants will be receiving the nutritional supplement and will not be randomized.

All patients randomized to the exercise intervention arm will undergo cardiopulmonary exercise testing before starting the exercise program at the Hamilton Health Sciences Cardiac Health and Rehabilitation Centre. A kinesiologist will use the stress test results to prescribe an individualized exercise program containing a combination of aerobic, strength and balance training for all major muscle groups. During months 1 to 3, intervention participants would attend supervised sessions 3 times per week. Participants will continue to attend 2 times per week during months 4 and 5, with additional home-based exercise undertaken to meet the exercise goal. After 5 months of supervised exercise, participants will be expected to continue exercise as a home-based program or at a private gym of their choice for months 6-12. If exercises became difficult, the program would be modified to meet the participants' fitness level. Participants will

be provided with a log to record their exercise participation. The control group will also undergo cardiopulmonary stress test to establish a baseline fitness level. They will receive general advice on health, exercise and nutrition, administered at a single group session. At present, this is equivalent to standard-of-care for cardiac device recipients. All participants in the RCT will receive a 12 month supply of a nutritional supplement blend containing whey protein powder and creatine taken once daily.

***Statistical analysis***

We used descriptive statistical methods (means and standard deviation) for continuous variables and frequencies for categorical variables. Characteristics of frail and nonfrail groups were compared with ANOVA for parametric variables and the Kruskal-Wallis test for nonparametric variables. The frailty variable was dichotomized into a non-frail group (Fried frailty score=0) and the pre-frail (Fried frailty score=1-2) and frail (Fried frail score $\geq$ 3) groups were combined into one "frail" cohort. We examined all potential variables associated with frailty using univariate logistic regression first and variables which had a p value of <0.1 were selected for inclusion into the multivariate regression model with backward elimination. We conducted analysis based on two models. Model 1 included only the frailty domains of grip strength, exhaustion and 15 feet walk time. Physical activity questionnaire (PAQ) scores and unintentional weight loss were skewed and not normally distributed as such regression analysis could not be performed

and were excluded from the analysis. Model 2 included all components of Model 1 as well as demographics and comorbidities. Results were presented as odds ratios and 95% confidence intervals.

**RESULTS**

From November 11, 2019 to March 13, 2020, a total of 67 patients were enrolled from the Hamilton Health Sciences Cardiac Device Clinic: 14 were eligible for randomization for the pilot randomized controlled trial and 53 were enrolled into the registry. One person refused the PAQ and was excluded from this analysis since a frailty score could not be calculated as such the total sample in the cohort was 66. The most commonly cited reasons for exclusion into the RCT were absence of frailty (64% were not-frail) and presence of dementia (40%). Three patients were excluded due to exercising >1 hour per week and 1 patient had moderate to severe congestive heart failure.

The baseline characteristics of the study cohort are presented in Table 1. The combined prevalence of frailty and pre-frailty was 48.5% (10.6% were frail and 37.9% were pre-frail) and 51.5% were non-frail. The frail cohort was older with a mean age of 76.3 ±8.1 years compared to 72.7 ±7.1 years in the non-frail cohort. A male predominance was observed in the overall study cohort (79%) with no significant differences between the frail and non-frail groups (p=0.64). There were 37 (56%) patients with permanent pacemaker, 15 (23%) had ICD and 14 (21%) CRT patients. There were no differences between frail and non-frail

groups with respect to device types, p=0.39. A higher proportion of non-frail patients had postsecondary education (64.7% vs. 40% in the frail group). The mean MOCA score was higher in the non-frail group at 24.3 ±3.2 compared to frail group who had a score of 19.7 ±4. Frail group had slightly higher mean number of medications 9.3 ±4.2 compared to non-frail group 7.4 ±3.9. Frail group also had higher mean number of comorbidities 5.2 ±2.6 compared to non-frail 4 ± 1.8. A history of myocardial infarction, prior PCI, CABG and diabetes were higher in the frail group compared to non-frail. Though non-frail group had higher history of cancer (14 vs. 9).

**Frailty domains**

Weight loss of >4kg in 1 year was very common in frail group (66%) compared to non-frail group which did not report any weight loss. Exhaustion of at least moderate amount was present in 22% of the frail group compared to none in the non-frail group. The mean PAQ scores were higher in the non-frail group compared to frail, 4890 kilocalories ±3931 vs 3689 kilocalories ± 3138. The mean handgrip strength, as measured by a dynamometer, was higher in the non-frail group 37.2kg ± 8.2 as opposed to 26.6kg ±7.5 in the frail group. The mean 15 feet walk time was quicker in the non-frail group 4.5 seconds ±0.8 compared to 5.9 seconds ±1.4 in the frail group.

