EFFICACY OF A TECHNOLOGY ENABLED HOME-BASED CARDIAC REHABILITATION PROGRAM ON AEROBIC FITNESS, VASCULAR HEALTH AND CVD RISK FACTORS

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PhD

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Submitted for the award of PhD.

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Declaration

I hereby certify that this material, which I now submit for assessment on the program of study leading to the award of PhD is entirely my own work, that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge breach any law of copyright, and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

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Abstract

Although cardiac rehabilitation (CR) is part of the current multidisciplinary approach to the management of cardiovascular disease (CVD), uptake and adherence is low. Reasons are multifactorial and include, time, accessibility, transport issues and motivation. Advances in technology have the potential to enable the delivery of home-based CR (HBCR). The purpose of this PhD research program was to evaluate the efficacy of a technology enabled HBCR program (PATHway) compared to usual care (UC)

Study 1

Heart rate (HR) monitoring using wrist-worn watches allows patients to monitor and adjust their exercise intensity to meet their rehabilitation goals. This study assessed the accuracy of commercially available wristwatch HR monitors. There was a significant correlation between wrist-worn monitors and the criterion measure (3-lead Holter monitor) at both rest and during exercise with appropriate limits of agreement.

Study 2

Exercise training is one of the core elements of CR. This study assessed exercise session duration, physiological and perceptual responses of participants (n=53) using PATHway, a 6 month, home-based technology enabled CR program. Participants used the PATHway system for an average of 36 min per session at an intensity

corresponding to 67% HRR. The average RPE per sessions was 5.2 on the 0-10 Borg scale.

Study 3

Study 3 compared anthropometric measures, cardiorespiratory fitness, strength (sit-to-stand, isokinetic and isometric strength and hand grip), vascular structure (cIMT) and function (FMD) and blood biomarkers between CVD patients (n=120) randomized to PATHway and UC. There was no change in cardiorespiratory fitness, strength, vascular structure or function in either PATHway or UC at 6-months.

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Abbreviations

Ach	Acetylcholine
ACCF	American college of cardiology foundation
ACS	Acute coronary syndrome
ACSM	American college of sports medicine
ACVD	Atherosclerotic cardiovascular disease
AHA	American heart association
AL	Active living
ANG II	Angiotensin II
ApoB	Apo lipoprotein B
AT III	Antithrombin III
BF	Blood flow
BMI	Body mass index
BP	Blood pressure
CBCR	Centre based cardiac rehabilitation
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CaMKII	Calmodulin-dependent kinase II
CCA	Common carotid artery
CHD	Coronary heart disease
CIMT	Carotid intima media thickness
CPET	Cardiopulmonary exercise test
CR	Cardiac rehabilitation
CRF	Cardiorespiratory fitness
CVD	Cardiovascular disease
d	Day
DALY	Disability adjusted life years
DBP	Diastolic blood pressure
EC	Exerclass
ECG	Electrocardiogram
ECM	Extracellular matrix
EDD	Endothelial – dependent dilation

EID	Endothelial – independent dilation
eNOS	Endothelial derived nitric oxide synthase
ET	Exercise training
ET-1	Endothelin
FITT	Frequency, intensity, time and type
FMD	Flow mediated dilation
GTN	Glyceryl trinitrate
h	hour
HBCR	Home-based cardiac rehabilitation
HDL-C	High-density lipoprotein cholesterol
HR	Heart rate
HRmax	Maximal heart rate
HRR	Heart rate reserve
IMT	Intima media thickness
kcals	Kilocalories
kJs	Kilojoules
LDL-C	Low-density lipoprotein cholesterol
LIMA	Left internal mammary artery
LIPA	Light intensity physical activity
MET	Metabolic equivalents
MHC	Myosin heavy chain
mHealth	Mobile health
MI	Myocardial infarction
MIPA	Moderate intensity physical activity
MMPs	Matrix myeloperoxidases
MVPA	Moderate to vigorous physical activity
NCX	Sodium-calcium exchanger
NO	Nitric oxide
PA	Physical activity
PAD	Peripheral arterial disease
PAR-Q	Physical activity readiness questionnaire
PATHWAY	PATHway intervention group
PCI	Percutaneous coronary intervention

PGI_2	Prostacyclin I_2
PKA	Protein kinase
PLB	Phospholamban
PPG	Photoplethysmography
PTCA	Percutaneous transluminal coronary angioplasty
UC	Usual care
QCA	Quantitative coronary angiography
RCP	Respiratory compensation point
REMOTE-CR	Remote exercise monitoring trial for exercise-based CR
RER	Respiratory exchange ratio
ROS	Reactive oxygen species
RPE	Rate of perceived exertion
SBP	Systolic blood pressure
Sec	Second
SERCA2a	Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase
SMC	Smooth muscle cell
SR	Sarcoplasmic reticulum
TC	Total cholesterol
UC	Usual care group
VAT	Ventilatory anaerobic threshold
VCO_2	Carbon dioxide elimination
VIPA	Vigorous intensity physical activity
V_E	Minute ventilation
$\dot{V}O_2$ max	Maximal oxygen uptake
$\dot{V}O_2$ peak	Peak oxygen uptake
$\dot{V}O_2$ R	Oxygen consumption reserve
VSMC	Vascular smooth muscle cell contraction
VT	Ventilatory threshold
WHO	World health organization
yr	year

CHAPTER I

INTRODUCTION

Rationale

Cardiovascular disease (CVD) refers to diseases of the heart and circulatory system, and typically includes coronary artery disease (CAD), cerebrovascular disease, peripheral vascular disease (PAD), rheumatic heart disease, congenital heart disease, aortic aneurysm, deep venous thrombosis and pulmonary embolism. Globally, CVD is responsible for over 17.3 million deaths annually and accounts for 45% of non-communicable deaths (1). In Europe, over 1.4 million people die prematurely from cardiovascular related deaths (2) with a projected 25% increase in the incidence of CVD by 2030 (2).

Cardiac rehabilitation (CR) is a multidisciplinary and multifaceted treatment designed to promote and facilitate lifestyle changes, improve exercise capacity, optimize medical treatment and risk factor control and address the social and psychological issues following the development of CVD (3). Participation in CR reduces premature mortality and CVD events and improves psychosocial outcomes and quality of life (4–8). CR programs have proven effective across a range of cardiovascular conditions including, myocardial infarction (MI), coronary artery bypass graft (CABG) surgery, percutaneous coronary intervention (PCI), current stable angina pectoris, heart or heart-lung transplantation, heart valve repair or

replacement, recent cerebrovascular accident, stable chronic heart failure (HF) and implantable cardioverter-defibrillator and pacemaker.

Typical CR programs involve in-hospital education (phase I), early outpatient/convalescence (phase II), gradual increase in outpatient supervised physical activity (PA), continuation of risk-factor modifications and development of maintenance programs (phase III) and community-based CR (phase IV), in which participants aim to sustain long-term behavior change, typically with encouragement by CR staff. Despite the growing evidence of the benefits and importance of CR, referral rates are suboptimal (9). Of all patients eligible to participate in CR, there is only 10-20% uptake in phase 3 (5). Engagement in community based CR (phase 4) are even lower and the number of patients effectively adhering to the long-term rehabilitation phase is extremely poor (10, 11). The reason for low participation rate is multifactorial (12), and includes time constraints, poor accessibility, transportation issues, lack of motivation to change behaviour and low self-efficacy (5, 13).

Interactive home-based programs have enormous potential to widen access to CR (14). Participation in these programmes has been found to increase self-efficacy to participate in exercise, leading to better adherence to a physically active lifestyle in comparison to usual care groups (10, 13, 14). Pinto et al., (2011) found that approximately three quarters of individuals who received usual care were more likely to stop exercising 1 year after their cardiac event compared to a group participating in a home-based, interactive CR program.

Although studies have proved the efficacy of a phase III HBCR program it was decided to assess the PATHway program as an alternative method of phase IV CR. In Ireland, the culture in CR involves participants training under continuous supervision by trained medical staff and as well as continuous heart rate monitoring. To introduce a technology-enabled HBCR program as a substitute for this heavily monitored CR program would be a radical shift in delivery mode. The study was undertaken for proof of concept purposes with the aim of the future in CR adopting a hybrid approach to incorporate a program like PATHway (15–18).

PATHway (Physical Activity Towards Health) is a novel, innovative internet-enabled, sensor-based exercise platform that combines online, and home-based interactive programs. It provides regular exercise sessions as the basis upon which to provide a personalized, comprehensive lifestyle intervention program to enable patients to self-manage their CVD and to lead a healthier lifestyle in general. The purpose of this PhD research program was to compare the efficacy of PATHway (PATHway) to usual care following completion of a hospital based (phase III) program.

Study Aims

1. To examine the validity and reliability of commercially available wrist worn watches for measuring heart rate at rest and during exercise

2. To evaluate participant usage of the PA/exercise component of PATHway

3. To evaluate the physiological and perceptual responses to the prescribed exercise component of PATHway

4. To compare the effect of participation in PATHway to usual care (UC) on body composition, PA levels, cardiorespiratory fitness (CRF) and muscle strength and muscle endurance

5. To compare the effect of participation in PATHway to UC on blood pressure (BP), selected biomarkers for CVD and vascular structure and function

CHAPTER II

LITERATURE REVIEW

Introduction

CVD is the leading cause of death worldwide and refers to disease of the heart and circulatory system. Manifestations of CVD include, coronary artery disease (CAD), peripheral artery disease (PAD), cerebrovascular disease, rheumatic heart disease, congenital heart disease, aortic aneurysm and deep vein thrombosis. Globally, an estimated 17.7 million people died from CVD in 2015, accounting for 31% of all deaths, representing a 6% increase from 1990 (2, 20). In Europe, approximately 4 million people die annually from CVD, accounting for 45% of all deaths (21). In 2015, there were more than 85 million people in Europe living with CVD with an estimated €210 billion annually cost to the EU economy (21).

Disability-adjusted life year (DALY) is a measure of overall total disease burden expressed as the cumulative number of years of life lost (premature death) and years lived with disability (ill-health). One DALY is equivalent to 1 year of healthy life lost. The estimated DALY attributed to CVD are 40/1000 and 29/1000 for Irish men and women, respectively (2).

Cardiac Rehabilitation

The treatment of individuals with CVD has evolved considerably over the last century (22). Bed rest was recommended to cardiac patients until the 1940's when physical activity in the form on sitting in a chair, was introduced to prevent many of the complications of bed rest. By the 1950's, patients were recommended to walk for 5 min daily after convalescing for 4 weeks. Due to concerns about patient safety during unsupervised exercise after hospital discharge, highly structured, hospital-based (phase II), physician-supervised CR programs were developed in the 1970's. These early phase II CR programs focused almost entirely on exercise training, with the primary aim to reverse the physical decline that resulted from extended bed rest (23). It was believed that in order to prevent cardiovascular-related complications that exercise sessions should be supervised with ambulatory electrocardiogram (ECG) monitoring to detect, document and characterize abnormal cardiac activity and/or abnormalities associated with the occurrence of myocardial ischemia.

CR evolved during the 1980's and 1990's from a solely exercise-based intervention to a more comprehensive and multifaceted programme that incorporated strategies to optimize cardiovascular risk reduction, promote adoption and adherence to healthy behaviours and an active lifestyle, enhance emotional well-being and reduce disability with the aim of increasing survival, reducing the risk of a recurring event and improving quality of life (23, 24). The recommended strategies and services required to achieve these goals included exercise training,

counselling, education, risk factor modifications and psychological and nutritional interventions (23).

CR is now recommended by the European Society of Cardiology, American Heart Association and the American College of Cardiology as an important component of the multidisciplinary approach to the management of patients with various presentations of CVD (25). These include acute coronary syndrome (ACS), MI, CABG procedure, PCI, current stable angina pectoris, symptomatic peripheral arterial disease (intermittent claudication), heart transplantation, heart valve surgery, recent cerebrovascular accident, stable HF and implantable cardioverter-defibrillator and pacemaker (25). The core components of CR include patient assessment, nutritional counselling, weight management, BP management, lipid management, diabetes management, smoking cessation, psychological management, PA counselling, and exercise training (24).

Phases of Cardiac Rehabilitation

Contemporary CR consists of four separate phases. Phase I takes place while the patient is in hospital with the major aim to reduce anxiety and depression and counteract the negative effects of deconditioning after a cardiac event (26, 27). The duration of phase 1 depends on the length of the hospital admission and is usually 2-5 days. A member of the CR team visits the patient in the ward. The key elements for discussion include medical evaluation, reassurance and education, correction of cardiac misconceptions, risk factor assessment, mobilization and discharge planning.

Phase II is the early post discharge phase prior to commencing Phase III during which support is provided to patients in the form of home visits and telephone calls. The objectives of this phase are to reinforce risk factor modification, provide education and support and promote adherence to lifestyle recommendations. Phase III is normally undertaken in a hospital or health care setting and is typically 6 weeks in duration. It involves a medically supervised structured exercise program along with educational and psychological support and advice on risk factor modification. Exercise classes usually comprise a warm-up followed by a combination of aerobic and resistance exercise and finishing with a cool down period. Finally, Phase IV, often referred to as the maintenance phase focuses on the maintenance of long-term lifestyle changes in order to lower risk of future heart events (26, 27). Phase IV programs are usually held at a community facility and/or at home.

Safety and Effectiveness of centre based CR

The safety and effectiveness of traditional medically supervised centre based CR (CBCR) are well established. Traditional CBCR programs are effective in reducing hospital readmissions, secondary events and mortality (5). Compared to usual care, CR services assist patients to reduce their risk of future CVD events by empowering them to stop smoking, increase PA levels, improve dietary habits, optimally adhere to prescribed medications, and to optimize psychosocial well-being (28).

In studies involving both low-and high risk patients, serious CVD events rate

were found to be 1 per 50,000 patient hours (29). In a more recent study, Pavy et al., (2006) evaluated complications over a 12-month period (2003) among 24,420 patients (78% men) attending 13 in-patient, 24 outpatient, and 28 mixed phase II CR centers in France. Cardiac diagnosis included CABG (34%), PCI (22%), recent revascularization (13%), valve surgery (18%) and other non-coronary (12%) (30). Patients attended medically supervised sessions approximately 1 h in duration that included calisthenics, cycle ergometry and treadmill. Although ECG monitoring is recommended, but not compulsory for Phase 2 CR in France, systematic and continuous monitoring was performed in 17 centres (26%), intermittent monitoring in 41 centres (63%) and no monitoring in two centres (8%). During 42,419 exercise stress tests and 74,347 patient-hours of exercise training, there were 20 severe cardiac events in 17 patients. The event rate was 1 per 49 565 patient-hours of exercise training. The cardiac arrest rate was 1.3 per million patient-hours of exercise. No fatal complications or emergency defibrillations were reported and interestingly, ECG monitoring had no effect on event rate.

Cardiorespiratory Fitness

Cardiorespiratory fitness (CRF), also termed cardiovascular fitness or aerobic capacity is an integrative measure of the capacity of the pulmonary, cardiovascular and musculoskeletal systems to uptake, transport and utilize oxygen during large-muscle, whole-body exercise at moderate to high intensities (31). Low levels of CRF, expressed as $\dot{V}O_2$ max or maximal metabolic equivalents (METs), is an independent

risk factor for all-cause and cardiovascular mortality in men and women with CVD or CVD risk factors.

CRF provides a strong, graded inverse association with all-cause mortality in patients, irrespective of sex, race and comorbidities (32–34). Individuals with low CRF are approximately 2 to 5 times more likely to die during follow-up compared with their higher CRF counterparts (35). In a study involving 13,344 participants who were followed for 12 years, Blair et al., (1989) found that age-adjusted all-cause mortality decreased across the fitness quintiles from 64% in the least fit to 18% in the most fit quintile for men. A similar trend was evident for women with a decrease from 39.5% to 8.5% from highest fit to least fit groups. Comparative values were observed for CVD mortality indicating that higher CRF fitness delays all-cause mortality because of lower incidence rates of CVD (36).

A number of studies have expressed CRF in the context of survival benefit per MET, a relatively small and achievable goal for most participants aiming to increase their CRF. Each MET increase in functional capacity is associated with a 10 to 25% improvements in survival (37). A meta-analysis on 33 studies involving 103,000 patients found a 13% decrease in all-cause mortality and a 15% decrease in CVD specific mortality for each 1 MET increase in CRF. This study also quantified the MET cut-off point for all-cause and CVD risk as 7.9 METS meaning those with low CRF < 7.9 METs had a substantially higher risk than those with a higher CRF > 7.9 METs suggesting that a minimum CRF of 7.9 MET is important for prevention of all-cause mortality and CVD. In addition, a small increase in CRF in individuals in the lowest

quintile was associated with substantial reduction in CVD events and all-cause mortality (33).

In relation to men, prospective studies have shown inverse associations between changes in CRF and risk of mortality. Over an 11-year period, Blair et al., (1995) assessed CRF on two occasions in 10,000 healthy and unhealthy men ranging in age from 20 and 82 years. Men who were classified as unfit at both time points had the highest death rate whereas men who were classified as fit at both visits had the lowest death rates. Men who were classified as unfit at the first visit but, moved into the fit category in the second visit had a 52% lower risk of CVD mortality than their peers who remained unfit at both visits. All cause mortality decreased by 15% in men who were initially fit and who further improved their fitness at the second visit. Each one min increase in treadmill time was associated with an 8.6% reduction in CVD mortality (36). In a more recent study involving 122,007 patients with a mean age of 53.4 year, an increased level of CRF was associated with reduced long-term mortality with no observed upper limit of benefit (38).

Supervised exercise-based CR programs ranging from 3 to 6 months in duration have been found to improve $\dot{V}O_2$ peak by 11 to 36% with the greatest improvements occurring in those patients who are most deconditioned at the commencement of the program (12). However, even patients with relatively high baseline fitness levels can also obtain significant improvements (40).

Vanhees et al., (1994) investigated whether $\dot{V}O_2$peak is an independent predictor for all-cause and cardiovascular mortality in 524 men ranging in age from

24 to 74 years who were referred to an outpatient CR program. Peak oxygen uptake was assessed by an exercise test performed to exhaustion ≥4 weeks after MI (n= 312) or CABG procedure (n=215) and, averaged 23.3 ±6.0 $mL \cdot kg^{-1} \cdot min^{-1}$ (6.6 ± 1.8 METs). The mean follow-up duration was 6.1 years (range 0 .07 to 11.9).

A 1.0 L increase in $\dot{V}O_2$peak was associated with a 57% and 71% decrease in all-cause and CVD mortality, respectively. There was also a progressive decline in all-cause and CVD mortality across quintiles of $\dot{V}O_2$peak ranging from 15.5 $mL \cdot kg^{-1} \cdot min^{-1}$ to 32.3 $mL \cdot kg^{-1} \cdot min^{-1}$. The largest difference in prognosis for all-cause mortality was observed between the two highest quintiles of fitness, whereas the largest difference in prognosis for cardiovascular mortality was seen between the two lowest quintiles of fitness. Interestingly, patients with the highest cardiovascular and all-cause mortality had a functional capacity that averaged ≤ 4.4 METs. In contrast, no deaths occurred among patients who averaged ≥ 9.2 METs (41). Dorn et al., (1999) reported that among post-MI patients each 1-MET increase in CRF after a training period was associated with a reduction in all-cause mortality that ranged from 8% to 14% during a 19 year follow up (42).

Using a retrospective study design Martin et al., (2013) examined the relation between peak-MET values at baseline, following participation in a 12-week endurance training-based CR program and at 1-year follow-up on mortality risk among 4282 men and 1359 women with documented CHD. In addition to 12-weeks of supervised exercise, 2 times per week, patients were also encouraged to participate in an additional 2 to 3 exercise training (ET) sessions on their own. At the

completing of the 12-week CR program, patients were given instructions for ongoing lifestyle changes at home, including an exercise program and dietary advice (43).

The peak-MET value was calculated from the speed and grade during the final stage of a graded exercise test. Patients were classified as having a low (<5 METs), moderate (5-8 METs), or high (>8 METs) CRF level. There were 424 (8%) low fit, 2475 (44%) moderately fit and 2742 (48%) high-fit patients. CRF fitness improved by 1.41 METs (39%), 1.01 METs (15%), and 0.80 MET (8.6%) in the low, moderate, and high fit patients, respectively following participation in the 12-week CR program. A subset of high fit (1848), moderately fit (1455) and low fit (211) patients underwent a repeat assessment at 1 year. The improvements in CRF at 1 year vs. baseline were maintained in all groups and remained highest in low fit patients (43).