**Univariate and multivariate analysis**

The results from the univariate analysis (Table 2) of the frailty domains and demographics showed significant association between a history of MI (OR 6.4; 95%CI 2.2 to 19.3, p<0.001), PCI (OR 3.97; 95%CI 2.2 to 19.3, p=0.02), CABG (OR 5.13; 95%CI 1.5 to 18.1, p=0.01), diabetes (OR 4.4; 95%CI 1.5 to 12.9, p=0.008), mean MOCA score (OR 0.75; 95%CI 0.64 to 0.89, p<0.001), exhaustion (OR 4.2; 95%CI 1.2 to 15.4, p=0.03), handgrip strength (OR 0.87; 95%CI 0.8 to 0.9, p <0.001) and 15 feet walk time (OR 4.2; 95%CI 1.8 to 9.6, p<0.001) and presence of frailty. Age (OR 1.06, 95%CI 1.0 to1.1, p=0.07), number of comorbidities (OR 1.2, 95%CI 0.99 to 1.6, p=0.06) and number of medications (OR 1.1, 95%CI 0.99 to 1.3, p=0.08) showed borderline association with presence of frailty.

In the multivariate (Table 3) logistic regression Model 1 (frailty domains only) handgrip strength (OR 0.9, 95%CI 0.82 to 0.98, p=0.02) and 15 feet walk time (OR 2.49, 95% CI 1.06 to 5.83, p=0.04) showed a significant association with presence of frailty, exhaustion (OR 2.99; 95%CI 0.81 to 11.05, p=0.1) did not. In multivariate (Table 4) logistic regression Model 2 (frailty domains, demographics and comorbidities), handgrip strength (OR 0.8, 95%CI 0.66 to 0.97, p=0.03) remained a significant association with presence of frailty but not 15 feet walk time (OR 2.73; 95%CI 0.52 to 14.31, p=0.23). Moreover, a history of

CABG (OR 63.7, 95%CI 1.2 to 3487, p=0.04) and diabetes (OR 20.8, 95%CI 1.7 to 250, p=0.02) were significantly associated with presence of frailty.

## DISCUSSION

This study presents baseline characteristics and clinical variables associated with frailty in elderly cardiac device recipients. The prevalence of frailty was 11% and 38% were prefrail. Over a 5 month period, we enrolled 14 (58%) patients of targeted 24 into the pilot RCT and 53 (53%) of planned 100 into the frailty registry. The recruitment for the study was halted due to the COVID-19 pandemic which affected patient recruitment, device clinic schedules and initiation of planned RCT intervention of a supervised exercise program at the cardiac rehabilitation centre which was also closed. We showed that our original estimate of 1 year to enroll all patients into the RCT and registry was feasible.

Frailty is common in elderly cardiac device patients. In a cross-sectional study of 219 cardiac device patients, the prevalence of frailty was 12.8% and 47.5% were pre-frail which is similar to our study findings.(74) Though, patients in that study were younger with a mean age of 68 years compared to 74.5 years in this study. An analysis of 83,792 Medicare patients undergoing primary prevention ICD implantation showed a similar prevalence of frailty of 10%.(75) In contrast, the prevalence of frailty was found to be substantially higher at 61% amongst cardiac resynchronisation therapy recipients. (76) The difference could be due to the method of frailty assessment which can produce widely different

results. This is one of the current issues involving frailty assessments as there is no gold standard measurement test.

There are many patient related characteristics that are associated with frailty. Studies have shown that increased age, low education, high number of comorbidities, and medications are associated with frailty.(77-80) Our study did not show a significant association with these variables though on univariate analysis there was a borderline significance. In terms of the individual frailty domains, hand grip strength and walking speed were associated with overall frailty. Grip strength alone is a validated instrument to measure frailty in multiple different populations.(81-83) The disadvantages of this test is that it requires special equipment such as a dynamometer and its use is limited if patients have severe hand deformities due to arthritis. Walking speed alone can be used to diagnose frailty and was shown to predict poor health outcomes.(84, 85) Both of these domains measure physical frailty which is only a component of overall frailty assessments. Nevertheless, physical frailty plays an important role in elderly patients quality of life and are an attractive target of interventions aimed at improving frailty.

A history of diabetes and CABG were strongly associated with frailty in multivariate model that included patient demographics, frailty domains and comorbidities. Certainly, the accumulation of deficits model would suggest that the higher the number of comorbidities the more likely the patient would have

frailty. This in essence is the premise with frailty index instrument. Other comorbidities including a history of cancer, depression, dementia and liver disease were not associated with frailty in this study but are strong predictors of frailty status.

**Limitations**

One of the limitations of this study is its small sample size as we were not able to complete enrollment due to the COVID-19 pandemic. However, given that we recruited over 50% of our target number of patients for the RCT and registry over the course of 5 months, it would indicate that our primary objective in terms of feasibility, consent and recruitment would be achieved over the goal of 1 year. Many of the variables used were self-reported as such are prone to some recall bias. Nevertheless, the assessment of frailty was done in an objective manner. Some patients did not qualify for the study on the basis of participating in >1 hour of physical activity as defined by the patient. This exclusion criteria should be removed as this cannot be standardized amongst the patients and what each patient defines as physical activity varies significantly. Since this is a supervised exercise program study with individualized programs, all patients could potentially benefit from the exercise program as well as nutritional supplement provided that they meet the prefrail and frailty criteria.

## Conclusion

In conclusion, frailty is common in cardiac device patients. We need to investigate whether supervised exercise programs and nutritional supplementation can improve frailty status and whether or not the change in frailty status would correlate with improved patient outcomes. We hope to secure funding in order to complete this study in the near future which would allow us to design a larger randomized controlled trial.

**Table 1: Baseline characteristics of the frail and non-frail groups**

| Characteristic | Frail (n=32) | Not-Frail (n=34) | P value |
|---|---|---|---|
| Age, yr | 76.34 ±8.1 | 72.7 ±7.1 | 0.07 |
| Male sex, no. % | 26 (81.3) | 26 (76.5) | 0.64 |
| Postsecondary education, % | 13 (40.1) | 22 (64.7) | 0.34 |
| BMI, kg/m2 | 30.1 ±4.5 | 30.4 ±6.0 | 0.49 |
| Waist circumference, cm | 104.9 ±13.3 | 105 ±15 | 0.58 |
| Systolic blood pressure, mmHg | 129 ±19 | 128 ±20 | 0.37 |
| Diastolic blood pressure, mmHg | 76 ±16 | 77.1 ±10.6 | 0.78 |
| Heart rate, bpm | 76 ±11 | 65 ±9 | 0.86 |
| MOCA score, no. | 19.7 ±4 | 24.3 ±3.2 | 0.17 |
| PAQ Score, no. (%) | | | 0.51 |
| Minimal depression (PAQ ≤4) | 25 (78.1) | 30 (88.2) | - |
| Mild depression (PAQ 5-9) | 6 (18.8) | 3 (8.8) | - |
| Moderate depression (PAQ 10-14) | 1 (3.1) | 1 (2.9) | - |
| Mean # comorbidities | 5.2 ±2.6 | 4.0 ±1.8 | 0.61 |
| Mean # of medications | 9.3 ±4.2 | 7.4 ±3.9 | 0.25 |
| Myocardial Infarction no. (%) | 20 (62.5) | 1 (2.9) | <0.001 |
| Unstable Angina no. (%) | 3 (9.4) | 1 (2.9) | 0.28 |
| Previous PCI no. (%) | 13 (40.6) | 5 (14.7) | 0.02 |
| Previous CABG no. (%) | 13 (40.6) | 4 (11.8) | 0.007 |
| Heart failure no. (%) | 13 (40.6) | 16 (47.1) | 0.61 |
| Valvular disease no. (%) | 8 (25) | 8 (23.5) | 0.89 |
| Atrial fibrillation no. (%) | | | 1.0 |
| Peripheral arterial disease no. (%) | 2 (6.3) | 0 | 0.14 |
| Stroke no. (%) | 3 (9.4) | 2 (5.9) | 0.56 |
| TIA no.(%) | 6 (18.8) | 4 (11.8) | 0.43 |
| Deep vein thrombosis no. (%) | 2 (6.3) | 2 (5.9) | 0.95 |
| Pulmonary embolism no. (%) | 2 (6.3) | 1 (2.9) | 0.52 |
| Hypertension no. (%) | 26 (81.2) | 25 (75.5) | 0.46 |
| Diabetes no. (%) | 17 (53.1) | 7 (20.6) | 0.006 |
| CKD no. (%) | 5 (15.6) | 5 (14.7) | 0.92 |
| COPD no. (%) | 4 (12.5) | 5 (14.7) | 0.80 |
| Liver disease no. (%) | 1 (3.1) | 1 (2.9) | 0.97 |
| Hemiplegia/Paraplegia no. (%) | 1 (3.1) | 0 | 0.31 |