In both unadjusted and adjusted statistical models, the moderate and high fit patients had a progressively lower overall mortality risk that the low fit patients at baseline. Improvement in CRF at 12 weeks was associated with decreased overall mortality. For each MET increase in functional capacity there was a 13% reduction in mortality, with the greatest reduction in mortality per MET increase (30%) among the low fit patients. At 1 year, each 1-MET increase in CRF was associated with a 22% reduction in overall mortality for the entire cohort. The investigators concluded that even at 1 year, in view of the very modest changes in conventional risk factors including cholesterol, triglycerides, and BMI, there was a significant mortality benefit of CR due to the ET component of the program (43).

Kavanagh et al., (2002) examined the predictive value of $\dot{V}O_2$peak among 12,169 men referred to an outpatient CR program after MI (n=7096), CABG (n=3077), or the onset of IHD (n=1996). Exercise capacity, as determined by directly measured $\dot{V}O_2$peak at entry to CR was found to be the most important single predictor of both cardiac and all-cause mortality across all 3 diagnostic categories during a median follow-up time of 7.9 (range, 4 to 29) years. The 15-year survival rates for patients with $\dot{V}O_2$peak values of <15, 15 - 22, and >22 $mL \cdot kg^{-1} \cdot min^{-1}$ were approximately 65%, 81%, and 88% for cardiac mortality and 48%, 69%, and 80% for all-cause mortality. The estimated 15-year mortality dropped from 35% in men with a mean $\dot{V}O_2$peak of 13.0 $mL \cdot kg^{-1} \cdot min^{-1}$ to 19% in those with a mean $\dot{V}O_2$peak of 18.6 $mL \cdot kg^{-1} \cdot min^{-1}$. A 1.0 $mL \cdot kg^{-1} \cdot min^{-1}$ increment in $\dot{V}O_2$peak was associated with a 9% reduction in cardiovascular mortality (44).

Using a very similar study design Kavanagh et al., (2003) found among 2380 women with CHD that $\dot{V}O_2$peak at entry to an outpatient CR program was a strong predictor of cardiovascular and all-cause mortality during an average follow up period of 6.1 years. The cutoff point, above which there was a marked benefit in prognosis, was 13.0 $mL \cdot kg^{-1} \cdot min^{-1}$ (3.7 METs). There was a 10% reduction in predicted cardiovascular mortality for each 1.0 $mL \cdot kg^{-1} \cdot min^{-1}$ increase in $\dot{V}O_2$peak (45).

Using a meta-analysis involving 31 studies, Sandercook et al., (2013a) evaluated the changes in CRF in response to participation in CR and reported an average improvement of 1.5 MET. This increase equates to a 16–54% reduction in

predicted cardiac mortality depending on the estimate used. Optimal features of CR to promote improvements in CRF were that it comprised >36 sessions of aerobic or mixed aerobic and resistance exercise and was delivered over a 12-week period (46). Interestingly, in a large, contemporary, multicenter UK sample, Sandercook et al., (2013b) reported an overall increase in fitness of only 0.52 METs following participation in CBCR. This MET value is only a third of the mean estimate (1.55 METs) reported in the meta-analysis and, is believed to be due to the smaller volume of exercise completed by UK patients compared to most other international programs (8 vs. 36 sessions) (47).

De Schutter et al., (2018) examined the prognosis and characteristics in 1171 CHD patients who were referred for a phase II CR program after therapy for an acute coronary syndrome, CABG procedure or a PCI and who underwent cardiopulmonary exercise testing before and after 36 CR sessions. Patients were stratified by absolute improvement in $\dot{V}O_2$ peak into non-responders (≤ 0 $mL \cdot kg^{-1} \cdot min^{-1}$ improvement), low-responders (≤ 2.5 $mL \cdot kg^{-1} \cdot min^{-1}$ improvement) and high responders (≥ 2.5 $mL \cdot kg^{-1} \cdot min^{-1}$ improvement) after CR and mortality was analyzed for a mean follow-up period of 6.4 years (range 0.5–13.4 years) (48).

Changes in $\dot{V}O_2$peak after participation in a CBCR were normally distributed with a mean improvement of 1.9 ± 3.3 $mL \cdot kg^{-1} \cdot min^{-1}$ (1.8 METs) (Figure 2.1). Approximately 23% of patients did not improve or had a decrease in $\dot{V}O_2$ peak (mean ± SD; 2.0 ± 2.4 $mL \cdot kg^{-1} \cdot min^{-1}$). There were 266 non-responders, 458 low responders, and 447 high responders.

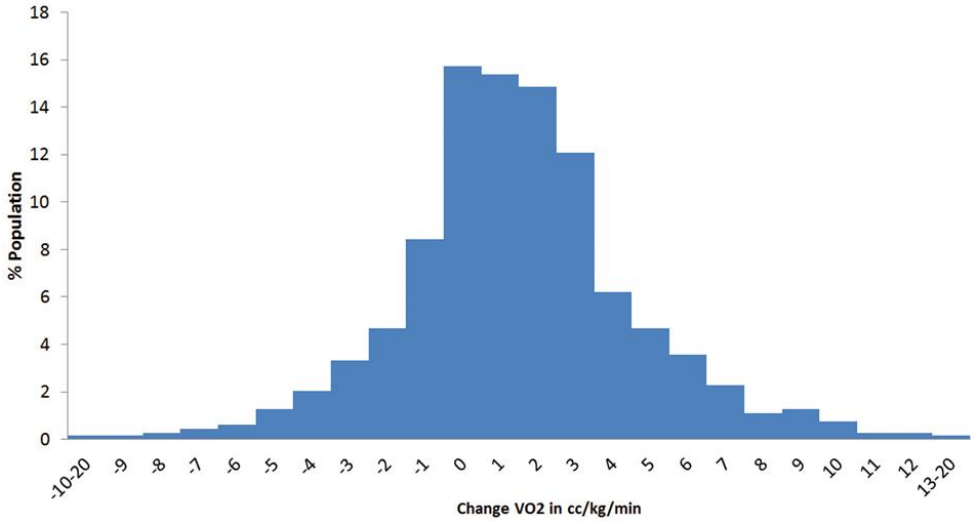


Figure 2.1: Gaussian distribution of changes in $\dot{V}O_2$peak (0 represents baseline $\dot{V}O_2$ prior to initiation of cardiac rehabilitation (48).

After adjustment for BMI, age, gender, left ventricular ejection fraction and baseline CRF, non-responders, and low-responders had a statistically significant three-fold and two-fold higher mortality, respectively, than high responders (Figure 2.2).

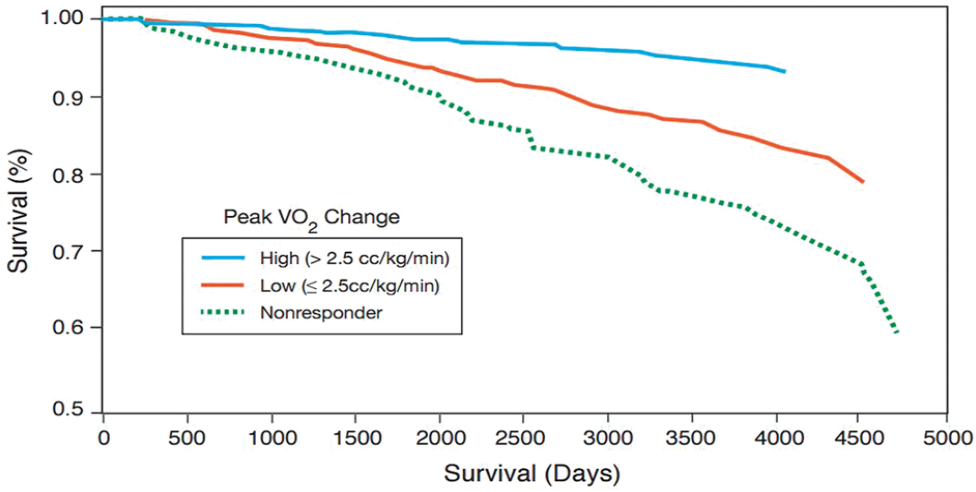


Figure 2.2: Cardiac rehabilitation patients were stratified by absolute improvement in $\dot{V}O_2$ (none, low, and high) and adjusted for predictors of mortality show a direct correlation between improvement in oxygen consumption and mortality (48).

CRF Benefits – Mechanisms

The beneficial effects of exercise on established modifiable CVD risk factors are well established. In most instances, exercise is prescribed in combination with pharmacotherapy. Current European Cardiovascular Prevention Guidelines in patients with established CAD recommend the use of antiplatelet therapy, a beta-blocker, lipid-lowering agents when LDL-C ≥2.5 $mmol.L^{-1}$, and additional BP-lowering agents in the case of a systolic BP ≥140 mm Hg, unless contraindicated (49). The American Heart Association and the American College of Cardiology Foundation (AHA/ACCF) Guidelines promote the standard use of cholesterol-and BP-lowering agents, regardless of the initial levels of LDL-C or BP in patients with established vascular disease (50, 51). Regular PA /exercise can, however, also exert direct beneficial effects on the heart and vasculature beyond favourable changes in traditional modifiable risk factors.

Central Adaptations

The increase in $\dot{V}O_2$ peak following exercise training is due to both central and peripheral adaptations. Central adaptations refer to an increase in cardiac output due primarily to an increased maximal stroke volume secondary to changes in submaximal heartrate, BP and vascular structure and function. The decrease in submaximal HR and SBP reduce the rate pressure product at a given workload. These adaptations allow patients with CAD who ordinarily experience myocardial ischemia during exertion to perform such tasks at a higher intensity before reaching

their ischemic ECG or angina threshold (12). Peripheral adaptations refer to the widening of the arteriovenous oxygen difference and reflect a greater efficiency in O_2 extraction and utilization by the skeletal muscles. Endurance exercise training increases skeletal muscle oxidative capacity, due in part to increases in capillary density, myoglobin content and oxidative enzyme concentration (52).

For both practical and ethical reasons, murine models have been extensively used to study the molecular and cellular features of cardiac remodeling in response to exercise. Heart size and weight increases in response to exercise training in rats with the increases in left ventricular weight ranging from 7 to 39%. An increase in cardiomyocyte length between 5 and 20% has been found following exercise training with an observation that this increased length is reversible following just 2 weeks of detraining (53). In rat models, there is evidence of regional differences in response to training with cardiomyocytes originating in the sub-endocardium wall displaying a greater response compared with those from the sub-epicardium. Wisloff et al., (2002) compared the effects of moderate intensity and high intensity treadmill exercise on ventricular weight and cardiac myocyte length in rats. Left ventricular weight increased 4% in the high intensity exercise group with no change observed in response to moderate intensity training. Although cardiac myocyte length increased in the both exercise conditions, the increase was much greater in the high intensity (14%) than the moderate intensity (5%) group (54).

In addition to cardiac hypertrophy, there are notable changes in cardiac myocyte content following exercise training. These include an increase in the

volume density of mitochondria, as well as an enlargement of the surface density of the sarcoplasmic reticulum per unit of myofibrils and a pronounced hyperplasia of the Golgi apparatus (53). Exercise training results in very small increase in T-tubule density and no change in T-tubule spacing (55).

Studies examining the effect of exercise training on both α-myosin heavy chain (α -MHC) and β-myosin heavy chain (β-MHC) isoforms of the major contractile proteins in the heart have been equivocal. An increase in expression of α-MHC ranging from 30 to 75% has been found following exercise training. It appears that the increased expression of α-MHC occurs early during exercise training, with one study reporting changes within one week of commencing exercise training (53). However, other studies involving running and resistance training programs have failed to find a change in α-MHC protein expressions in response to exercise training (53).

Troponin, another protein complex integral to myocardial contraction consists of three distinct subunits, troponin C, troponin I and troponin T. Results from the few studies that have directly assessed the effects of exercise training on troponin levels have yielded divergent results between rats and humans. Swim training in rats increased the expression of troponin C and the increase was greater when the exercise was performed at high intensity (56). Conversely, a study in older men and women found no difference in troponin T or troponin I expression following 12 weeks and 24 weeks of resistance exercise training. In rats, 8-10 weeks of treadmill training improved in cardiac myocyte shortening, time to peak contraction

and time to half relaxation (53). Interestingly, the improvement of cardiomyocyte contractility was reversed after 4 weeks of detraining.

The contraction of cardiac myocytes involves the binding of intracellular free calcium to the troponin C subunit. Depolarization of both the sarcolemma and T-tubules membrane activates L-type Ca^{2+} channels allowing entry of a small amount of Ca^{2+} from the extracellular fluid. The rise in intracellular Ca^{2+} stimulates the ryanodine receptors located on the membrane and 'triggers' the release of stored Ca^{2+} form the sarcoplasmic reticulum (SR). During cardiomyocyte relaxation, calcium ions are removed from the cardiac myocyte by the combined action of the SR Ca^{2+}ATPase (SERCA2a) pump and the sodium-calcium exchanger (NCX) on the sarcolemma. Activation of SERCA2a activity is regulated by the integral protein phospholamban (PLB). Phosphorylation of PLB by both cAMP-dependent protein kinase (PKA) and Ca^{2+}/calmodulin-dependent kinase II (CaMKII) at serine Ser-16 and threonine Thr-17, removes it from SERCA, which in turn is activated.

The fact that Ca^{2+} transient kinetics and the contraction-relaxation signaling are closely related indicates that the effect of exercise training on contraction-relaxation rate could originate from changes in Ca^{2+} cycling. There are many stages of the Ca^{2+} cycling process that have been identified as potential targets for exercise training. Some studies show an increase in SERCA2a expression following exercise training in mice and rats. Others show increased PLB phosphorylation at both Ser-16 and Thr-17. Several studies have found an increase in RyR2 protein content and gene expression induced by aerobic training (53).

Ligation of the left anterior descending coronary artery, ischemia-reperfusion and administration of isoproterenol are three commonly used procedures to induce an MI in animals. LAD is the most commonly used method, as its effect on the organ systems are most similar to that observed in humans. In contrast, the ischemia-reperfusion model is generally used to study the effects of reperfusion stress on reactive oxygen species behavior.

Early remodeling following an MI is characterized by the expansion of the infarcted area due to degradation of the structural collagen present in the extracellular matrix by myeloperoxidases (MMPs) secreted by the immune. In addition to preserving cardiac output, the autonomic control of the heart is adjusted resulting in an increase in HR and contractility. These changes work in tandem in the first few hours post-MI to maintain blood perfusion to the tissues. The release of pro-inflammatory cytokines in response to ischemia increases activity of reactive oxygen species (ROS), activates MMP's and increases activity of the renin angiotensin aldosterone system. Immediately after MI, neutrophils migrate to the infarcted area and further recruit MMP's, which initiate collagen breakdown. This in turn induces fibroblast migration and differentiation in myofibroblasts causing scar tissue formation.

Exercise training modulates the cardiac remodeling process by altering the MI induced changes in the extracellular matrix (ECM). Bozi et al., (2013) found that 8 weeks of ET prior to an induced MI decreased post-MI cardiac myocyte collagen content of rats (57). A similar reduction in collagen in infarcted areas was reported

by Xu et al., (2008) and Yengo et al., (2012) in response to ET programs undertaken for 8 and 10 weeks post MI, respectively (58, 59). There was also a decrease in TNF-α and TNF-α/IL-10 ratio following exercise training.

Exercise training in rats following an induced MI also increases heart weight, heart weight to body weight ratio as well as myocyte length and width when compared to rats who remain sedentary. Trained rats also display elevated cardiac function when compared with sedentary rats. Using a mouse model, Bito et al., (2010) studied the effect of access to voluntary wheel running for 8 weeks after an induced MI (60). Heart weight to body weight ratio and cell width increased in mice randomized to both the sedentary and physically active group. Cell shortening induced by electrical stimulation decreased in sedentary compared to physically active mice. Transient calcium was also increased in the physically active mice due to an elevated capacity of Ca^{2+} removal by the plasma membrane NCX. A similar study by Puhl et al., (2015) also found that PA did not modulate cardiac hypertrophy with no difference in weight or cardiomyocyte diameter between the PA and sedentary group (61).

Autonomic dysfunction and impaired baroreflex sensitivity also occur following an induced MI. Several studies involving animal models have found improved baroreflex sensitivity and normalisation of autonomic dysfunction following exercise training. Chen et al., (2014) also found that endurance training normalized autonomic control and adrenergic receptor balance post MI. Endurance training also improves cardiac hemodynamics and functioning post MI (62).

Blood Vessel Structure

All segments of the vascular system are composed of an intimal, media and adventitia layer (Figure 2.3). A single monolayer of endothelial cells resting on a basement membrane of collagen cells (basal lamina) is in direct contact with the arterial lumen. A layer of loose connective tissue (subendothelial connective tissue) surrounds the basal lamina and a layer of elastin fibers, the internal elastic lamina separates the intima from the media layer.

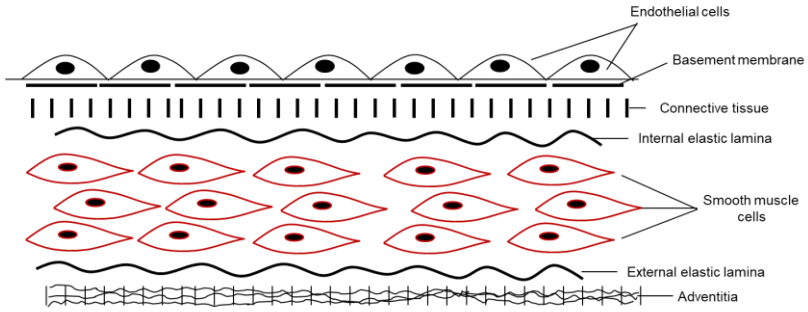


Figure 2.3: Basic morphological structure of blood vessels

The media layer is responsible for the contractile and elastic functions of the artery and consists of multiple concentric layers of smooth muscles outside the internal elastic lamina and up to and including the external elastic lamina. The composition and thickness of the media layer changes according to the size of the vessel. For example, in elastic arteries such as the aorta and major arteries there are a large number of elastic layers within each of the smooth muscle layers. In muscular arteries, the media is composed primarily of smooth muscles with very few elastic layers. Connective tissue, collagen fibers and proteoglycans are located between the smooth muscles. The collagen fibers are produced and secreted by the

smooth muscles. The media is covered by the external elastic lamina which is a boundary between the media and adventitia. The outer layer, the adventitia contains the nerves, lymphatics and blood vessels that nourish the cells of the arterial wall.

Vascular Endothelium – Structure and Function

The vascular endothelium is a semipermeable barrier of simple squamous cells that lines the entire circulatory system (63). Until quite recently, the vascular endothelium was viewed as an inert barrier that regulated the transfer of different molecules through blood vessels and the transport of macromolecules between the vascular lumen and vascular smooth muscle. It is now well established that the vascular endothelium is a dynamic organ that plays a key role in maintaining vascular health by regulating vascular tone, thrombosis and thrombolysis, platelet adherence and activation (64–66) and that endothelial damage and associated dysfunction is crucial in the initiation, progression and clinical complications of atherosclerotic CVD (67–69).

Platelets are small (2-3 μm) enucleated membrane bound cytoplasm containing cells that when activated undergo a series of reactions that result in the formation of a platelet plug (70). By acting as a biological partition between the platelets and the extracellular matrix, the vascular endothelium prevents platelets from binding directly to exposed collagen fibers on the basement membrane. The production and release of nitric oxide (NO), prostacyclin I_2 (PGI_2) and ADP

diphosphophosphatase by healthy endothelial cells inhibits platelet activation (71). NO and PGI_2 bind to, and inactivate surface receptors on platelets, whereas ADP diphosphophosphatase, by breaking down ADP, inhibits circulating platelets from attaching directly to the surface of endothelial cells.

The blood coagulation pathway is composed of a cascade of proteolytic reactions that ultimately generates fibrin thrombi. In a healthy blood vessel, the activity of the coagulation cascade is balanced by natural anticoagulant mechanisms that involve the presence of several endothelial cell surface receptors including, heparan sulfate, thrombin, thrombomodulin, tissue plasminogen activator and tissue factor pathway inhibitor. Thrombin (factor II) is a serine protease and the principal enzyme of hemostasis. It catalyzes the conversion of fibrinogen to fibrin and activates procoagulant factors V, VIII, XI, and XIII. Heparan sulflate achieves its anticoagulant activity by interacting with antithrombin III (AT III), a small (432 amino acids) hepatic derived glycoprotein molecule that inhibits coagulation by neutralizing the enzymatic activity of factors IIa, IXa, Xa.

Thrombomodulin is an integral membrane protein constitutively expressed on the surface of vascular endothelial cells. It plays an important role as a natural anticoagulant by acting as a cofactor for the thrombin-dependent rapid activation of protein C that degrades activated factor V and factor VIII. When bound to thrombomodulin, thrombin's procoagulant activities are neutralized, and the rate of inactivation of thrombin by antithrombin is increased. Healthy endothelial cells also

produce tissue plasminogen activator that functions to convert liver derived plasminogen to plasmin that degrades fibrin strands into fibrin degradation factors.

Vascular Endothelial Dysfunction

The location of the endothelium at the interface between the blood and vessel makes it susceptible to injury from mechanical forces and processes related to CVD risk factors. The functional and structural changes following endothelial damage provoke deleterious vascular phenotypes that are associated with most forms of CVD including atherosclerotic cardiovascular disease (ACVD), hypertension, HF and renal disease among others. The loss of normal endothelial function is termed 'endothelial dysfunction' and is characterized by an imbalance between substances with vasodilating, anti-mitogenic and anti-thrombogenic properties and those with vasoconstricting, pro-thrombotic and proliferative characteristics. Among the most important manifestations of endothelial dysfunction is impaired NO bioavailability (72). Importantly, endothelial dysfunction represents an important antecedent to CVD development, with declines in endothelial vasodilator function occurring prior to angiographic detection of the disease.

Modifiable CVD risk factors including smoking, physical inactivity, hyperlipidemia, hypertension, diabetes mellitus, obesity have been found to promote the development of atherosclerosis through their deleterious effects on endothelial structure and function (73, 74). The underlying mechanisms through which risk factors initiate vascular injury are multifactorial. The predominant

mechanism is believed to be oxidative stress and redox injury resulting in decreased synthesis or increased degradation of NO (75). The progressive inability of endothelial cells, exposed to risk factors, to generate sufficient NO promotes a vascular phenotype prone to atherogenesis (76).

Aging is associated with endothelial cell senescence, a pathophysiological process associated with structural and functional vascular changes including dysregulation of vascular tone, reduced endothelial cell mitochondrial biogenesis, increased endothelium permeability, arterial stiffness, and impairment of angiogenesis and vascular repair (77). Dysregulation of cell cycle, oxidative stress, altered calcium signaling, hyperuricemia, and vascular inflammation have been implicated in the development and progression of endothelial cell senescence and vascular disease in aging.

Assessment of Endothelial Function

Clinically, coronary endothelial function is commonly assessed by measuring the endothelial receptor–mediated vasomotor response to intracoronary infusion of acetylcholine (ACh) or other agonists, and measurement of the subsequent change in vessel diameter using quantitative coronary angiography (QCA). The costly, time-consuming and invasive nature of QCA renders this technique impractical in exercise training studies that involve repeated testing during serial follow-up.

More recently, flow mediated dilation (FMD) has been developed as a non-invasive surrogate of coronary artery endothelial function (64) and measures the

ability of healthy, intact endothelial cells to detect, and respond appropriately, to changes in shear stress with acute adjustments in vascular tone. Typically, high-resolution ultrasonography is used to measure the change in the diameter of the brachial artery (expressed as a percentage change from baseline diameter) in response to a brief period of forearm occlusion.

The assessment of brachial artery FMD is technically challenging and a strict, standardized protocol is essential to provide accurate and reproducible data (78, 79). Briefly, baseline brachial artery diameter is recorded and blood flow is estimated above the anti-cubital fossa using high-resolution ultrasound. The artery is then occluded for 5 min at approximately 50 mm Hg above systolic blood pressure using a pneumatic cuff. Following the release of the cuff, the brachial artery diameter is measured continuously for 5 min (80) using an automated edge tracking software. The change in brachial artery diameter is expressed as a percentage change relative to the diameter prior to cuff inflation. The change in blood vessel diameter in response to reactive hyperemia is referred to as endothelium-dependent FMD. The vasodilator response to glycerlytrinitrate is a measure endothelial independent FMD and is as indication of smooth muscle function. A baseline image of the brachial artery diameter is obtained prior to the administration of sublingual glycerlytrinitrate after which the diameter is measured continuously for 5 min.

Endothelial Dysfunction – Prognosis

Endothelial dysfunction is an independent predictor of cardiovascular events,

providing valuable prognostic information additional to that derived from conventional risk factor assessment (81). Halcox *et* al., (2002) retrospectively evaluated the relation between coronary endothelial function and cardiovascular mortality in individuals with and without coronary atherosclerosis. Participants underwent cardiac catheterization at baseline and follow-up at 46 ± 3 months (82). There was improved survival among participants in both groups who were in the tertile with the best microvascular response to ACh, and had epicardial dilation in response to Ach.

In 147 patients undergoing either routine catheterization, evaluation of chest pain or PTCA for single vessel disease, endothelial-dependent coronary vasoreactivity was associated with a significantly higher incidence of cardiovascular events over a 7.7-year period even after statistically adjusting for traditional cardiovascular risk factors, or the presence of atherosclerosis (83). Similarly, coronary artery endothelial dysfunction was associated with a higher rate of cardiac events over a 28-month period in patients with non-obstructive CAD (84). In patients with a normal coronary angiogram, abnormal vasoreactivity of epicardial coronary arteries (0 - 30% vasoconstriction) in response to sympathetic stimulation was associated with the risk of developing cardiovascular events (85).

Shimbo et al., (2007) found a significant relation between impaired FMD and the risk of experiencing a cardiovascular event over a 3-year period in a group of 842 ethnic diverse, asymptomatic, low risk individuals (86). The predictive value of FMD however, was not however independent of traditional risk factors such as older age,

diabetes mellitus, and history of smoking. Using a similar prospective study design, Fathi et al., (2004) also found that among 444 individuals at risk of CVD, those with the greatest impairment in FMD had significantly greater risk of cardiovascular events than those with a normal or mildly impaired FMD response (87).

Neunteufl et al., (2000) reported that over a 5-year follow-up period, patients with impaired brachial artery FMD and chest pain were more likely to undergo PTCA and CABG surgery than individuals with normal FMD (88). In contrast, patients with chest pain and a normal brachial artery FMD had a low risk of cardiac events. In older men and women (72-98 years) brachial artery FMD was found to be a good predictor of future cardiovascular events even after adjustment for conventional risk factors (89).

During a median follow-up period of 21 months, Brevetti *et al*., (2003) found that reduced brachial artery FMD was an independent predictor for increased cardiovascular risk, in 131 patients with intermittent claudication who did not require vascular surgery (90). The predictive value of FMD was independent of traditional risk factors and of previous incidence of cardiovascular events. Brachial artery FMD improved the prognostic value of ankle-brachial pressure index, the most powerful marker of cardiovascular risk in PAD. Modena et al., (2002) found that improvements in brachial artery FMD in response to antihypertensive treatment decreased the risk of cardiovascular events over a mean period of 6 – 7 years in postmenopausal women with mild to moderate baseline hypertension and impaired FMD (91). Interestingly, there was an increased risk of CVD events in the women

who failed to show an improvement in endothelial function in response to hypertension medication.

Exercise and Endothelial Function

A large number of studies have found systemic changes in conduit artery structure and function in response to exercise training in patients with CVD. The largest improvements occur in individuals possessing established CVD risk factors or with established CVD (92–94). Hambrecht et al., (2003) examined the effects of hospital-based exercise training for 10 min, 6 times per day for 4 weeks on epicardial artery vascular function in men (mean ± SD; 60 ± 2 yr) with abnormal baseline ACh-induced vasoconstriction (95). Four weeks of exercise training resulted in a 12% increases in $\dot{V}O_2$ max. Compared to pre-training values, coronary blood-flow velocity increased 96%, 73% and 73% in response to acetylcholine at a dose of 0.072, 0.72, and 7.2 $\mu g \cdot min^{-1}$, respectively. Coronary blood flow also increased in a dose-dependent manner in response to ACh administration following the 4-week exercise training program. At the highest dose of ACh, mean coronary blood flow increased by 27% and 110% at four weeks. Exercise training attenuated the vasoconstrictive response by 54% to 7.2 $\mu g \cdot min^{-1}$ of ACh. There was no change in the vasodilatory response of the epicardial arteries in response to the endothelium-independent vasodilator nitroglycerine.

In a follow-up study Hambrecht et al., (2003) examined the effects of exercise training on endothelial vasomotor function and eNOS expression in the left internal

mammary artery (LIMA) in response to intracoronary infusions of ACh in men with stable CAD. Increases in blood flow were also measured after adenosine administration. Patients were randomized to 4 weeks of supervised, hospital-based, aerobic exercise training or an inactive control group. Exercise training involved 10 min of rowing ergometry, followed by 10 min of cycle ergometry, 3 times per day for 4 weeks (95). Compared to pre-training values, 4 weeks of exercise training resulted in a 109%, 94% and 116% increase in mean LIMA vasodilatory response and a 767%, 194% and 197% increase in mean LIMA blood flow velocity to intracoronary ACh infusions of 0.072, 0.72, and 7.2 $\mu g \cdot min^{-1}$. Similarly, adenosine-induced flow-dependent vasodilation of the LIMA was markedly improved after exercise training. There was no change in EID in response to training.

Vascular endothelial cells are constantly exposed to mechanical stimuli associated with blood flow (hydrostatic pressure), stretching in response to pulsatile distension and shear stress caused by tangential frictional force of blood flow on the endothelium. These hemodynamic forces are important in modulating the vascular adaptations to exercise training (96). Mechanosensors on the surface of the vascular endothelium converts the various mechanical stimuli into chemical signals that lead to the activation of intracellular signaling cascades (97). Cyclic circumferential strain associated with the aortic distension during dynamic rhythmical dynamic exercise has direct effects on endothelial cell gene expression, resulting in increases expression of eNOS[10].

Data from harvested LIMA indicated that both eNOS mRNA expression and

eNOS protein content doubled. The rise in eNOS expression is thought to be mediated by shear stress-responsive elements in the promotor region of the eNOS gene, or by stabilization of eNOS mRNA. Phosphorylation of eNOS at position Ser^{1177} increased four fold. It is believed that that the Ser1177 residue functions as a sensor of shear stress, because exposure of endothelial cells to laminar shear stress specifically, increases phosphorylation at this site leading to a rise in the enzymatic activity of eNOS and, enhanced NO production. The shear stress-induced phosphorylation of eNOS is maintained, whereas the agonist-mediated Ser1177 phosphorylation, e.g., bradykinin, is only transient, indicating that a sustained eNOS phosphorylation, resulting in an increased NO production or availability mediates the improvement in endothelial function in response to exercise training.

Vasoconstrictor pathways, including endothelin (ET-1) and angiotensin II (ANG II) are up regulated and contribute to endothelial dysfunction in patients with CVD or CVD risk factors. In contrast, vasoconstrictors are not a major contributor to vascular tone in healthy individuals. Exercise training significantly reduces the contribution of ET-1 to vascular tone in older adults (98–101). In addition, exercise training reduces ANG II-induced vasoconstriction in patients with CAD by approximately 50% (102).

Carotid Intima Media Thickness

Carotid intima-media thickness (CIMT) is defined as the area of tissue beginning at the luminal-intimal interface and the media-adventitia interface of the

common carotid artery (103). It is a commonly used index of vascular structure and is measured noninvasively using ultrasonography. In 2001, the American Heart Association acknowledged that the traditional risk factors were not sufficient in categorizing risk of patients and recommended the use of CIMT for risk stratification in asymptomatic individuals or patients at risk of CHD. The validity of CIMT as a non-invasive surrogate marker for atherosclerotic CVD has been well documented (104).

Strength

Strength training prevents age-related loss of muscle mass. Current PA guidelines recommend that adults perform muscle-strengthening activities, resistance or strength training, on ≥ 2 days per week in addition to aerobic activity (105, 106). In addition, current European guidelines for patients with CVD recommend that exercises for the lower limbs should be performed 40-50% of 1-RM and 30-40% for the upper limbs. It recommends that patients perform 12-15 repetitions in a single set two to three times per week.

Upper and lower body muscular strength is a fundamental component of overall health related fitness. Aging is associated with a decline in muscle strength. Handgrip strength using a hand held dynamometer is a simple, reliable and inexpensive assessment tool that has demonstrated prognostic utility for both all-cause and cardiovascular mortality (107–111). Several studies have reported reference ranges of handgrip strength with respect to the dynamometer chosen and the method used. To date, most reference values have been derived from Caucasian

populations (108).

Lower limb strength is usually assessed using objective measures such as isometric or isokinetic testing or a surrogate (112). The 30-sec chair stand test is an integrative measure of lower body power, balance and endurance that mimics many of the activities of daily living. It is widely used to evaluate functional fitness, monitor training and rehabilitation and can be a predictor of falls.

Underutilization of Cardiac Rehabilitation

Despite the evidence of the clinical and cost effectiveness of CR, uptake varies worldwide and by patient group, with participation rates ranging from 20% to 50%. Poor uptake has been attributed to several factors, including physician's reluctance to refer eligible patients, lower socioeconomic class, ethnic minority, gender (less attendance of females), age, access to facilities, transport, parking, lack of information, work responsibilities, family responsibility or fear of exercise (3, 113, 114). Across all countries the most common CR barrier reported was lack of physician referral (115).

Age, is a major barrier to CR, with older patients less likely to be referred to CR. In addition, older cardiac patients have less understanding of what CR entails and what to expect from participation in CR (116). This is likely to be linked to the finding that lack of physician encouragement was more often a barrier to older patients. Indeed, strength of physician referral was reported as a key factor in patients deciding to participate in CR (116). Older patients particularly believe that

CR would not benefit their health and they can self-manage their condition. Older patients are also more likely to suffer from additional comorbidities such as diabetes, angina, heart, shortness of breath and limited mobility that may further deter participation in CR.

Illness perceptions, independent of age are another common barrier to participation in CR. Non-attenders often report other chronic conditions that they believe would impair their ability to perform physical exercise. In contrast, some non-attenders and non-completers have indicated that the exercise intensity and duration were set lower than their current level of physical fitness (114).

Women are substantially less likely to be referred to CR, to enroll in CR once referred and to complete the CR program, compared to men. For women, many of the same barriers are reported but, to a greater extent. Age and co-morbidities are again two of the most influential barriers for both non-participation and drop out, as well as patient's lack of information and familiarity with CR (117, 118). Women often perceive CR as unnecessary and believe that heart attacks could not be prevented and often believe they could manage their heart disease without any CR. Women's role as a caretaker is regularly cited as a significant barrier to CR participation and drop out. Group format activities have also be identified as a barrier, particularly among women and older adults.

On a practical level, cost and lack of financial support from insurance providers can be a barrier for non-participation and drop out of CR (118). A meta-

analysis of CR studies found a large disparity between low and middle-income countries to high-income countries in terms of CR availability and uptake. Lower education level and gross income lower than €27,000 per year significantly decreased the odds of participation in CR (119).

Poor uptake and use of traditional hospital-based CR programs have prompted the need to develop more attractive, adaptable and accessible programs. One potential approach is the provision of alternative site (community centers, health clubs) or home-based CR (HBCR). A recent scientific statement from the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology defined HBCR as 'systematic, comprehensive, and personalized services that involve medical evaluation, prescribed exercise, cardiovascular risk factor modification, patient education, and behavioral activation/counseling that are delivered mostly or entirely outside of the traditional CBCR setting (28). Provision of HBCR offers a number of advantages over CBCR programs. These include no travel/transportation barriers, greater privacy (particularly for patients who dislike group settings) greater flexibility in scheduling and minimizing disruption to daily life. In addition, HBCR has the potential to expand the breadth and depth of educational, counseling and monitoring options for patients compared to CBCR programs.

A frequently cited example of the HBCR is the Heart Manual Program, a widely used 6-week, self-management program in the UK that includes health education, exercise and stress management (120). A trained health care facilitator

delivers the program, including home visits and telephone support. Studies have found the Heart Manual program to be as successful as center based CR programs (121, 122). Arthur et al., (2002) developed a 6-month exercise based HBCR program for post CABG patients (123). Participants were contacted by phone every 2 weeks to monitor progress, assess adherence, revise exercise prescription, and provide support and education. Compared to hospital-based CR, HBCR resulted in greater improvements in health-related quality of life and perceived social support. In addition, improvements in exercise capacity were significantly greater in HBCR than CBCR.

In general, the magnitude of the improvement in exercise capacity measured as $\dot{V}O_2$peak, work capacity on a cycle ergometer, peak MET level, distance achieved on either an incremental shuttle walk test or a 6-min walk test are similar in HBCR and CBCR. Likewise, changes in modifiable risk factors including body weight, tobacco use/smoking behaviors, blood pressure, and lipids are also similar in HBCR and CBCR (28). Studies examining the impact of HBCR and CBCR on HRQOL have found similar on no improvements.

Technological advances including telemedicine, mobile phones, smartphones, tablets, wearable devices, smart watches and personal health sensors provide the capacity for an attractive media option to support HBCR programs. For example, automated physiological monitoring and activity tracking along with smartphone applications and web-based/social media can be used to promote patient engagement through personalized physical activity interventions, convenient, and

easily accessible patient education and behavior change support.

Blasco et al., (2012) evaluated the efficacy of a web-based telemonitoring system for patients with CVD. Patients were provided with mobile phone, self-measurement devices (BP monitor, glucose and lipid meter) and interacted with care managers through mobile phone messages over the web. Weekly recordings of body weight, BP and HR and monthly glucose and lipids measurements were sent by text message to a cardiologist who accessed the clinical data through a web-based application. Individualized short messages based on the submitted information were sent from the cardiologist to the participants. The treatment goal for both BP and Hba1c was reached by significantly more participants in the telemedicine group compared with the control group (124). Varnfield et al., (2014) compared traditional 6-week, phase II CR with a smartphone-enabled home-based 6-week, Phase II CR program on CR use and health outcomes (modifiable risk factors and health related QOL). Participants in the home-based program were provided with daily text messages, multimedia education, relaxation audio and a light-to-moderate physical activity program. Participants in the smartphone intervention group had significantly higher adherence and completion rates as well as significantly improved 6-min walking test distances and depression scores (125).

The Heart Exercise and Remote Technologies intervention (HEART) was a 6-month single-blind, parallel, two-arm RCT that in addition to standard CR used text messaging, supporting Website as well as behavioral support to initiate and improve self-reported leisure PA among 171 people with CAD (18). Participants in the

intervention group (n=85) received 3–5 text messages per week and were encouraged to log onto the Website once per week to view new information, and short video messages. Both groups received standard CR. There was no change in $\dot{V}O_2$max in either group, but there was a significant improvement in leisure time PA and in the number of min per week spent walking in the intervention group.

Dale et al., (2015) evaluated the effect of a bidirectional text messaging intervention (Text4Heart) in addition to traditional CR on adherence to recommended lifestyle behaviors including PA, diet, smoking cessation, and non-harmful alcohol use in 61 individuals with diagnosed CVD (126). Participants received one text message per day for 24 weeks, had access to a supporting Website and received a pedometer to self-monitor their PA. The control group was encouraged to attend center-based CR. The Text4Heart intervention was based on social cognitive theory. Compared to the usual care control group, the Text4Heart intervention improved adherence to ≥3 lifestyle behaviors at 3 months, but not at 6 months. Text4Heart also improved adherence to medication.

The Tobacco Exercise and Diet Messages (TEXT ME) RCT examined the effect of a simple, low cost, automated lifestyle-focused semi personalized mobile phone messages on cardiovascular risk factors (127). Individuals with CHD were randomized to receive the text message intervention (n=352) or usual care (358). Patients in the intervention group received 4 messages per week for 24 weeks. The text messages providing motivation, advice, and information on how to improve diet, increase physical activity, and encourage smoking cessation (if relevant).

Compared to usual care, the lifestyle-focused text messaging service resulted in significant improvements in PA levels, LDL-C, blood pressure, BMI, waist and hip circumference and smoking status.

The remote exercise monitoring trial for exercise-based cardiac rehabilitation (REMOTE-CR) was a RCT that compared the effectiveness remotely monitored exercise-based cardiac-telerehabilitation with center-based CR in adults with CHD (16). Participants undertook 3 individually prescribed exercise sessions per week for the 12-weeks and were encouraged to be physically active on at least 5 d of the week. REMOTE-CR consisted of a smartphone, wearable sensor, web-based apps and custom middleware platform. Exercises HR and respiration rate were monitored in real-time. In addition, participants had access to specialized coaching in their home or local environment. The effect of REMOTE-CR on functional, risk factor and behavioral were similar to center-based CR immediately post intervention and at 24 weeks.