| | | | |
|---|---|---|---|
| Arthritis no. (%) | 15 (46.9) | 16 (47.1) | 0.99 |
| Diagnosis of depression/anxiety | 5 (15.6) | 5 (14.7) | 0.92 |
| Cancer no. (%) | 9 (28.1) | 14 (41.2) | 0.27 |
| Weight loss >4kg in 1 year, % | 21 (65.6) | 0 | - |
| Moderate or greater exhaustion no. % | 7 (21.9) | 0 | - |
| Mean PAQ score, kcal | 3689 ±3138 | 4890 ±3931 | - |
| Mean handgrip strength, kg | 26.6 ±7.5 | 37.2 ±8.2 | - |
| Mean 15 feet walk time, seconds | 5.9 ±1.4 | 4.5 ±0.8 | - |
| Device type | | | 0.39 |
| Pacemaker, no. (%) | 19 (59.4)) | 18 (52.9) | |
| ICD, no. (%) | 5 (15.6) | 10 (29.4) | |
| CRT, no. (%) | 8 (25) | 6 (17.6) | |

The plus-minus (±) are means and standard deviations. BMI represents body mass index. MOCA denotes Montreal Cognitive Assessment. TIA represents transient ischemic attack. PCI denotes percutaneous coronary intervention. CABG represents coronary artery bypass grafting. ICD denotes implantable cardiac defibrillator. CRT represents cardiac resynchronization therapy.

**Table 2: Univariate analysis of variables associated with frailty**

| Variable | Odds ratio | 95% Confidence Interval | Standard error | P value |
|---|---|---|---|---|
| Age | 1.06 | 1.0-1.1 | 0.033 | 0.07 |
| BMI | 1.004 | 0.9-1.1 | 0.046 | 0.93 |
| Waist size | 1.008 | 0.97-1.04 | 0.018 | 0.67 |
| Number of comorbidities | 1.23 | 0.99-1.63 | 0.127 | 0.06 |
| Number of medications | 1.12 | 0.99-1.26 | 0.062 | 0.08 |
| MI | 6.43 | 2.15-19.26 | 0.56 | <0.001 |
| UA | 3.4 | 0.34-34.65 | 1.18 | 0.30 |
| PCI | 3.97 | 1.22-12.95 | 0.603 | 0.02 |
| CABG | 5.13 | 1.46-18.08 | 0.643 | 0.01 |
| Heart failure | 0.77 | 0.29-2.04 | 0.50 | 0.60 |
| AF | 1.00 | 0.38-2.63 | 0.493 | 1.0 |
| Valvular disease | 1.01 | 0.35-3.34 | 0.575 | 0.89 |
| Stroke | 1.66 | 0.26-10.62 | 0.95 | 0.60 |
| TIA | 1.73 | 0.44-6.8 | 0.70 | 0.43 |
| DVT | 1.01 | 0.14-8.06 | 1.032 | 0.95 |
| PE | 2.20 | 0.19-25.51 | 1.25 | 0.53 |
| Hypertension | 1.56 | 0.48-5.03 | 0.60 | 0.46 |
| DM | 4.37 | 1.48-12.91 | 0.55 | 0.008 |
| CKD | 1.07 | 0.28-4.13 | 0.69 | 0.92 |
| Liver disease | 1.07 | 0.06-17.78 | 1.44 | 0.97 |
| COPD | 0.83 | 0.20-3.41 | 0.72 | 0.79 |
| Depression/Anxiety | 1.07 | 0.28-4.13 | 0.69 | 0.92 |
| Cancer | 0.56 | 0.20-1.57 | 0.53 | 0.27 |
| MOCA | 0.75 | 0.64-0.89 | 0.083 | <0.001 |
| PAQ | 1.62 | 0.56-4.74 | 0.55 | 0.38 |
| Exhaustion | 4.24 | 1.17-15.4 | 0.657 | 0.03 |
| Handgrip | 0.87 | 0.80-0.93 | 0.04 | <0.001 |
| 15 feet walk time | 4.16 | 1.81-9.56 | 0.42 | <0.001 |