A common criticism of mobile and Internet technologies is that they create a digital divide where some patients may lack access to affordable technologies and/or the knowledge to operate them. However, mobile use and smartphone penetration have increased exponentially in recent years. A recent study involving patients attending community based CR programs found that 97% owned a mobile phone of which 64% were smart phones. Nine out of every 10 participants regularly accessed the Internet with 76% doing so on a daily basis. A personal computer was used to access the Internet by 98% of participants, with 44% using a tablet and 43% a mobile

phone. More than three quarters (77%) of participants responded positively when asked about their preference to receive CR support through the Internet. Interest in internet based CR support was higher in patients with a higher educational level but was not related to age or gender (128). As well as the use of mobile technology, 35% of all patients questioned used a heart rate monitor to measure HR during their exercise sessions. A summary table of technology enabled HBCR can be found in Appendix H.

Wrist worn Heart rate monitors

The development of wrist worn heart rate monitors has enabled the recording of RR interval data in situations where it was not previously possible without lab based electrocardiograms or ambulatory ECG's. However, these heart rate monitors are consumer available devices that are not specifically designed for research application and are characterized by their practicality, portability and affordable cost. To evaluate the accuracy and precision of the devices available on the market, validation studies are essential. Several studies have conducted validation tests on wrist worn heart rate monitors in comparison to polar chest strap or ECG in a lab setting. Experimental protocols were conducted in a lab between 21 and 23 degrees Celsius with relative humidity between 40% and 60%. Participants were advised to avoid, alcohol or stimulants such as caffeine (129, 130).

No study to date has compared the validity of the Fitbit charge HR and the Microsoft band 2 against one another and the gold standard. Studies have looked at

different heart rate monitors compared with the gold standard including the V800 Polar heart rate monitor. Both ECG and Polar RR waves were manually matched and compared using interclass correlation and Bland-Altman plots. Pearson correlation was used in another study to examine the validity of the Polar S810.

CHAPTER III

STUDY I

Validity of a Commercially Available Wrist-Worn, Sensor-Based Measurement of Heart Rate at Rest and During Exercise

Introduction

Exercise prescription for patients with CVD is based primarily on the recommendations of what is safe and will improve or maintain physical fitness and reduce the risk of major cardiac events. Quantification of exercise exposure is typically accomplished using the concept of exercise dose, the product of exercise frequency, duration and intensity (131). The sum of duration and frequency reflects the total amount of time spent in exercise over a given period. Exercise intensity describes the level of effort and may be expressed in a number of ways including objectively measured thresholds of caloric expenditure, relative to maximal heart rate (HRmax), $\dot{V}O_2$max, and blood lactate levels, or based on ratings of perceived exertion (RPE).

Prescribing intensity as a percentage of $\dot{V}O_2$max or oxygen consumption reserve ($\dot{V}O_2$R) provides a high degree of accuracy. However, the fact that the measurement of oxygen uptake is typically performed in a specialized laboratory and requires sophisticated equipment and trained personnel renders this method impractical for general use (132). The linear relation between oxygen uptake and HR

at submaximal exercise intensities allows HR to be used as an effective alternative to measure and monitor submaximal exercise intensity.

Wearable sensors, often worn as a wristband or embedded in a smartwatch or mobile phone, are now ubiquitous and provide real time HR information that allows patients to monitor and adjust exercise intensity to meet their rehabilitation goals. Smartwatch based HR measurement is based on optical sensing technique called photoplethysmography (PPG) that operates at a red or a near infrared wavelengths (133). A light source (LED) that illuminates the skin is linked to a photodetector that measures the small variations in light intensity in the catchment volume. The most recognized waveform feature, the peripheral pulse, is synchronized to each heartbeat and is recognised as the AC component of the photoplethysmograph (PPG) waveform.

Motion artefact is a major challenge faced by the PPG technology. In addition, there is no international recognised standards for clinical PPG measurement. For proprietary reasons, many technology companies do not reveal their validation protocols and/or data for their wrist worn HR monitors. The lack of available validation data is a drawback to their potential application in clinical exercise related research. The purpose of this study was to assess the accuracy of two commercially available wristwatch HR monitors, Microsoft Band 2 and Fitbit Charge HR™ at rest and during exercise.

Study Aims

1. To evaluate the accuracy of the Microsoft Band 2 and Fitbit Charge HR™ wristwatch HR monitors at rest
2. To evaluate the accuracy of the Microsoft Band 2 and Fitbit Charge HR™ wristwatch HR monitors during exercise

Study Hypothesis

1. The Microsoft Band 2 and Fitbit Charge HR™ wristwatch HR monitors will accurately and reliably measure resting HR
2. The Microsoft Band 2 and Fitbit Charge HR™ wristwatch HR monitors will accurately and reliably measure HR during exercise

METHODOLOGY

Study Participants

Healthy college age men (n=24) and women (n=22) (mean ± SD; Age, 26.42 ± 3.24 yr, BMI, 23.04 ± 3.08 $kg.m^{-2}$) participated in the study. Participants were fully informed of the experimental procedures and provided with a plain language statement before written informed consent was obtained in accordance with the Research Ethics Committee at Dublin City University (DCU). Participants completed a physical activity readiness questionnaire (PAR-Q) prior to commencing the study.

Study Overview

Participants visited the School of Health and Human Performance at DCU on two occasions, separated by at least 7 d. They fasted for 4 h and refrained from strenuous physical activity for 24 h prior to each visit. During each visit, participants were fitted with a Microsoft band 2 monitor and Fitbit Charge HR™ monitor on separate wrists. A Contec TLC9803 3-lead Holter monitor system was used as the reference HR (Figure 3.1). Following 10 min of supine rest, resting BP, height and weight were measured, after which participants performed a number of validation trials (Figure 3.2). HR was continuously recorded on all three devices.

Contec TLC9803 3-Lead Holter monitor

Fitbit Charge wrist worn HR monitor

Microsoft Band 2 wrist worn HR monitor

Figure 3.1: Holter monitor and wrist worn HR monitor

Validation Protocol

The validation protocol is outlined in figure 3.2. Briefly, resting HR was recorded for 3 min in a supine position followed by 3 min in a sitting position. Participants then walked on a treadmill (Cosmed T170, Rome, Italy) for 3 min at 6 $km \cdot h^{-1}$ followed by continuous 3 min running bouts at 9 and 10 $km \cdot h^{-1}$. Following the 3 min run at 10 $km \cdot h^{-1}$, participants remained standing on the treadmill for 3 min and HR recovery was recorded.

Figure 3.2: Validation Protocol

Holter Monitor

Electrodes were placed on 5 anatomical landmarks that provided 3 separate ECG leads (Figure 3.3). The signal to noise ratio at the skin electrode interface was reduced by cleansing the area with an alcohol saturated gauze pad. The superficial layer of skin was then removed using light abrasion with fine grain emery paper.

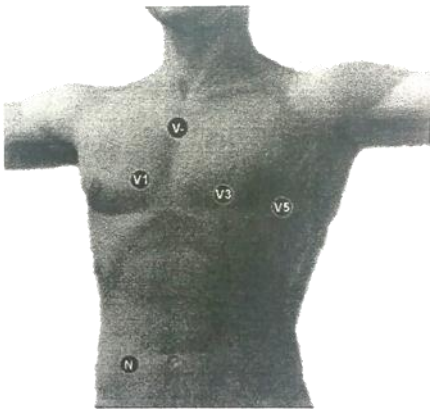


Figure 3.3: Electrode placement for the Holter monitor

Fitbit Charge HR™

Participants were fitted with the most appropriate Fitbit based on the recommended Fitbit Charge HR™ sizing guide. For optimal HR readings, the Fitbit Charge HR™ was fitted securely on the participant's left wrist at a location three fingers width above the ulnar styloid process as per the manufacturer's guidelines.

Microsoft Band 2

Participants were fitted with a Microsoft Band 2 using the recommended sizing chart. The Band was placed on the participant's right wrist with the PPG sensor on the inside of the wrist as recommended by the Microsoft guidelines.

Height and Weight

Height and body weight were measured using a wall stadiometer and electronic balance (Seca 797, USA), respectively. Footwear and heavy clothing were removed prior to the measurement. Height was measured to the nearest 0.1 cm and body weight to the nearest 0.1 kg. BMI was calculated as weight (kg)/height (m^2).

Blood Pressure

Participants' rested supine for 10 min after which BP was measured using an automatic blood pressure cuff (Omron M6-comfort). They fasted for 4 h and refrained from strenuous physical activity for 24 h prior to each visit. The measurement was repeated 3 times, and an average of the three blood pressure readings was recorded.

Data Analysis

Descriptive statistics were calculated using standard statistical procedures. Intraclass correlations were used to assess the reliability of the wrist-worn HR monitors for each experimental condition. The relation between HR measured using

both wrist-worn monitors and the Holter monitor was determined using the Pearson product-moment correlation. Bland-Altman plots were utilized to examine the limits of agreement of the HR recorded by each wrist-worn monitor and the Holter monitor. The Bland–Altman analysis calculates the mean difference between two methods of measurement, and 95% limits of agreement as the mean difference ± 1.96 times the standard deviation of the differences. It is expected that the 95% limits include 95% of differences between the two measurement methods. Proportional bias in the HR measurement was assessed using linear regression.

RESULTS

Intraclass correlations

The intraclass correlation coefficients between the Microsoft Band and the Holter monitor and between the Fitbit HR™ and the Holter monitor at rest and during each exercise condition are presented in table 3.1. There was a significant positive correlation between the HR measured with both wrist worn devices and the HR measured by the Holter monitor at rest and during each exercise bout. The intraclass correlation coefficient between the Microsoft Band and Holter monitor ranged from 0.79 to 0.91. The intraclass correlation coefficient between the Fitbit HR™ and Holter monitor ranged from 0.58 to 0.97.

Table 3.1: Intra-class correlation coefficient between both the Microsoft Band and the Holter monitor and the Fitbit HR™ and the Holter monitor at rest and during exercise.

	Wrist Worn HR Monitor	
Experimental condition	**Microsoft Band**	**Fitbit**
Rest		
Supine	r = 0.811 p < 0.001	r = 0.973 p < 0.001
Sitting	r = 0.912 p < 0.001	r = 0.869 p < 0.001
Exercise		
6 $km \cdot h^{-1}$	r = 0.853 p < 0.001	r = 0.573 p < 0.001
10 $km \cdot h^{-1}$	r = 0.786 p < 0.001	r = 0.891 p < 0.001

Limits of Agreement Between the Microsoft Band and Holter Monitor

Microsoft Band - Rest

The upper and lower limit of agreement was 12.49 beats·min^{-1} and -15.00 beats·min^{-1} respectively, while resting in a supine position (Figure 3.4A). The upper and lower limit of agreement was 9.12 beats·min^{-1} and 9.82 beats·min^{-1}, respectively while seated (Figure 3.4B).

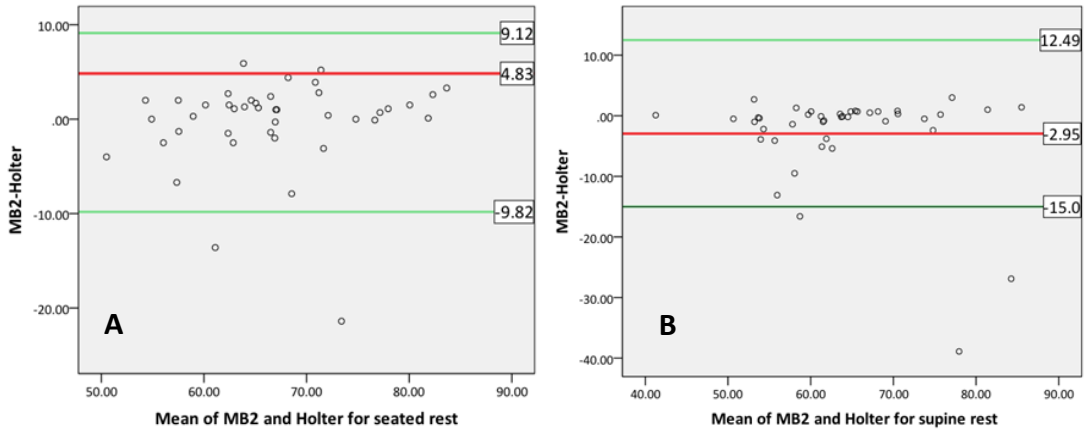


Figure 3.4: The limits of agreement for the 95% upper and lower confidence interval between the Microsoft Band and the Holter monitor while (A) supine and (B) sitting

Microsoft Band - Exercise

The upper limit of agreement was 15.97 beats·min^{-1} and the lower limit of agreement was 10.49 beats·min^{-1} while walking on a treadmill at 6.0 km·h^{-1} (Figure 3.5A). The upper limit of agreement was 21.36 beats·min^{-1} and the lower of agreement was -25.20 beats·min^{-1} while running on a treadmill at 10.0 km·h^{-1} (Figure 3.5B)

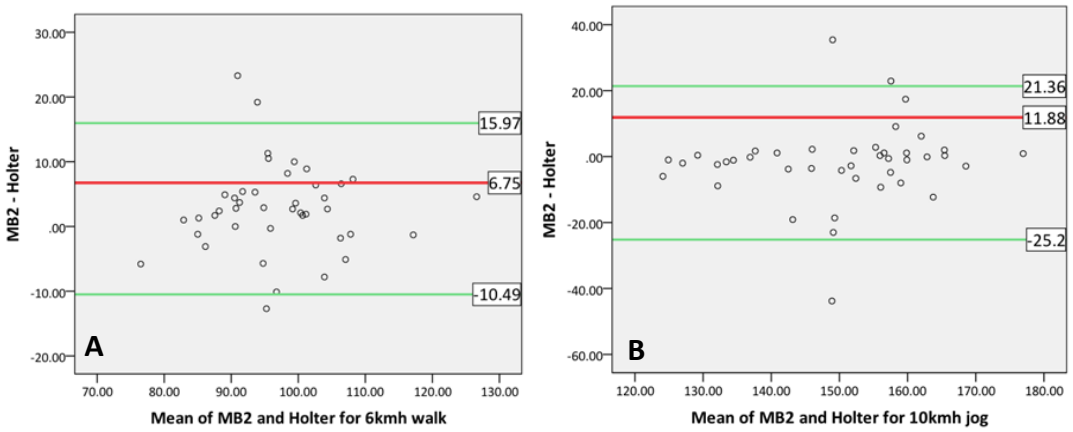


Figure 3.5: The limits of agreement for the 95% upper and lower confidence interval between the Microsoft Band and the Holter monitor while (A) walking at 6 km·h^{-1} and (B) running on a treadmill at 10 km·h^{-1}.

Limits of Agreement Between the Fitbit Monitor and Holter Monitor

Rest

The upper limit of agreement was 5.88 beats·min^{-1} and the lower limit of agreement was 5.28 beats·min^{-1} while resting supine (Figure 3.6A). The upper and lower limit of agreement was 12.33 beats·min^{-1} and -8.39 beats·min^{-1} while seated (Figure 3.6B).

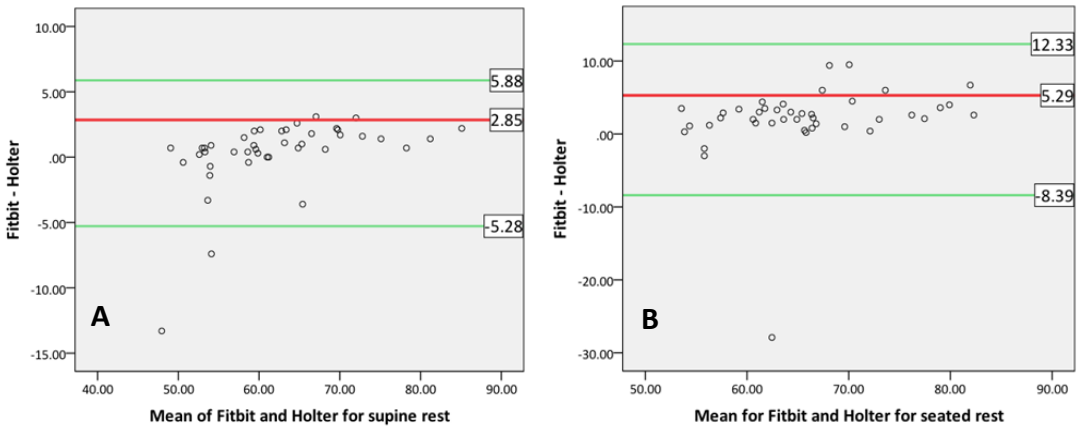


Figure 3.6: The limits of agreement for the 95% upper and lower confidence interval between the Fitbit and the Holter monitor while (A) supine and (B) sitting

Exercise

The upper limit of agreement was 28.87 beats·min^{-1} and the lower limit was 9.55 beats·min^{-1} while walking on a treadmill at 6 km·h^{-1} (Figure 3.7A). The upper limit was 18.60 beats.min^{-1} and the lower -12.68 beats.min^{-1} while running on a treadmill at 10.0 km·h^{-1} (Figure 3.7B).

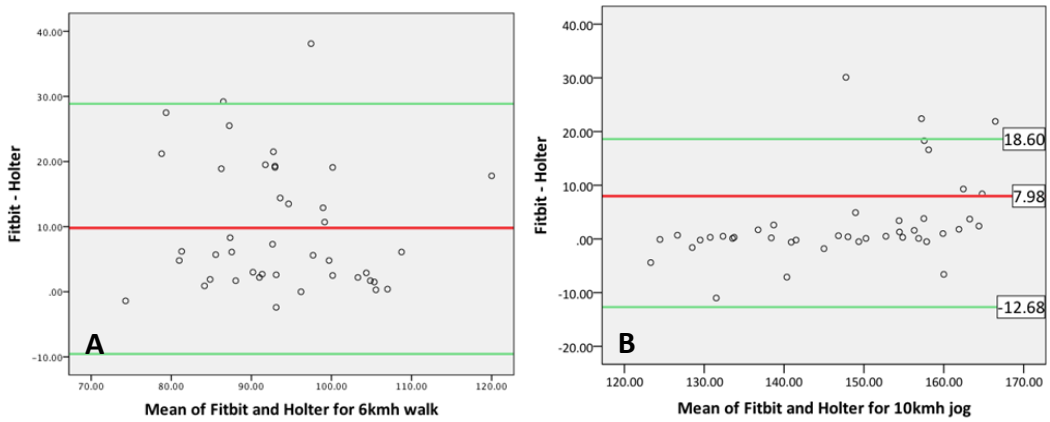


Figure 3.7: The limits of agreement for the 95% upper and lower confidence interval between the Fitbit and the Holter monitor while (A) walking at 6 km·h^{-1} and (B) running on a treadmill at 10 km·h^{-1}.

The relation between HR recorded from both wrist-worn monitors and the Holter monitor while sitting and supine is shown in Figure 3.8. There was a strong positive correlation between the HR measured with the Fitbit Charge HR™ and the Holter monitor while supine ($p < 0.001$ $r = 0.973$) and sitting ($p < 0.001$ $r = 0.869$). There was also a strong positive correlation between the HR measured with the Microsoft Band 2 and the Holter monitor while supine ($p < 0.001$ $r = 0.811$) and sitting ($p < 0.001$ $r = 0.912$).

The relation between HR recorded from both wrist-worn monitors and the Holter monitor while exercising is shown in Figure 3.9. There was a strong positive

correlation between the HR measured with the Fitbit Charge HR™ and the Holter monitor while exercising at 6 km·h^{-1} ($p < 0.001$ $r = 0.573$) and 10 km·h^{-1} ($p < 0.001$ $r = 0.891$). There was a strong positive correlation between the HR measured with the Microsoft Band 2 and the Holter monitor while exercising at 6 km·h^{-1} ($p < 0.001$ $r = 0.853$) and 10 km·h^{-1} ($p < 0.001$ $r = 0.786$).

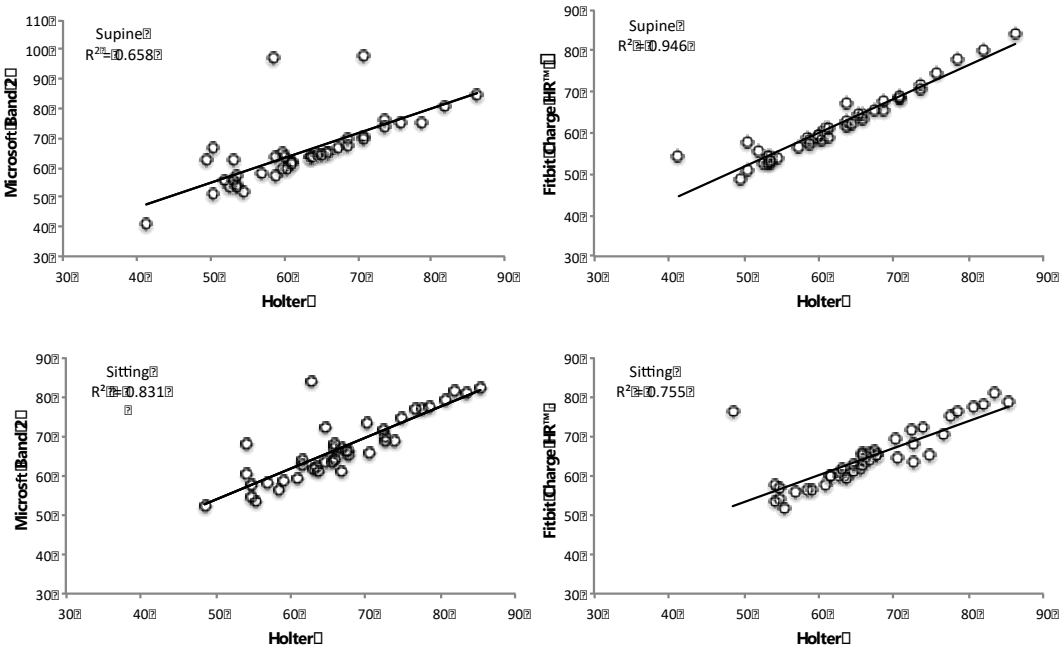


Figure 3.8: Relation between HR measured with a Holter monitor and Fitbit Charge HR™ and Microsoft Band while supine and sitting.

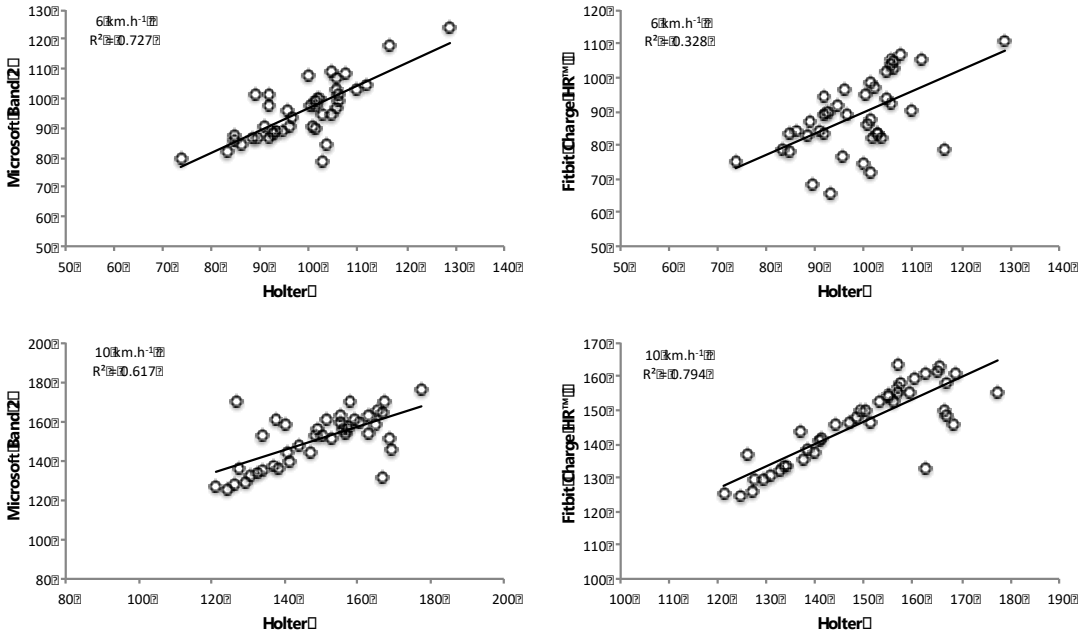


Figure 3.9: Relation between HR measured with a Holter monitor and Fitbit Charge HR™ and Microsoft Band while exercising on a treadmill at 6 km.h-1 and 10 km.h-1

SUMMARY

The current study investigated the accuracy of 2 commercially available wrist-worn monitors to continuously measure HR at rest and during exercise. The criterion measure was a Holter 3-lead ECG monitor. Both wrist worn monitors correlated with the Holter monitor over all resting and exercising condition. The Fitbit monitor underestimated HR over all conditions compared with the MB2. Therefore the MB2 was chosen as the wrist worn device to use in the PATHway intervention.

CHAPTER IV

STUDY II

Usage and Acute Physiological Responses During a Technology-Enabled Home-Based Cardiac Rehabilitation Program

Introduction

The primary objective of CR, an integral component in the continuum of care for patients, is to optimize cardiovascular risk reduction, enhance healthy behaviors and reduce hospital readmissions and cardiovascular morbidity and mortality. Despite the growing evidence of the clinical effectiveness of CR, uptake varies worldwide with participation rates ranging from 20% to 50%. Reasons underpinning poor uptake are complex but are linked to geographical, logistical and other access related barriers.

Advances in health technology, including smartphone applications and wearable sensors that capture activity metrics and physiological data have the potential to improve accessibility, delivery and engagement of personalized secondary prevention programs for people with CVD. Technology-based interventions are more effective if they also provide evidence- and theory-based behaviour support along with a suite of behaviour change techniques such as self-monitoring, feedback, goal setting and rewards (49).

PATHway (Physical Activity Towards Health) is a technology-based platform with the goal of supporting self-management of CVD through a supportive, holistic, home-based (phase IV) CR program. The program provides regular exercise sessions as the basis upon which to provide a personalized, comprehensive lifestyle intervention program. Behaviour change techniques are delivered using text-based resource content, media files and push notifications. In addition, participant empowerment and autonomy is facilitated through interaction with a customized avatar. The PATHway system consists of two exercise modules, exerclass (EC) and Active Living (AL) along with an assessment module and education module.

The EC module involves an individually tailored exercise program. Each exercise session involves a combination of aerobic, resistance and relaxation exercises. A customized algorithm was used to select individually tailored activities for each EC session. Each exercise was demonstrated by an avatar and was categorized in terms of difficulty, intensity, muscle group(s) involved and type of exercise e.g., aerobic, dynamic resistance, stretch and balance. AL involved any PA performed outside of the EC sessions.

The purpose of this study was to evaluate participant usage along with their physiological (HR and $\dot{V}O_2$) and perceptual (RPE) responses during the EC and AL components of PATHway system.

Study Aims

1. To evaluate participant usage of the EC and AL components of PATHway

2. To evaluate the HR and $\dot{V}O_2$ response during the EC and AL components of PATHway
3. To evaluate participants perception of effort during the EC component of PATHway

METHODOLOGY

Study Design

The study used a single blind, parallel two group, multi-centre randomized controlled design. A convenience sample of 120 men and women were recruited and randomized to the PATHway intervention or UC. Standard operating procedures for each assessment were created and followed by both participating sites. Extensive proprietary preparation was implemented insuring quality assurance in both sites. Site visits were conducted between both participating sites to practice and prepare for the testing protocol.

Participants

Participants between 40-80 years of age with documented CVD and who were enrolled for the first time in a phase III hospital-based CR program (Beaumont Hospital, Dublin, Mater Misericordiae University Hospital and UZ Leuven Belgium) were recruited for the study. The inclusion and exclusion criteria are summarized in table 4.1.

Table 4.1: Inclusion and exclusion criteria for the PATHway study.

Inclusion criteria	Exclusion criteria
Men and women with documented CVD	Significant undercurrent illness in the last 6 weeks
Age 40-80 years	Known severe ventricular arrhythmia with functional or prognostic significance
Patients are on optimal medical treatment and stable with regard to symptoms and pharmacotherapy for at least 4 weeks	Significant myocardial ischemia, hemodynamic deterioration or exercise-induced arrhythmia at baseline testing
Patients must have completed the phase III ambulatory in hospital program and received clinical approval from their treating physician to continue exercising outside the hospital program	Cardiac disease that limits exercise tolerance (valve disease with significant hemodynamic consequences, hypertrophic cardiomyopathy etc.)
Internet access at home	Co-morbidity that may significantly influence one-year prognosis
Sufficient space to deploy and use the system adequately	Functional or mental disability that may limit exercise
	Acute or chronic inflammatory diseases or malignancy, the use of anti-inflammatory drugs or immune suppression
	Glomerular Filtrate Rate <25ml/min/1.73m^2
	Hemoglobin < 10g/dl
	Severe chronic obstructive pulmonary disease (FEV1 < 50%)
	New York Heart Association class 4
	Participation in another clinical trial

Recruitment

Patients were assessed for eligibility by a cardiac nurse during phase III CR. A local investigator of the research team arranged a meeting with the eligible participant to give a full oral explanation of the design and purpose of the study, responsibilities of the participants, reasonable foreseeable inconveniences, confidentiality of the information collected and contact details. Written informed consent was obtained in accordance with the research ethics committee in the participating sites (Appendix D). The study complied with the World Medical

Association Declaration of Helsinki on ethics in medical research (134). Patients were only enrolled in the study after signing written informed consent. An American Heart Association (AHA)/American College of Sports Medicine (ACSM) Health/Fitness Facility Preparticipation Screening Questionnaire was completed by each participant prior to commencing the study (Appendix G).

Figure 4.1 summarizes participant recruitment and dropout. Recruitment took place between June 2017 and December 2017. A total of 209 patients met the inclusion criteria. From this pool of potential participants, 60 indicated they were not interested in participating in the study and 29 could not participate for other reasons. The 120 eligible participants (98 male) who agreed to participate were evenly distributed between Ireland and Belgium. Fourteen participants dropped out of the study at 3-months, and a further six participants had dropped out at 6-months. Reasons for dropout included loss of interest, serious adverse events, fatigue, family commitments, change of address and mental health issues.

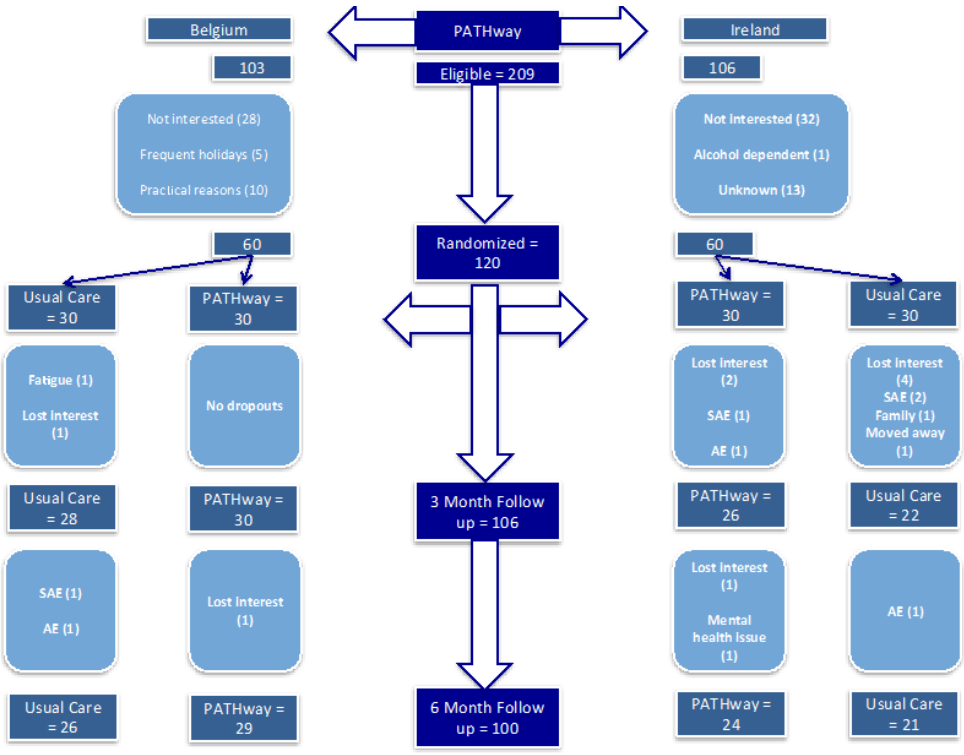


Figure 4.1: Summary of recruitment and dropout

Randomization and Concealed Allocation

Participants were randomized to the PATHway intervention group or the UC control group. Blocked randomization was performed in a 1:1 ratio, stratified by centre of enrolment. Randomization schedules were generated using a computerized random number generator. After signing informed consent, participants were assigned a randomization number by an independent designated member of the coordinating centre. This ensured concealed allocation to experimental condition and helped to minimise selection bias. Participants received a personal identification code (PIC) that was used on all subsequent documents to assure anonymity of all data.

Baseline measurements of cardiovascular fitness, vascular structure and function, strength, physical activity and blood biomarkers were taken 4 weeks prior to completion of phase III CR. Participants randomized to the PATHway group were familiarized with the components of the PATHway system during the final 4 weeks of the phase III CR program. Due to the design of the intervention, it was not possible to blind the participants or the researchers who delivered the familiarization phase. The researchers performing the outcome measurements were blinded to the treatment condition.

Methods

Participants in PATHway and UC underwent baseline testing approximately 4 weeks before the end of their phase III CR program and at 3-months and 6-months after completion of the CR program. At each of the three time points, participants attended the testing site on two occasions separated by at least 7 d. The first visit was used to collect anthropometric data after which participants underwent a maximal aerobic exercise test on a cycle ergometer. During the second visit, BP, vascular structure and function, and upper and lower body strength were measured, and a series of questionnaires were completed. A fasting blood sample was drawn at baseline and 6 months. The order of tests undertaken by the participant during each visit is outlined in Table 4.2.

Table 4.2: Data collection outline

	Allocation T0	Baseline T1	3-month FU T2	6-month FU T3
Enrolment				
Eligibility screen	X			
Informed consent	X			
Intervention				
PATHway intervention		◆———	———	———◆
Usual care (control) intervention		◆———	———	———◆
Assessments				
Demographic characteristics	X	X	X	x
Health related physical fitness tests				
-CPET		X	X	X
-Muscle strength and flexibility		X	X	X
-Quality of the vascular system		X	X	X
-Blood sampling		X		X
-Body composition		X	X	X
Safety monitoring				
-3 day ECG Holter monitoring		X		X
-Adverse event reporting	◆———	———	———	———◆

Maximal Aerobic Capacity ($\dot{V}O_2$peak)

Maximal aerobic capacity ($\dot{V}O_2$peak) was assessed on a cycle-ergometer (Marquette 2000, General Electric, USA) using one of three incremental protocols; 10 W·min^{-1}, 20 W·min^{-1} or 25 W·min^{-1}. Depending on the selected protocol, participants performed a 1 min warm-up at 10 W, 20 W or 50 W that was immediately followed by a 10 W·min^{-1}, 20 W·min^{-1} or 25 W·min^{-1} incremental exercise test until volitional fatigue. Participants were requested to maintain a constant cadence between 60 - 75 rev·min^{-1}. The protocol was designed to ensure that participants reached volitional fatigue between 8-12 min (135). Participants were verbally encouraged to give a maximal effort by the same researcher

Respiratory and metabolic measures were continuously monitored throughout the test and $\dot{V}O_2$peak was determined by averaging the three highest consecutive 20 sec values. RPE was recorded during the final 15 sec of each min using the Borg 16-point category rating scale. HR and electrical activity were continuously monitored using a 12-lead ECG. The test was deemed maximal if at least two of the following criteria were met: (i) a plateau in oxygen consumption (defined as a ≤ 2.1 mL·kg^{-1} min^{-1} change in $\dot{V}O_2$ during the last min of exercise), (ii) RER > 1.10 or (iii) Borg scale > 18.

Cardiorespiratory Measures

Respiratory and metabolic responses were determined using standard open-circuit spirometry techniques (Sensormedics Vmax 229, Sensormedics Corp, CA). Prior to testing, the gas analyzers were calibrated with standard gases of known

concentration. The mass flow sensor (Sensormedics, CA) used to collect breath-by-breath measurements of ventilation was calibrated prior to each test.

Mass Flow Sensor Heated Calibration

A 3.0 L syringe was connected to the mass flow sensor, and stroked twice in order to measure inspired and expired volumes. The volumes were calculated by expressing 3.0 L as a fraction of each measured inspired and expired volume achieved during calibration. An average correction factor was calculated for inspired and expired volumes, and used to fine-tune the volume measurement. The flow sensor then stabilized and, automatically calibrated to zero gas flow.

Four inspiratory and expiratory strokes were performed, each for a different target range to verify various velocities of air flow. The first stroke had an average flow rate of <0.6 $L \cdot sec^{-1}$, the second between 0.9 and 1.6 $L \cdot sec^{-1}$, the third between 2.4 and 5.5 $L \cdot sec^{-1}$and the final stroke between 7.0 and 12.0 $L \cdot sec^{-1}$. The final verification stage of the flow sensor calibration involved performing five full inspiratory and expiratory strokes.

Gas Analyzer

The Vmax 229 utilizes a rapid response infrared measurement technique. Separate O_2 and CO_2 analyzers are integrated within the Vmax 229. A small sample of inspired air is drawn through a band pass filter to the sample cell. The amount of infrared light that passes through the sample cell varies according to the concentration of CO_2 and is measured using an infrared detector. The CO_2 analyzer

is linearly scaled across the 0-100% range with a resolution of 0.01% CO_2 and a response time of <130 $m \cdot sec^{-1}$ (10-90%) at 500 $mL \cdot min^{-1}$ flow. The O_2 analyzer is based on the high paramagnetic susceptibility of O_2. A diamagnetic glass dumbbell suspended in a magnetic field rotates in proportion to the PO_2. The analyzer is linearly scaled across 0-100% with a resolution of 0.01% O_2 and a response time of < 130 $m \cdot sec^{-1}$ (10-90%).

Calibration of CO_2 and O_2 Analyzers

The gas analyzers were calibrated with the standard gases of known concentration. The first calibration gas contained 26.00 ± 0.02% O_2 and the balance nitrogen (N_2). The second calibration gas contained 4.00 ± 0.02% CO_2, 16.00 ± 0.02% O_2 and the balance N_2. A small bore drying tube connected to the CO_2 and O_2 analyzers sampled the calibration gases. The absorption and evaporative properties of the drying tube ensured that the relative humidity of the calibration gas was equilibrated to the ambient conditions prior to sampling by the O_2 and CO_2 analyzers. The calibration gas was sampled at a rate of 125 Hz. The response time was similar between the O_2 and CO_2 analyzer.

Electrocardiographic and Blood Pressure Monitoring

Heart rate and electrical activity were continuously monitored using a 12-lead ECG monitor (GE Case 8000 12 Lead ECG). The signal to noise ratio at the skin electrode interface was reduced by cleaning the area with an alcohol saturated gauze. The superficial layer of skin was then removed by abrading the areas using

fine grain emery paper. Electrodes were placed on the 10 standard anatomical landmarks to generate 12 leads. BP was measured at the left upper arm during seated rest before and throughout the maximal exercise test using an automated BP monitor (Omron M6-comfort, Omron, Kyoto, Japan).

Ventilatory Threshold

A number of methods were used to determine the VT. The V-slope method examided the change in relation between $\dot{V}CO_2$ and $\dot{V}O_2$. A breakpoint was identified in which $\dot{V}CO_2$ begins to increase more rapidly than the $\dot{V}O_2$. The ventilatory equivelent method defined VT as the exercise intensity at which the ventilatory equivelent of oxygen ($\dot{V}_E$/ $\dot{V}O_2$) increased without a concurrent rise in the ventilatory equivelents of carbon dioxide ($\dot{V}_E/\dot{V}CO_2$). Both methods were computed for each individual exercise test and were subsequently analyzed by three members before the best fit method was chosen.

Resipatory Compensation Point

Respiratory compensation point (RCP) marks the onset of hyperventilation during an incremental exercise test. The breakpoint was identified when $\dot{V}_E$ increased without a concurrent rise in $\dot{V}CO_2$.

PATHway Intervention Group

The PATHway intervention involved a comprehensive self-care, home-based CR program with the primary aim of promoting long-term adherence to exercise.

The intervention involved the implementation of a technology-based platform with the goal of facilitating participants to better self-manage their disease. The PATHway system consisted of four separate modules; an EC module, AL module, assessment module and education module. Realistic goals in relation to PA/exercise, diet, smoking, alcohol consumption and stress reduction were agreed with each participant based on personal choice and results of the lifestyle questionnaires.