**Table 3: Multivariate analysis of Model 1-frailty domains only**

| Variable | Odds ratio | 95% Confidence Interval | Standard error | P value |
|---|---|---|---|---|
| Exhaustion | 2.99 | 0.81-11.05 | 0.67 | 0.1 |
| Handgrip | 0.9 | 0.82-0.98 | 0.05 | 0.02 |
| 15 feet walk time | 2.49 | 1.06-5.83 | 0.434 | 0.04 |

**Table 4: Multivariate analysis of Model 2-frailty domains, demographics and comorbidities**

| Variable | Odds ratio | 95% Confidence Interval | Standard error | P value |
|---|---|---|---|---|
| Exhaustion | 2.65 | 0.31-22.49 | 1.09 | 0.37 |
| Handgrip | 0.8 | 0.66-0.97 | 0.2 | 0.03 |
| 15 feet walk time | 2.73 | 0.52-14.31 | 0.85 | 0.23 |
| Age | 0.94 | 0.81-1.09 | 0.08 | 0.43 |
| Comorbidities | 0.91 | 0.53-1.58 | 0.28 | 0.75 |
| # of medications | 0.71 | 0.47-1.07 | 0.21 | 0.1 |
| MI | 3.22 | 0.23-45.83 | 1.36 | 0.39 |
| PCI | 2.03 | 0.11-36.18 | 1.47 | 0.63 |
| CABG | 63.7 | 1.16-3486.8 | 2.04 | 0.04 |
| DM | 20.83 | 1.74-249.7 | 1.27 | 0.02 |
| MOCA | 0.80 | 0.56-1.09 | 0.16 | 0.16 |

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# CHAPTER 4

# PROPOSED PROTOCOL AMENDMENTS TO ADAPT TO CHANGES RESULTING FROM THE COVID-19 PANDEMIC

The COVID 19 pandemic has presented significant challenges to conducting clinical research. On March 11, 2020 the World Health Organization declared COVID-19 a global pandemic. As the number of cases increased, federal and local health authorities placed restrictions on delivery of health care such as reduced elective procedures and large-scale physical distancing rules. Research authorities also paused or modified ongoing clinical research that was not directly related to COVID-19 affecting many research studies including our own. At the onset of the pandemic, it was difficult to predict the impact of those initial decisions and there was uncertainty regarding when things may return to normal. In the current landscape of clinical research, changes to the DEFINIT-P protocol are required to re-engage in recruitment efforts and to conduct the study. The principal change will require flexibility on the study team to interact with patients remotely either through telephone visits or video calls. In order to ensure that study team practices meet the recommendations of physical distancing guidelines and to instill confidence in patients to participate in the study, we need to make a number of changes to the existing protocol to meet the challenge of today's pandemic landscape.

**Patient recruitment**

We planned to recruit 24 patients for the pilot randomized controlled trial (12 in the intervention arm and 12 in the control arm) and 100 patients into the DEFINIT-P registry. The recruitment stopped at 67 patients, of which 14 were

eligible for the RCT and 53 were enrolled into the registry. Due to physical distancing recommendations, in-person patient recruitment was temporarily halted and as the situation continued to unfold with increased case counts, we were unable to restart. The following protocol changes would be required to restart this study:

1) **Virtual baseline visit:** Screen all patients through their electronic medical records prior to their visit for inclusion and exclusion criteria. As per existing protocol, the Device Clinic staff would gage interest of patients to participate in the DEFINIT-P study and notify the study coordinator who would then arrange a convenient time to proceed with "Baseline Visit" protocols. The main exclusion criteria were a) are non-frail; b) existing referral for cardiac rehabilitation; c) severe heart failure (New York Heart Association class IV); d) dementia as identified by a Montreal Cognitive Assessment score <21; e) unstable angina; f) any other medical condition that will prevent exercise participation.