Participants randomized to the PATHway group were familiarized with the platform by a cardiac nurse during one of the weekly CR sessions in each of the final 4 weeks of the phase III CR program. Participants continued to participate in two standard-care exercise sessions during each of the final 4 weeks. In addition, the PATHway platform was installed in each participant's home prior to discharge from the phase III CR program. Participants were encouraged to discuss their PATHway induction experience with the PATHway nurse.

Exercise Consultation

Prior to beginning the PATHway program, participants undertook an exercise consultation session. They set personal goals for the program and were advised on how best to use the PATHway system to maximize potential health benefits. Each participant was provided with an individualized exercise prescription. They were encouraged to explore the benefits and barriers to using PATHway and were facilitated in developing strategies to overcome barriers. Advice was provided on how PATHway could enable them to achieve their exercise goals.

Exerclass Module

The exercise module (exerclass) involved the delivery of an individually tailored exercise program. Each exercise session involved a combination of aerobic, resistance and relaxation exercises. Before commencing an EC session, a virtual coach appeared on the computer screen to demonstrate and verbally explain how to place the Microsoft band 2 on the wrist, and advise participants on appropriate clothing to wear. Participants then measured and recorded their resting BP and HR while in a seated position. Participants were not permitted to begin an EC session until their HR ≤ 120 bpm, SBP ≤ 180 mm Hg and DBP ≤ 100 mm Hg. If the HR or BP values were outside the normal range, participants were required to rest for an additional 5 min before retesting.

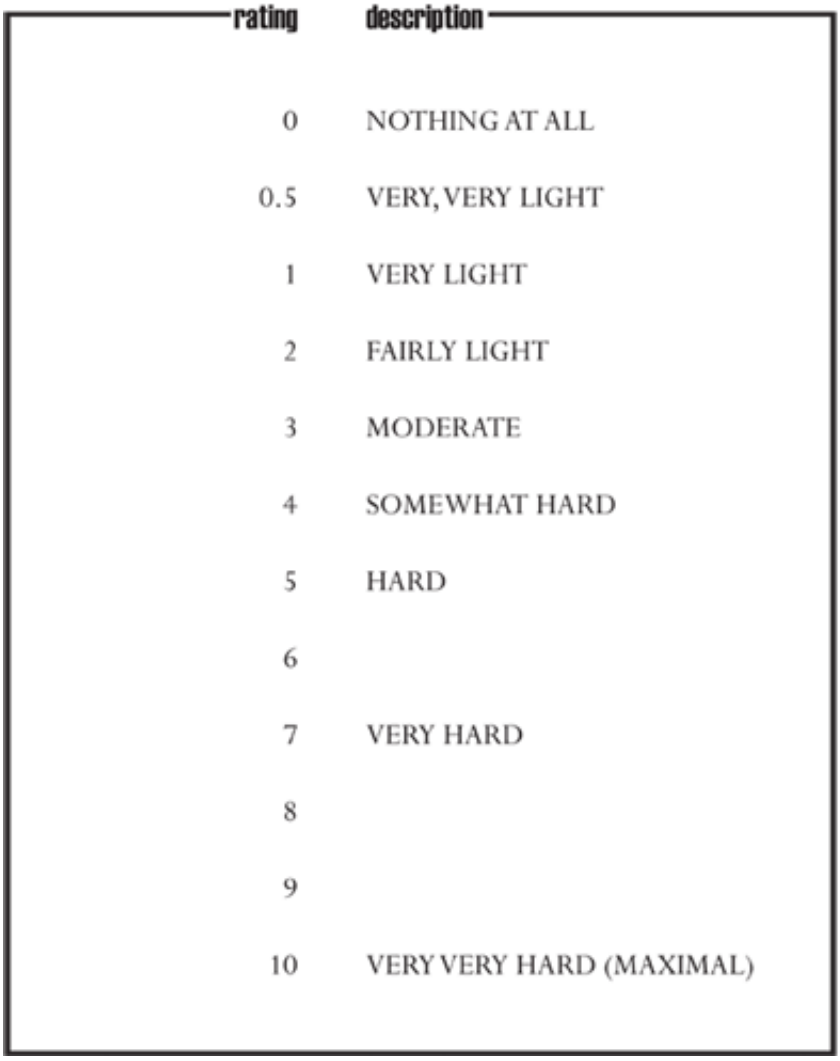
The PATHway system required participants to exercise within an individually prescribed HR range determined from the results of a maximal exercise test at baseline and 3-months. The lower limit of the prescribed intensity range corresponded to the HRR at the ventilatory threshold (VT) and the upper limit of the range corresponded to the HRR at the respiratory compensation point (RCP). When RCP could not be determined, the HR corresponding to 80% $\dot{V}O_2$max was used to calculate the upper limit of the HRR range.

The PATHway system used a customized algorithm to select individually tailored activities for each EC session. The algorithm selected from a bank of over 100 exercises, each demonstrated by an avatar (Figure 4.2) and tagged in terms of

difficulty, intensity, body part involved and type of exercise e.g., aerobic, dynamic resistance, stretch and balance. Participants were required to keep their HR within the prescribed range for at least 80% of the duration of each EC session.

Figure 4.2: An example of an avatar illustrated exercise

Each selected activity was performed for 1 min. Participants movement patterns were monitored in real time using a Microsoft Kinect® camera. Personalized feedback, based on the accuracy of their exercise performance, was provided by a virtual avatar coach during each exercise session. The PATHway algorithm selected the next exercise, based on muscle group, intensity and difficulty, taking into account each participants accuracy score during the previous exercise. In the event that a participant did not like performing the selected exercise, they had the option to manually trigger the PATHway algorithm to select the next activity. Following each EC session participants using the Borg 10-point RPE scale (Figure 4.3), selected an RPE to accurately reflect their perceived intensity of effort, strain, discomfort and/or fatigue experienced during the session.



rating	description
0	NOTHING AT ALL
0.5	VERY, VERY LIGHT
1	VERY LIGHT
2	FAIRLY LIGHT
3	MODERATE
4	SOMEWHAT HARD
5	HARD
6	
7	VERY HARD
8	
9	
10	VERY VERY HARD (MAXIMAL)

Figure 4.3: Borg 10-point RPE scale

The Pathway system had an option to allow participants view additional demonstrations of each exercise and to read the key teaching points for each exercise. Following each EC session, participants were sent a congratulatory SMS message and were provided with feedback regarding duration and intensity of the session and accuracy with which they completed the individual exercises. Only EC session above 10 min in duration counted as a valid session and participants were encouraged to complete 3, 30 min EC sessions per week.

Active Living Module

Active living for the purpose of this study was defined as any light, moderate or vigorous-intensity activity performed outside of the EC sessions. The wrist worn Microsoft band 2 watch was used to measure step count and HR during daily PA. Data derived from both the EC and AL were combined to generate a weekly report for each participant. This allowed participants to self-track their PA behaviour.

Assessment Module

The assessment module involved participants self-monitoring their cardiovascular fitness, BP, HR and rhythm at rest and during a submaximal step test (136). An ambulatory patient-monitoring device (Zensor) with a 3-lead ECG and commercially viable integrated WiFi positioning was used to measure HR. Following 5 min of seated rest, participants recorded their BP.

Educational Module

The educational module provided advice on established lifestyle related risk factors for CVD. It focused on individual goal setting with regard to healthy diet, sedentary behaviour, stress management, alcohol moderation and smoking cessation.

Acute Physiological Responses to PATHway

The Karvonen formula was used to calculate %HRR; [(Session HR-Resting HR/HRR)*100] during both EC and AL sessions. The average %$\dot{V}O_2$max during EC and AL sessions was estimated for each participant using the slope and intercept of the linear relation between HR and $\dot{V}O_2$.

Usual Care (Control Group)

During the 4 week familiarization phase, participants randomly assigned to the UC continued to participate as normal in 2-3 exercise-based CR sessions. Following completion of the phase III CR program, these participants received the standard 'usual care' exercise consultation and PA advice. They were free to participate in any type of fitness classes, walking groups, cycling groups etc. They were not provided with a specific exercise prescription, feedback or support regarding their PA behaviour during the 6-month follow-up period.

Concomitant Care

Both intervention and control group received usual medical and pharmacological management as well as the standard lifestyle advice according to existing guidelines (137, 138).

Data Management

Each randomized participant was assigned a PIC. This unique identification number was used on all case report forms and in all electronic databases. Data was

recorded in hardcopy and subsequently entered electronically into an open source clinical trial software for electronic data capture and data management. Hardcopies of the data were stored in a secured filing cabinet on site. The data entry screens in the open source clinical trial software resembled the hard copy case report forms approved by the ethical committee. Checks were automatically applied when entering the data based on preset ranges. Missing data was automatically detected and data query reports were sent to the data manager.

All data analyses and reporting were performed according to best practice and reported in agreement with Consolidated Standards of Reporting Trials (CONSORT) guidelines and the Consolidated Criteria for Reporting Qualitative Research (COREQ)(139, 140). Baseline demographic characteristics and parameters were reported descriptively and were first compared across countries and between treatment groups to assess whether further analyses was needed for any unbalanced variables. Data was analyzed using SPSS (v24). A one way repeated measures ANOVA was employed to detect differences in usage between months. All statistical tests were two-sided and a p-value <0.05 was considered statistically significant. Where participants had incomplete data for a given variable, participants were excluded from analysis of this variable only.

RESULTS

Total Session Use

Participant usage of the PATHway system was recorded and averaged over the 6-month intervention period and separately for each month. There was a gradual decline in the combined number of AL and EC sessions throughout the duration of the study. The highest number of combined AL and EC sessions was 1088 during first month and the lowest number was 338 in month 6 (Figure 4.4).

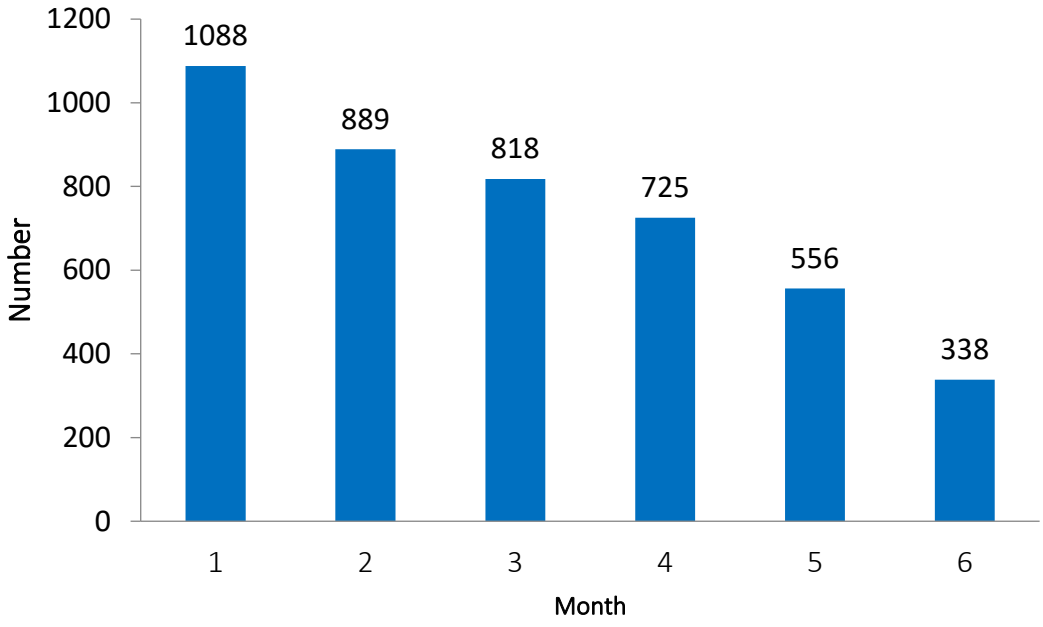


Figure 4.4: Total number of combined AL and EC sessions during each month of the HBCR program

The combined number of AL and EC sessions per month decreased by an average of 150 with the largest decreases occurring between month 1 and 2 (199) and month 5 and 6 (218) (Figure 4.5)

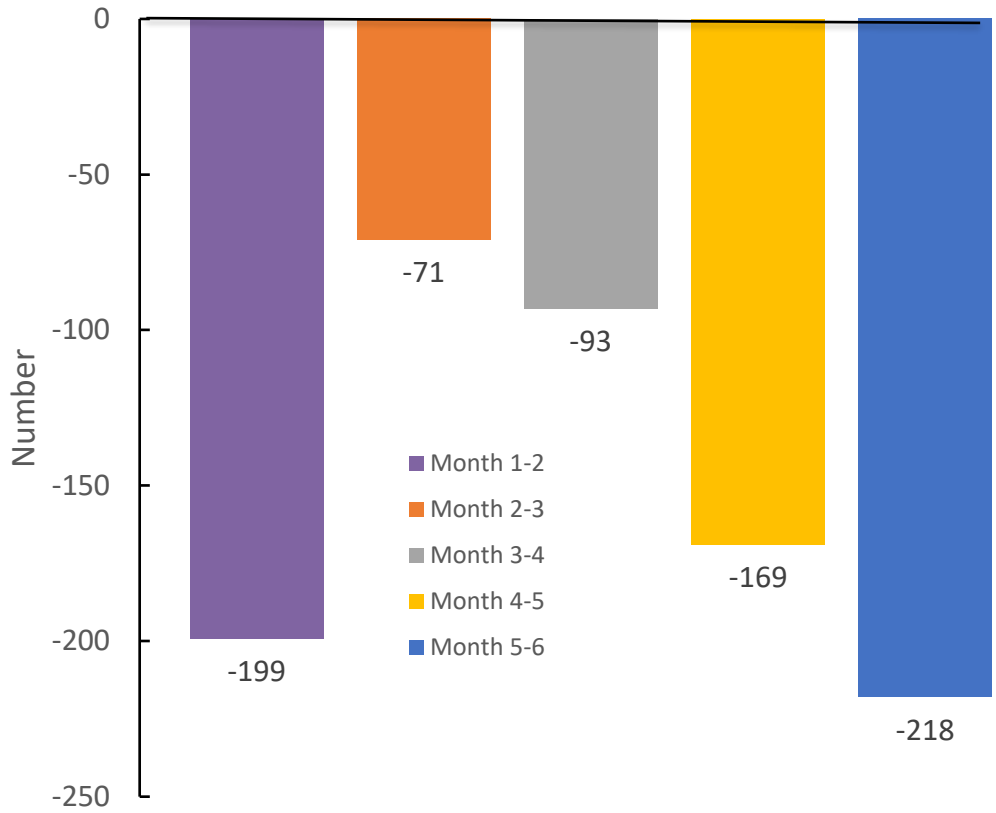


Figure 4.5: The monthly decrease in the combined number of AL and EC sessions

The average number of AL sessions was significantly greatly than EC sessions ($p<0.001$) during the 6-month intervention period (Figure 4.6).

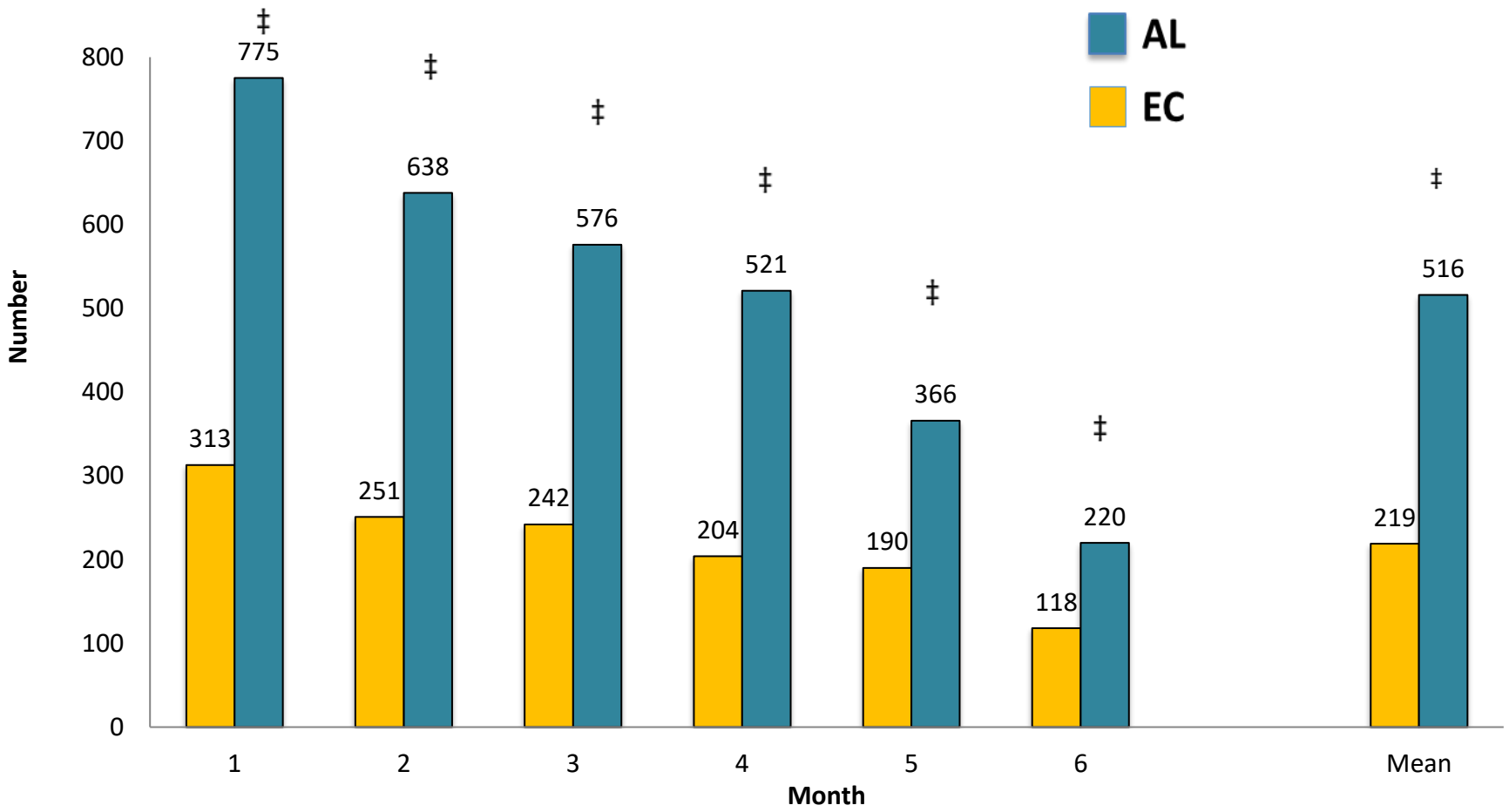


Figure 4.6: Total number of monthly AL and EC sessions and averaged over the 6-month intervention; ‡p<0.001 vs EC

Average Session Use

The combined average EC and AL usage over the entire 6-month period was 48.6 ± 47.8 sessions. There was no significant difference in the average number of combined EC and AL sessions each month (Figure 4.7).

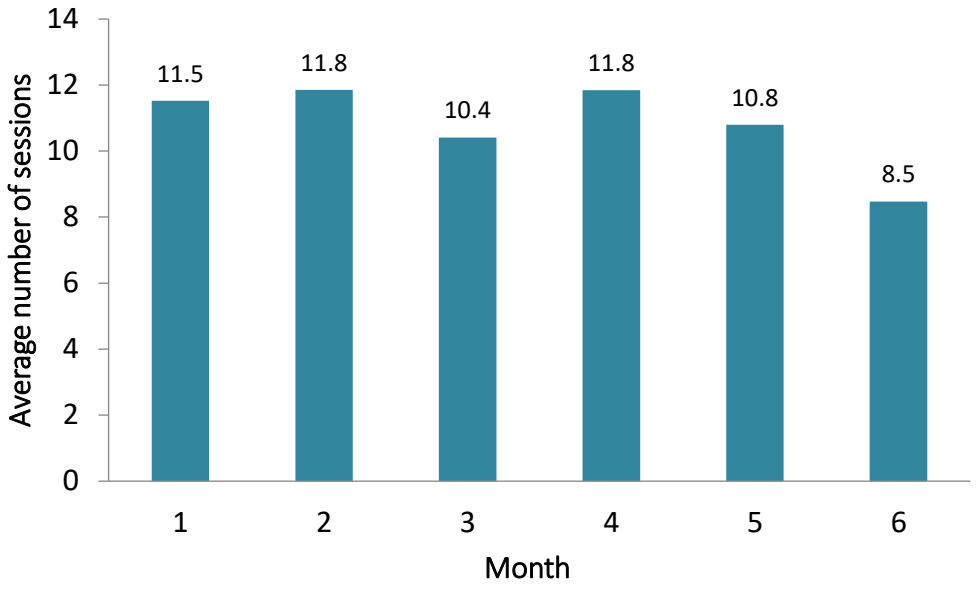


Figure 4.7: Average number of combined AL and EC sessions undertaken each month

When averaged across the entire 6-months, the number of AL and EC sessions selected by the participants was 67.0 ± 65.1 and 30.4 ± 30.6, respectively ($p<0.000$). Participants selected a significantly higher number of AL than EC sessions each month (Figure 4.8). There was no significant change in the average number of AL and EC sessions selected each month during the PATHway intervention. The average monthly usage was 16.4 ± 1.90 for AL and 6.6 ± 0.83 for EC.

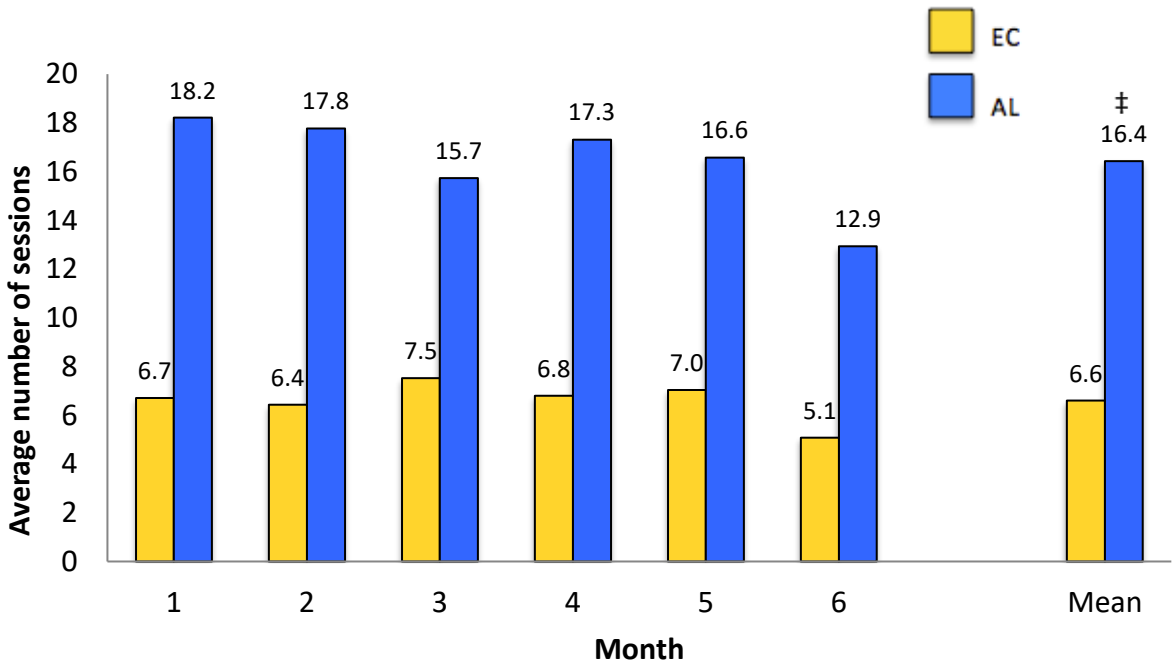


Figure 4.8: Average number of EC and AL sessions from month 1-6; ‡p<0.001 vs EC

Session Duration

The average duration of EC and AL sessions over the 6 months was 23.5 ± 8.0 min and 58.2 ± 26.8 min, respectively (p<0.001) The average monthly session duration was significantly higher (p<0.001) in AL than EC. There was no significant difference in the duration of AL sessions from month 1 - 6. EC duration was significantly lower (p<0.05) in month 1 compared to the other 5 months (Figure 4.9).

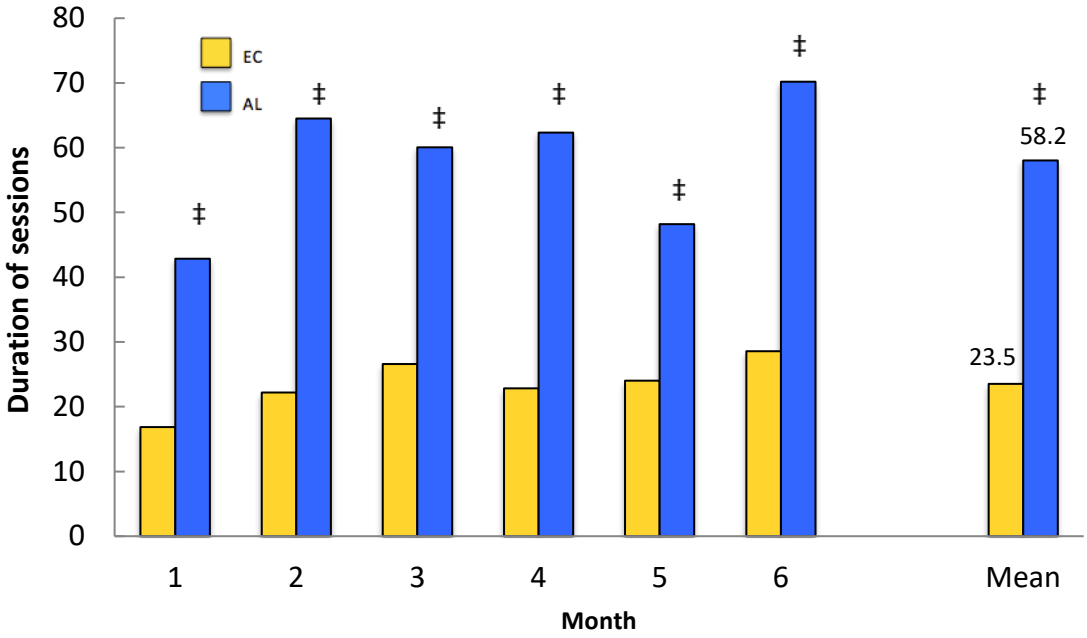


Figure 4.9: Duration of EC and AL sessions from month 1-6; ‡p<0.001 vs EC

Rating of Perceived Exertion

RPE was only recorded during the EC sessions. The session RPE ranged between 4.6 and 5.6 with an average of 5.2± 2.2 (Figure 4.10). These values are associated with the verbal descriptor 'hard'. There was no significant change in the session RPE over the course of the 6 months.

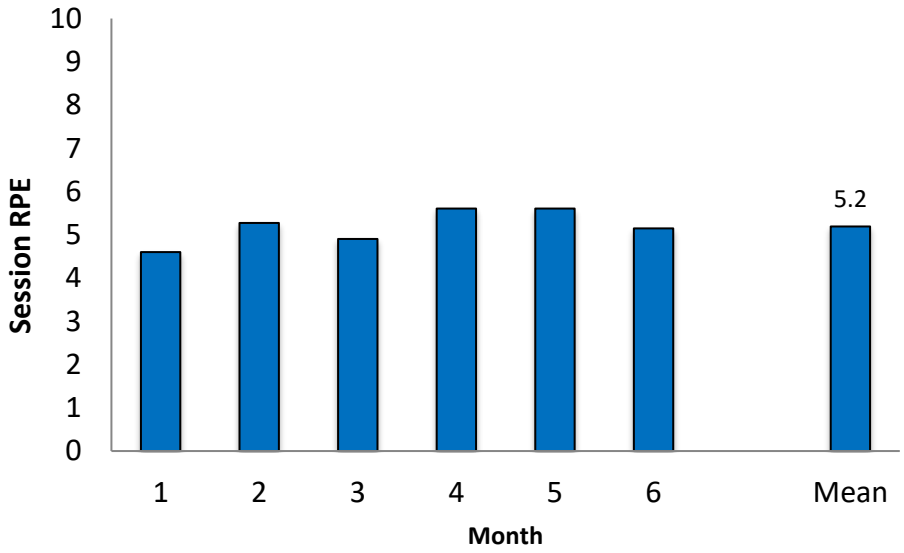


Figure 4.10: Average monthly RPE value during the EC sessions

Caloric Expenditure

The average estimated caloric expenditure was 212.6 ± 133.4 kcals and 435.8 ± 171.6 kcals for the EC and AL sessions, respectively ($p<0.001$). Estimated average monthly caloric expenditure remained constant during the monthly AL sessions and was significantly higher during EC session performed during the third ($p<0.05$) and fifth month ($p<0.04$) compared to the first month of the intervention. The average energy expenditure during the AL session was greater than that of the EC.

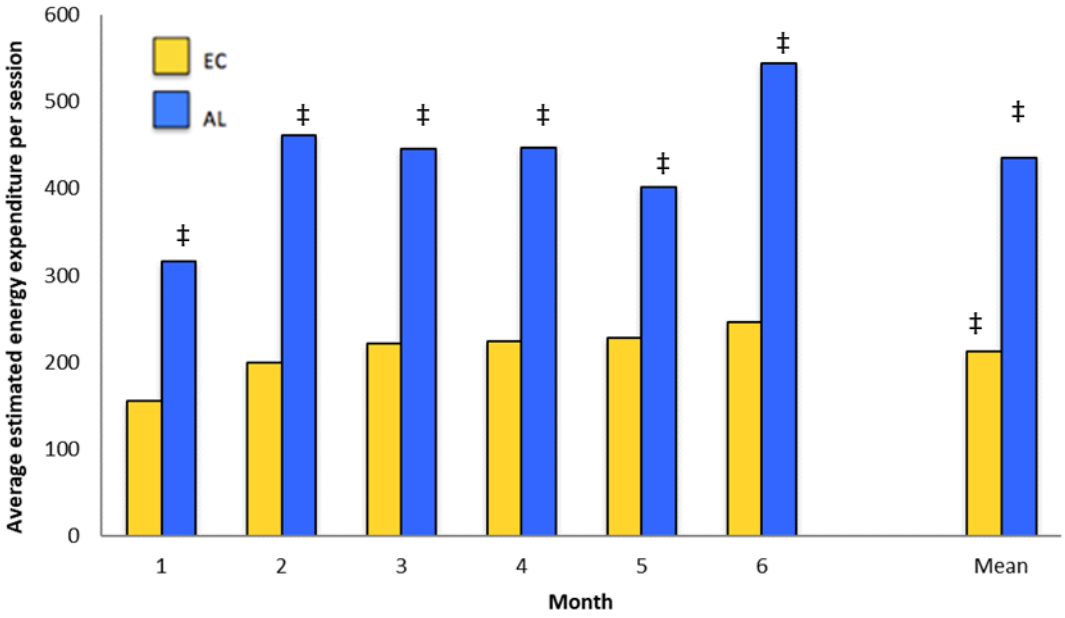


Figure 4.11: Average monthly estimated energy expenditure during EC and AL sessions and averaged over the entire 6 months; ‡$p<0.001$ vs EC

Heart rate

The average HR per session over the duration of the PATHway intervention was 109.6 ± 12.9 beats·min^{-1} and 121.5 ± 9.1 beats·min^{-1} for the AL and EC sessions, respectively ($p<0.000$) (Figure 4.12). Average monthly HR remained constant during the AL and EC sessions. Participants exercise at an average exercise intensity of 86 ± 14% HRM and 74 ± 26% HRR during the EC sessions and 75 ± 11 % HRM and 52 ± 21% HRR during the AL sessions.

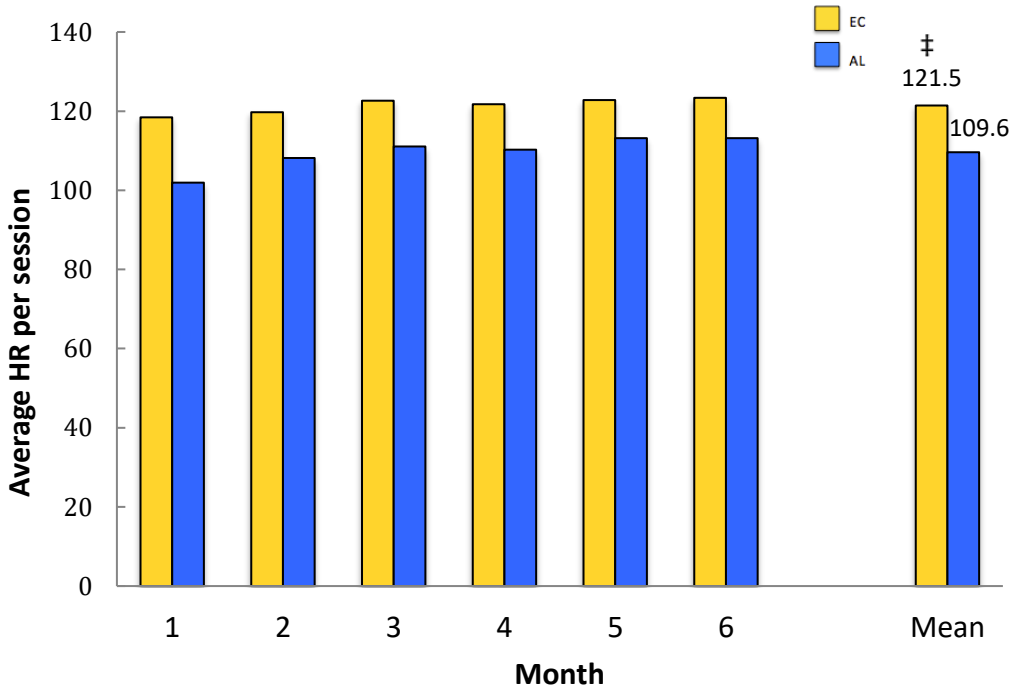


Figure 4.12: Average monthly HR during EC and AL sessions and averaged over the entire 6 months; ‡$p<0.001$ vs AL

Table 4.3: Average EC, AL and combined EC and AL usage over the entire 6-month PATHway intervention

	Overall	**Exerclass**	**Actilife**
No of sessions	48.65	30.35 ± 30.59	67.02 ± 65.05
Duration of session (min)	36.16	20.75	51.05
RPE (0-10)	4.67	4.67	-
Energy expenditure (kcals)	308.65	217.36	376.72
Heart Rate	113.56	120.36	105.99

Values are mean ± SD

Table 4.4: Combined total and average monthly EC and AL usage during the PATHway intervention

	Month 1	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**
Total sessions (n)	1088.00	889.00	818.00	725.00	556.00	338.00
Session per month (n)	11.64 ± 9.50	10.72 ± 9.87	11.75 ± 10.16	11.32 ± 9.74	10.55 ± 8.94	7.83 ± 6.94
Session duration (min)	29.19 ± 15.83	42.10 ± 26.16	44.83 ± 20.41	42.69 ± 24.55	36.19 ± 17.03	46.41 ± 22.36
RPE)	4.60 ± 2.06	5.27 ± 2.81	4.90 ± 2.28	5.61 ± 2.88	5.61 ± 2.40	5.15 ± 2.28
Energy expenditure (kcals)	135.96 ± 42.84	331.03 ± 155.38	361.41 ± 134.48	352.80 ± 178.22	326.94± 142.25	404.66 ± 157.71
Heart rate (beats·min^{-1})	110.80 ± 9.65	114.54 ± 12.31	116.23 ± 10.57	116.81 ± 11.64	118.58 ± 12.83	119.79± 12.36

Values are mean ± SD

Table 4.5: Monthly EC usage during the PATHway intervention

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Total no of sessions	313.00	251.00	242.00	204.00	190.00	118.00
Avg No of sessions	6.71 ± 4.68	6.43 ± 4.80	7.53 ± 4.84	6.80 ± 6.24	7.04 ± 7.31	5.08 ± 4.89
Duration of session (min)	16.86 ± 6.89	22.17 ± 8.75	26.58 ± 13.09	22.85 ± 8.08	24.01 ± 7.00	28.55 ± 10.55
RPE (0-10)	4.60 ± 2.06	5.27 ± 2.81	4.90 ± 2.28	5.61 ± 2.88	5.61 ± 2.40	5.15 ± 2.28
Energy expenditure (kcals)	167.73 ± 66.68	216.62 ± 84.19	255.17 ± 115.09	228.15 ± 84.55	238.02 ± 74.25	273.94 ± 109.18
Heart Rate	118.46 ± 10.39	119.69 ± 10.83	122.62 ± 10.51	121.76 ± 10.90	122.81 ± 7.14	123.38 ± 10.21

Values are mean ± SD

Table 4.6: Monthly AL usage during the PATHway intervention

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Total no of sessions	775.00	638.00	576.00	521.00	366.00	220.00
Avg No of sessions	18.21 ± 16.42	17.77 ± 17.38	15.74 ± 18.32	17.31 ± 15.05	16.57 ± 10.44	12.94 ± 9.45
Duration of session (min)	42.86 ± 29.54	64.50 ± 34.81	60.04 ± 31.46	62.31 ± 39.91	48.19 ± 19.51	70.19 ± 36.91
Energy expenditure (kcals)	315.48 ± 198.06	461.46 ± 198.03	445.26 ± 168.85	446.57 ± 201.77	401.74 ± 168.24	544.33 ± 168.01
Heart Rate	101.90 ± 12.94	108.15 ± 12.80	111.08 ± 12.43	110.23 ± 13.66	113.21 ± 17.48	113.15 ± 12.92

Values are mean ± SD

CHAPTER V

Study III

Physiological and Vascular Responses to a Technology Enabled Home-Based Cardiac Rehabilitation Program.

Introduction

Exercise based CR is an integral part of secondary prevention of CAD that confers psychological, physiological, functional and social benefits and reduces mortality. For decades, the protective effect of exercise and moderate to high level of PA on patients with CAD has focused on modifying established risk factors such as hypertension, lipids, diabetes and body composition, particularly obesity. However, it is estimated that positive changes in CVD risk factors account for approximately 40-50% of the beneficial effect of exercise in reducing morbidity and mortality from CAD. Regular exercise can also improve cardiovascular health through non-traditional mechanisms.

The increase in shear stress, pulsatile distension and circumferential strain associated with exercise can have direct anti-atherogenic effects in the vasculature, independent of traditional CVD risk factors. Indeed, the largest improvements in vascular health occur in individuals possessing established CVD risk factors or with established CVD. Flow mediated dilation (FMD) has been developed as a non-invasive surrogate of coronary artery endothelial function and measures the ability

of healthy, intact endothelial cells to detect, and respond appropriately, to changes in shear stress with acute adjustments in vascular tone. The loss of normal endothelial function termed 'endothelial dysfunction' is an independent predictor of cardiovascular events, providing valuable prognostic information additional to that derived from conventional risk factor assessment.

Carotid intima-media thickness (CIMT) is defined as the area of tissue beginning at the luminal-intimal interface and the media-adventitia interface of the common carotid artery (103). It is a commonly used index of vascular structure and is measured noninvasively using ultrasonography. The validity of CIMT as a non-invasive surrogate marker for atherosclerotic CVD has been well documented (104).

The aim of this study was to evaluate the effect of the PATHway program on traditional CVD risk factors and vascular structure and function.

Study Aims

1. To compare the effect of PATHway and UC on CRF
2. To compare the effect of PATHway and UC on muscle strength and function
3. To compare the effect of PATHway and UC on body composition, BP, blood lipids, fasting glucose and insulin.
4. To compare the effect of PATHway and UC on cIMT and FMD

METHODOLOGY

Study Design

As previously described in methods section of Chapter IV

Participants

As previously described in methods section of Chapter IV

Recruitment

As previously described in methods section of Chapter IV

Methods

As previously described in methods section of Chapter IV

Outcome Measures

Body Mass Index

Height and body weight were measured using a wall stadiometer and electronic balance (Seca 797, USA), respectively. Footwear and heavy clothing were removed prior to the measurement. Height was measured to the nearest 0.1 cm and body weight to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight (kg)/height (m^2).

Body Fat

Body fat was measured using bioelectrical impedance (Tanita BF300, Tokyo, Japan). The device measures the resistance and reactance of the participant's body tissues in reference to a small electrical current produced by the device. Footwear and socks were removed prior to the measurement. Body fat was recorded in kg and as a percentage of the total body mass. Each participant was measured twice and, an average value was obtained.

Waist-to-Hip Ratio

Waist and hip circumference was measured in duplicate using a non-elastic flexible standard measuring tape (RollFix, Hoechstmass, Germany). Measurements were recorded to the nearest 0.1 cm. A third measurement was performed if the difference between measurements was > 1.5 cm. Waist circumference was measured at the iliac crest. When the iliac crest could not be palpated, the measurement was taken at the bellybutton. Hip circumference was recorded at the greater trochanter. The measurement was taken at the maximum circumference over the buttocks if the greater trochanter could not be palpated. Waist-to-hip ratio was calculated by dividing the mean waist measurement by the mean hip measurement.