2) **Change the frailty instrument:** The Fried Frailty Scale has two components that must be measured in-person, these include the walk time of 15 feet and grip strength as measured by a specialized equipment called a dynamometer. This would clearly be a major limitation to recruitment. Though we were able to complete the Fried Frailty Scale in

98.5% of patients (with 1 patient opting not to do it), another study found that all 5 domains could only be measured in 65% of patients due to physical limitations that limited their abilities to walk.[1] The Edmonton Frail Scale (EFS) is another instrument which is widely used in clinical practice and research studies.[2] A version of the EFS called the Reported EFS has been modified from its original version to replace the physical task of the timed up-and-go with three questions relating to self-reported performance (Appendix A).[3] The score ranges from 0 to 18 with higher numbers denoting increased frailty. In a study of 461 hospitalized elderly, the REFS was compared with Frieds Frailty Phenotype and was found to have a moderate correlation (Kappa coefficient 0.57, 95% CI 0.49-0.66).[4] Interestingly, the prevalence of frailty identified by either of the scores was very similar though Frieds criteria was associated with a 2-fold increase in 6 month mortality and when REFS was used it was associated with a 4 fold increase in mortality.[4] Therefore, REFS is a practical alternative instrument to Frieds scale for measuring frailty. Administration of the REFS scale also does not require specialized tools or training for the study team and various electronic versions are available that can help with the scoring and provide instant frailty status.

Another option would be to construct a frailty index based on the available electronic medical records. The frailty index is constructed by identifying the number of deficits present out of total number of deficits measured. One study utilized electronic medical records of 931,541 patients available through primary care offices to construct an electronic frailty index with 36 variables tested (Appendix B).[5] The electronic frailty index showed good discrimination for the outcomes of mortality and nursing home admission, and moderate discrimination for the outcome of hospitalization. The *c* statistic estimates for these outcomes at 12 months were 0.72, 0.74 and 0.66, respectively.[5] This would be a good alternative as the majority of patients in the Cardiac Device Clinic would have all their medical records including lab results and testing available for review. If there are any data missing, study coordinators can ask directed questions during the virtual visit.

3) **Remove blood collection requirement**. As part of the pilot RCT, we planned to collect a blood sample at baseline, 6 months and 12 months which would be stored and used for assessment of frailty biomarkers and whether these biomarkers changed over time with improvement in physical frailty with our interventions. However, due to physical distancing rules for our study coordinators, we could remove this requirement from the

protocol. At this time, the landscape for biomarkers of frailty is in its very early stages of development as such excluding this component from this small pilot RCT would not change the study aims greatly.

4) **Built in flexibility for collection of vital signs and anthropometric measurements**. If patients have a home blood pressure monitor, a video call can be used to ensure proper technique has been followed otherwise this can be an optional component of the initial screening visit. There are no planned interventions based on the specific values of these measurements as such recording them when available would suffice.

**Intervention**

The crucial element of our study is that the exercise intervention is supervised compared to other studies that had self-directed exercise programs. All patients in the RCT would undergo a cardiopulmonary stress test at baseline which is a standard of care at our institution. An exercise physiologist will use the results of the test to prescribe an exercise program tailored specifically to person's ability. Patients would then attend the cardiac rehabilitation program three times a week for the first three months, followed by two times a week for two months, transition to once-a-week along with home-based workouts until month six and then the remainder of the 6-months are home-based. This was a

major limiting step in conducting this pilot trial since the Cardiac Rehabilitation Centre at the Hamilton Health Sciences was closed as a result of the pandemic. To circumvent this, virtual home-based programs could be used. A recent article published in the *Canadian Journal of Cardiology* provides a framework for developing a virtual cardiac rehabilitation program which we can adapt to implement the exercise intervention.[6]

One of the limitations of a virtual program is the lack of risk stratification prior to exercise prescription which relies on the availability of a stress test. In our study, the main reason we planned to perform the cardiopulmonary stress test was because of its requirement for attending the cardiac rehabilitation program. The aim of our intervention is not to test whether cardiac rehabilitation improves physical frailty but rather whether exercise and nutrition do. We planned to use the cardiac rehabilitation program for its convenience of having available workout equipment and trained staff. The LIFE trial, which is one of the largest RCTs involving 1635 elderly patients, did not perform a cardiopulmonary stress test in their patients prior to initiating a supervised exercise program.[7] The Duke Activity Status Index is a 12 item questionnaire that can be used to estimate functional status without the need for physical performance. Another option would be a self-administered 6-minute walk test.[8] Data from these tests can provide a starting point for exercise physiologist to program exercises which can be

performed at home. The exercises will include aerobic in the form of walking, running or climbing stairs as well as strength training and balance exercise.

The exercise physiologist can also create a one hour follow along program in which the instructor can demonstrate the movements in a group setting whilst observing participants virtually to ensure proper technique. Video exercises can utilize body weight as well as resistance bands. Since these are virtual classes, exercise physiologist and study coordinators would be able to check in one-on-one to ensure that patients are able to complete the movements and also modify any movement that cannot be performed. This would also function as a way to enhance and monitor compliance. The program's success will depend on patients having access to internet and a laptop or computer device to be able to participate. Budget permitting tablets can be provided to patients who do not have access to computers for the initial six month supervised exercise program.

**Follow-up**

Follow up visits were intended for 3 months, 6 months and 1 year. The 3 month follow up was already planned as a phone interview. The subsequent two follow ups were in person and would need to be adapted to a video visit instead. The vital signs and anthropometric measurements can be optional. If the

landscape changes over the course of the trial period such that in-person visits are allowed, these visits would turn back to in person visits.

**Adherence to intervention**

One of the challenges of an exercise intervention program is compliance particularly in an elderly population with multiple comorbidities. There are a number of strategies that can be implemented to enhance compliance and monitor adherence: 1) study coordinator can have short video calls with patients during the exercise days, 2) group exercise participation can enhance satisfaction, 3) random check-ins with patient to answer any questions or concerns, 4) Exercise levels will be assessed using the International Physical Activity Questionnaire, 5) Objective measures of physical activity will be downloaded from the participant's cardiac device (cardiac devices contain several mechanisms to allow measurement of activity levels, including piezoelectric motion sensors that allow continuous quantification of movement, estimation of minute ventilation from the body's bioimpedance, as well as data on cardiac arrhythmias, 6) Measurement of adherence to the nutritional supplement will be by a direct question about adherence.

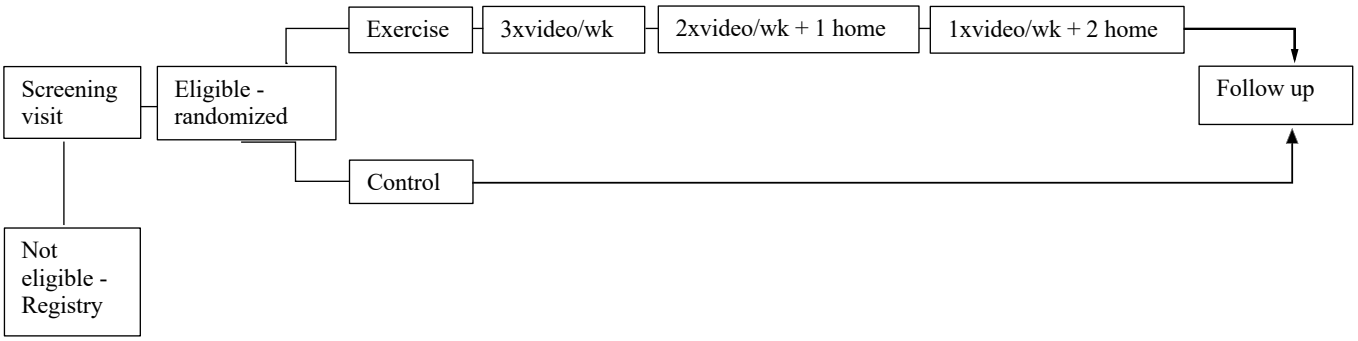


**Figure 1:** Study Flow

## Conclusion

The COVID-19 pandemic has changed how clinical research is conducted. The physical distancing recommendations have affected not only recruitment of patients into studies but also administering intervention, elective imaging, labs and follow ups. The DEFINIT-P study was stopped due to these reasons and funding period lapsed. Given the uncertainty surrounding the pandemic and local guidelines constantly changing it was difficult to predict when the study could have resumed recruitment. A number of protocol changes including virtual recruitment, delivery of the supervised exercise program over video and follow ups can help in continuing the study in the foreseeable future and perhaps reduce the associated costs. We plan to use the results of our interim analysis and apply for funding for fall of 2021 in order to complete this important study involving an elderly population that is understudied.

## Appendix A: Edmonton Frail Scale and the Reported Edmonton Frail Scale

*The main difference between the REFS and EFS is the timed up-and-go is replaced with “Self-Reported Performance” questions.

| Frailty domain | Item | 0 point | 1 point | 2 points |
|---|---|---|---|---|
| Cognition | Please imagine that this pre-drawn circle is a clock. I would like you to place the numbers in the correct positions then place the hands to indicate a time of ‘ten after eleven’ | No errors | Minor spacing errors | Other errors |
| General health status | In the past year, how many times have you been admitted to a hospital? | 0 | 1–2 | ≥2 |
| | In general, how would you describe your health? | ‘Excellent’, ‘Very good’, ‘Good’ | ‘Fair’ | ‘Poor’ |
| Functional independence | With how many of the following activities do you require help? (meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications) | 0–1 | 2–4 | 5–8 |
| Social support | When you need help, can you count on someone who is willing and able to meet your needs? | Always | Sometimes | Never |
| Medication use | Do you use five or more different prescription medications on a regular basis? | No | Yes | |
| | At times, do you forget to take your prescription medications? | No | Yes | |
| Nutrition | Have you recently lost weight such that your clothing has become looser? | No | Yes | |
| Mood | Do you often feel sad or depressed? | No | Yes | |
| Continence | Do you have a problem with losing control of urine when you don’t want to? | No | Yes | |
| Functional performance | I would like you to sit in this chair with your back and arms resting. Then, when I say ‘GO’, please stand up and walk at a safe and comfortable pace to the mark on the floor (approximately 3 m away), return to the chair and sit down’ | 0–10 s | 11–20 s | One of : >20 s , or patient unwilling , or requires assistance |
| Totals | Final score is the sum of column totals | | | |

**Scoring :**
0 - 5 = Not Frail
6 - 7 = Vulnerable
8 - 9 = Mild Frailty
10-11 = Moderate Frailty
12-17 = Severe Frailty

**TOTAL** /17

Administered by : _____

| Frailty Domain | Item | 0 Point | 1 Point | 2 Points |
|---|---|---|---|---|
| **Cognition** | Please imagine this pre-drawn circle is a clock. I would like you to place the numbers in the correct positions, then place the hands to indicate a time of ‘ten after eleven’. | No errors | Minor spacing errors | Other errors |
| **General Health Status** | In the past year, how many times have you been admitted to a hospital? | 0 | 1-2 | ≥ 2 |
| | In general, how would you describe your health? | Excellent/Very Good/Good | Fair | Poor |
| **Functional Independence** | With how many of the following activities do you require help? meal preparation / shopping / transportation / telephone / housekeeping / laundry / managing money / taking medications | 0-1 | 2-4 | 5-8 |
| **Social Support** | When you need help, can you count on someone who is willing and able to meet your needs? | Always | Sometimes | Never |
| **Medication Use** | Do you use five or more different prescription medications on a regular basis? | No | Yes | |
| | At times, do you forget to take your prescription medications? | No | Yes | |
| **Nutrition** | Have you recently lost weight such that your clothing has become looser? | No | Yes | |
| **Mood** | Do you often feel sad or depressed? | No | Yes | |
| **Continence** | Do you have a problem with losing control of urine when you don’t want to? | No | Yes | |
| **Self Reported Performance** | Two weeks ago, were you able to: | | | |
| | (1) Do heavy work around the house like washing windows, walls, or floors without help? | Yes | No | |
| | (2) Walk up and down stairs to the second floor without help? | Yes | No | |
| | (3) Walk 1 km without help? | Yes | No | |

**Scoring for the Reported Edmonton Frail Scale ( /18):**

Not Frail: 0-5 Apparently Vulnerable: 6-7 Mildly Frail: 8-9 Moderate Frailty: 10-11 Severe Frailty: 12-18

**Appendix B: Deficits measured in the Electronic Frailty Index**

| **Deficits Measured** |
|---|
| Activity limitation |
| Anaemia & haematinic deficiency |
| Arthritis |
| Atrial fibrillation |
| Cerebrovascular disease |
| Chronic kidney disease |
| Diabetes |
| Dizziness |
| Dyspnoea |
| Falls |
| Foot problems |
| Fragility fracture |
| Hearing impairment |
| Heart failure |
| Heart valve disease |
| Housebound |
| Hypertension |
| Hypotension/syncope |
| Ischaemic heart disease |
| Memory & cognitive problems |
| Mobility & transfer problems |
| Osteoporosis |
| Parkinsonism & tremor |
| Peptic ulcer |
| Peripheral vascular disease |
| Polypharmacy |
| Requirement for care |
| Respiratory disease |
| Skin ulcer |
| Sleep disturbance |
| Social vulnerability |
| Thyroid disease |
| Urinary incontinence |
| Urinary system disease |
| Visual impairment |
| Weight loss & anorexia |

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