Maximal Aerobic Capacity ($\dot{V}O_2max$)

As previously described in methods section of Chapter IV

Cardiorespiratory Measures

As previously described in methods section of Chapter IV

Electrocardiographic (ECG) and Blood Pressure Monitoring

As previously described in methods section of Chapter IV

Maximal Handgrip Strength

Handgrip strength was measured using a grip strength dynanometer (TAKEI physical Fitness Test, Grip-D T.K.K. 5101). Hand dominance was recorded for each participant and a demonstration was provided. Participants sat on a chair with a back support and fixed arms, and rested their forearms on the arms of the chair with their wrist in a neutral position and thumb facing upwards. Participants held the dynamometer in their dominant hand so that the middle part of each finger was placed on the back pad of the dynamometer. Participants were encouraged to squeeze the dynamometer as tightly as possible for 3 sec and the results were recorded to the nearest kg. The test was repeated with the non-dominant hand. Two further measurements were recorded for each hand and the best value for each hand was used (141).

Quadricep Force

Quadriceps force was measured using an isokinetic-test (Biodex Medical Systems Inc, 830-000-J800 System 3). Participants performed a total of three voluntary maximal quadriceps isometric contractions for 6 sec each at a 60° angle

with a 60 sec rest period between each test and the highest value was recorded. Following a 1 min recovery period, participants then performed two bouts of 25 repetitive maximal isokinetic knee extensions at $180°\cdot sec^{-1}$, interspersed with 2 min recovery intervals. Muscle endurance was calculated for each bout using the equation; ((mean peak torque of the last 8 repetitions/mean peak torque of the first 8 repetitions) X 100). Standardized verbal instructions and encouragements were given to participants (142).

Sit to Stand

The test involved participants standing and sitting as many times as possible within a 30 sec time period. While in a seated position, participants crossed their arms and placed one hand on each shoulder. The test began after a 3 sec countdown and the total number of repetitions performed in 30 sec recorded. Participants performed two trials with a recovery interval of at least 1 min. The highest number of sit-to-stand repetitions was recorded (136).

Blood Sampling and Storage

Blood samples were taken in the participant's respective hospitals at baseline and 6-months. Blood samples were drawn from the anti-cubital vein following an overnight fast. Prior to the blood draw, participants rested in a seated position for 5 min with legs uncrossed in order to minimize plasma volume shifts. Serum vacutainers were allowed to stand for 30 min before centrifugation within 1 h at 3000 rpm (1600 g) for 15 min at 4°C. Blood samples were analyzed for glucose,

insulin, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (LDL-C), triglycerides and hemoglobin.

Blood Pressure

Resting BP was recorded during the second visit to the testing site, at baseline, 3-months and 6-months. Participants rested supine for 10 min after which BP was measured using an automatic blood pressure cuff (Omron M6-comfort). The measurement was repeated 3 times and an average value of the three BP readings was recorded.

Assessment of Vascular Structure and Function

Vascular structure and function was assessed between 8.00 and 11.00 am, following an overnight fast. Participants were not permitted to exercise, or ingest substances that might affect FMD such as caffeine, vitamin C, tobacco or medication for at least 6 h before the study. Only water consumption was permitted.

Carotid Intima Media Thickness

Carotid intima media thickness (cIMT) was assessed using a multi hertz linear-array transducer (Siemens, Acuson P500). Images were obtained with the participant resting in a supine position, with the head turned slightly to the contralateral side. The common carotid artery (CCA), including the carotid bulb, were visualized, and longitudinal B-mode images of the left and the right CCA were obtained. A software program (Carotid Studio, Quipu, Italy) was used to

instantaneously measure IMT by processing B-mode ultrasound image sequences from a longitudinal section of the artery or from the video recording imported to the software. The method used an edge detection algorithm and worked in real-time with a frame rate of 25 frames·sec^{-1}. cIMT was computed during the last 8 sec of the examination.

Vascular Function - FMD

Brachial artery FMD was determined using high-resolution ultrasonography. Measurements were performed by the same investigator using a Siemens Acuson P500® ultrasound system with a user-selectable MultiHertz linear array transducer. Brachial artery images were acquired with the participants in a supine position in a quiet, temperature-controlled room, with their right arm rested on an examination table perpendicular to the bed and extended and externally rotated to permit imaging of the right brachial artery. An automated pneumatic cuff was placed on the right forearm.

Anatomic landmarks such as veins and facial planes were noted and used to ensure that all images were recorded at the same site. A longitudinal image of the brachial artery was obtained using B mode ultrasound. The brachial artery was insolated 3-7 cm above the antecubital crease. Images were magnified using a 'zoom' function if required, and the screen was calibrated depending on the level of 'zoom' used.

Endothelial -Dependent Dilation (EDD)

Following a 10-min rest period the brachial artery was imaged continuously for 60 sec. A pneumatic cuff was then inflated to 250 mm Hg (143) and the brachial artery was imaged continuously. Following 300 sec of occlusion, the cuff was released and the vessel diameter and blood flow velocity were continuously imaged for 240 sec using duplex ultrasound for simultaneous B-mode diameter and pulse–wave Doppler velocity, respectively (143). Optimal quality of B–mode imaging was obtained parallel to the vessel orientation (79).

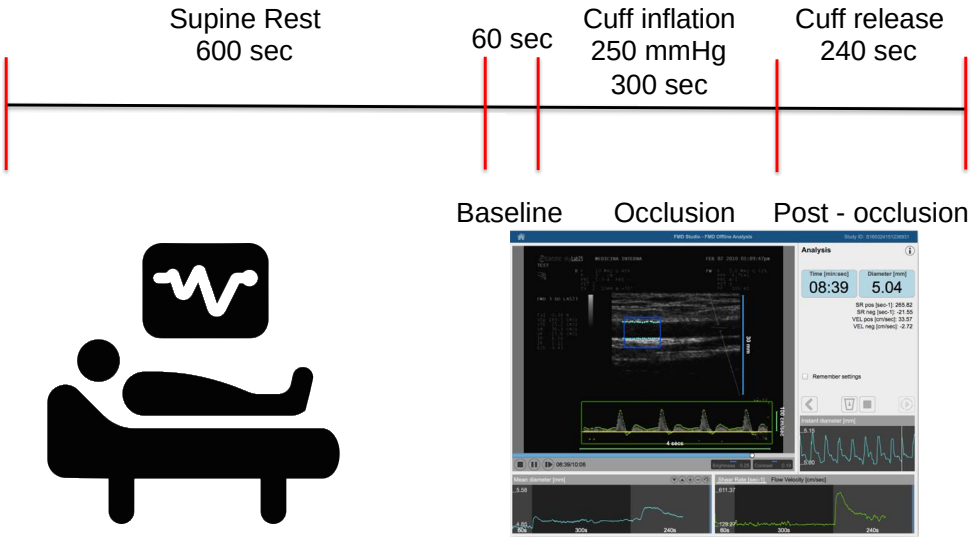


Figure 5.1: Endothelial dependent dilation protocol

Edge Detection and Wall Tracking

Computer assisted analysis, utilizing edge-detection and wall tracking (Quipu FMD suite) software was used to track the diameter of the vessel and compute the brachial artery diameter in real-time with a temporal resolution of 25 samples·sec^{-1}.

The procedure was initialized by manually tracing two approximate starting borders that define the region of interest for the algorithm to adjust. The elaboration began immediately afterwards. The diameter was numerically displayed and plotted on two separate graphs. The first graph illustrated the instantaneous measurement of the vessel diameter over a timescale of 5 sec and the second illustrated the rolling average computed over 2 sec and displayed over the 9 min timescale of the complete test (144). ECG gating was not used due to the advanced software that automatically detects the diameter waveforms as a result of systole and diastole and, a filter was applied to obtain the mean diameter over a large number of measurements (145).

Endothelial-Independent Dilation (EID)

Following a 15 min rest, a new baseline diameter was obtained by measuring the brachial artery diameter continuously for 60 sec. The brachial artery was imaged for 300 sec following the sublingual administration of 400 µg glyceryl trinitrate (GTN). Similar to EDD, blood flow velocity and diameter were continuously measured. Quipi edge detection and wall tracking software was used to record diameter of the brachial artery in real-time.

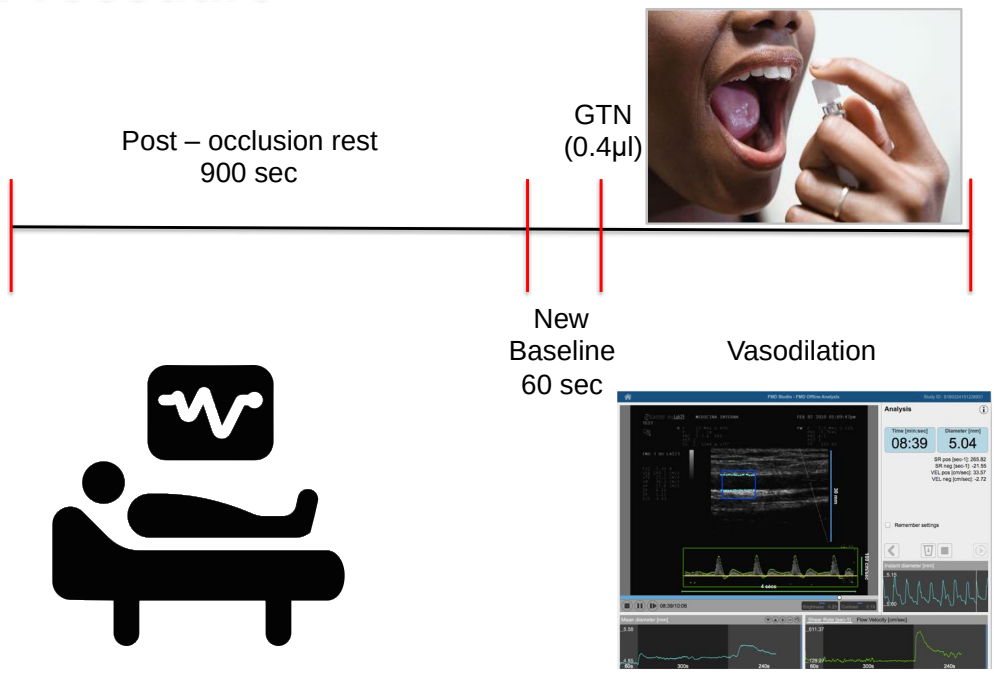


Figure 5.2: Endothelial independent dilation protocol

Randomization and Concealed Allocation

As previously described in methods section of Chapter IV

PATHway Intervention Group

As previously described in methods section of Chapter IV

Exercise Consultation

As previously described in methods section of Chapter IV

PATHway Intervention

As previously described in methods section of Chapter IV

Exerclass

As previously described in methods section of Chapter IV

Physical Activity Module

As previously described in methods section of Chapter IV

Assessment Module

As previously described in methods section of Chapter IV

Educational Module

As previously described in methods section of Chapter IV

Acute Physiological Responses to PATHway

As previously described in methods section of Chapter IV

Usual Care (Control Group)

As previously described in methods section of Chapter IV

Concomitant Care

As previously described in methods section of Chapter IV

Data Management

As previously described in methods section of Chapter IV

Data Analysis

Descriptive statistics were calculated using standard statistical procedures. Preliminary assumption testing was conducted to check for normality, linearity, univariate and multivariate outliers, homogeneity of variance-covariance matrices and multicollinearity, with no serious violations noted. An independent t-test was used to compare mean differences between PATHway and UC at baseline. BMI was the only outcome variable that was significantly different between PATHway and UC at baseline.

A two-way repeated measures multivariate analysis of variance with BMI as a covariate was performed to investigate the effect of the PATHway intervention on all outcome variables that met the statistical assumptions. A two way repeated measures ANOVA was used to investigate the effect of the PATHway intervention on outcome variables that violated the multicollinearity assumption. Data were analyzed using SPSS (v 24) statistical package. Analysis was conducted according to the per protocol principle based on the initial randomization and using data collected at 6 months of follow-up. All statistical tests were two-sided and a p-value of <0.05 was considered statistically significant.

RESULTS

Participants

A total of 120 patients were recruited (82% male) age 60.3 ± 9.2 (SD) yr from Beaumont Hospital, the Mater Misercordiae hospital and University Hospital Leuven, Belgium. Of the 120 patients recruited, 100 completed the 6-month follow-up testing, 53 in the PATHway group and 47 in the usual care group. 68% of patients had undergone PCI, 13% CABG, 5% valve repair surgery and 14% had other CVD treatment.

Anthropometric

With the exception of BMI there was no significant difference between UC and PATHway in any of the measured anthropometric parameters. Baseline BMI was significantly higher ($t(118) = 1.739$, $p= 0.043$) in UC than PATHway. The results of the MANOVA RM analysis with BMI as a covariate are summarized in table 5.1. There were no statistically significant main effects for group, time, or group by time interactions among any of the measured anthropometric variables.

Table 5.1: Anthropometric measures in UC and PATHway at baseline and 6-months

	UC		PATHway		Group	Time	Interaction
	Baseline	**6 Months**	**Baseline**	**6 Months**			
Weight (kg)	83.81 ± 14.85	85.05 ± 15.25	79.01 ± 12.50	78.73± 12.68	0.965	0.176	0.855
Body fat (%)	30.75 ± 6.85	31.50 ± 6.44	28.54 ± 5.83	28.84 ± 5.06	0.930	0.064	0.267
Waist circumference (cm)	99.91 ± 11.46	99.76 ± 12.22	95.94 ± 11.98	93.45 ± 11.08	0.292	0.368	0.506
Hip circumference (cm)	103.34 ± 7.56	104.08 ± 7.96	101.14 ± 7.02	100.40 ± 5.58	0.792	0.318	0.356

Values are mean ± SD

Cardiorespiratory Responses

There was no statistically significant difference between UC and PATHway in any of the measured cardiorespiratory responses at baseline. The results of the MANOVA RM analysis for the physiological responses at maximal and submaximal exercise with BMI as a covariate are summarized in table 5.2 and table 5.3, respectively.

With the exception of peak $\dot{V}_E$, there were no statistically significant main effects for group, time, or group by time interactions among any of the other measured responses at maximal exercise. There was a significant main effect of time ($p=0.035$) for peak $\dot{V}_E$. There were no statistically significant main effects for group, time, or group by time interactions for any of the measured cardiorespiratory responses during submaximal exercise.

The results of the MANOVA RM analysis for HR recovery with BMI as a covariate are summarized in table 5.4. There were no statistically significant main effects for group, time, or group by time interactions for any of the HR measurement during recovery.

Table 5.2: Baseline to 6-month follow up cardiovascular responses at maximal exercises in UC and PATHway

	UC		PATHway		Group	Time	Interaction
	Baseline	6 Months	Baseline	6 Months			
Peak $\dot{V}O_2$ ($mL \cdot min^{-1}$)	2056.75 ± 605.23	2089.48 ± 624.15	1912.79 ± 565.29	1963.33 ± 599.41	0.309	0.191	0.304
Peak $\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	24.74 ± 7.11	24.56 ± 6.28	24.12 ± 5.61	24.88 ± 5.86	0.241	0.091	0.317
Percentage predicted $\dot{V}O_2$ (%)	100.88 ± 22.48	101.57 ± 21.25	95.90 ± 21.72	99.24 ± 17.60	0.344	0.141	0.553
Peak CO_2 ($mL \cdot min^{-1}$)	2512.97 ± 724.39	2587.44 ± 726.23	2376.29 ± 676.42	2437.61 ± 698.75	0.209	0.161	0.288
Peak $\dot{V}_E$ ($mL \cdot min^{-1}$)	82.25 ± 26.42	84.88 ± 33.12	77.88 ± 27.30	79.48 ± 24.77	0.245	0.035	0.256
Peak HR ($b \cdot min^{-1}$)	138.78 ± 19.86	139.09 ± 18.23	141.44 ± 20.18	143.51 ± 21.77	0.920	0.870	0.608
Peak Load (Watts)	172.25 ± 55.58	168.48 ± 52.96	160.96 ± 48.39	168.27 ± 48.87	0.426	0.973	0.179
Peak SBP (mmHg)	187.02 ± 32.59	186.25 ± 25.25	177.63 ± 24.64	186.02 ± 27.31	0.128	0.913	0.063
Peak RER	1.24 ± 0.09	1.25 ± 0.10	1.26 ± 0.11	1.27 ± 0.09	0.242	0.631	0.421
Test duration (s)	599.24 ± 146.05	581.64 ± 152.11	561.31 ± 140.37	561.96 ± 124.28	0.550	0.307	0.519

Values are mean ± SD

Table 5.3: Cardiovascular responses during submaximal exercises at baseline to 6-months in UC and PATHWAY

	UC		PATHway		Group	Time	Interaction
	Baseline	6 Months	Baseline	6 Months			
Percentage $\dot{V}O_2$ at VT (%)	58.95 ± 9.45	56.09 ± 8.26	59.38 ± 9.45	56.73 ± 10.96	0.122	0.334	0.243
Absolute $\dot{V}O_2$ at VT ($mL \cdot min^{-1}$)	1192.82 ± 385.11	1152.96 ± 352.48	1115.85 ± 329.31	1094.86 ± 302.48	0.525	0.844	0.203
Work load at VT (W)	82.16 ± 36.07	73.70 ± 30.65	74.81 ± 29.67	72.65 ± 24.73	0.491	0.434	0.073
Heart rate at VT ($b \cdot min^{-1}$)	97.86 ± 15.44	92.11 ± 11.52	97.12 ± 15.05	96.55 ± 19.94	0.580	0.815	0.587
Percentage $\dot{V}O_2$ at RCP (%)	85.44 ± 7.96	83.67 ± 8.99	86.49 ± 6.87	85.51 ± 7.96	0.203	0.742	0.530

Values are mean ± SD

Table 5.4: Baseline to 6-month follow up Heart Rate responses during recovery in UC and PATHway

	UC		PATHway		Group	Time	Interaction
	Baseline	**6 Months**	**Baseline**	**6 Months**			
Min 1 ($b \cdot min^{-1}$)	114.73 ± 20.62	114.89 ± 16.14	119.23 ± 19	121.80 ± 21.35	0.571	0.457	0.354
Min 2 ($b \cdot min^{-1}$)	101.41 ± 18.13	102.22 ± 14.08	105.60 ± 16.67	108.41 ± 18.96	0.547	0.474	0.266
Min 3 ($b \cdot min^{-1}$)	94.06 ± 16.39	95.61 ± 13.71	97.75 ± 14.45	100.08 ± 18.96	0.727	0.415	0.427

Values are mean ± SD

Strength

There were no statistically significant group differences in any of the strength measurements at baseline. The results of the MANOVA RM analysis with BMI as a covariate are summarized in table 5.5. There were no statistically significant main effects for group, time, or group by time interactions among any of the measured strength variables.

Table 5.5: Baseline to 6-month follow up for strength measures in UC and PATHway

	UC		PATHway		Group	Time	Interaction
	Baseline	**6 Months**	**Baseline**	**6 Months**			
Sit-to-stand (repetitions))	18.38 ± 6.66	21.78 ± 6.96	18.85 ± 4.47	22.51 ± 6.29	0.351	0.635	0.145
Handgrip dominant (NKg)	40.30 ± 10.97	40.04 ± 11.82	39.94 ± 10.72	40.10 ± 10.75	0.284	0.938	0.206
Handgrip non-dominant (NKg)	37.68 ± 9.95	37.17 ± 10.86	38.06 ± 9.66	38.61 ± 9.74	0.339	0.121	0.158
Quadriceps Isometric (N)	149.63 ± 47.87	156.11 ± 47.04	144.44 ± 42.23	149.48 ± 47.76	0.348	0.926	0.518
Quadriceps Isokinetic (N)	2123.39 ± 639.35	2147.54 ± 638.11	2031.71 ± 670.71	2125.29 ± 670.25	0.097	0.065	0.284

Values are mean ± SD

Vascular Health

There were no statistically significant changes in cIMT or FMD between PATHway and UC at baseline. The results of the MANOVA RM analysis with BMI as a covariate are summarized in table 5.6. There were no statistically significant main effects for group, time, or group by time interactions among any of the measured vascular health variables.

Table 5.6: Baseline to 6-month follow up for vascular health measures in UC and PATHway

	UC		PATHway		Group	Time	Interaction
	Baseline	**6 Months**	**Baseline**	**6 month**			
Systolic BP (mm Hg)	125.34 ± 12.18	131.73 ± 21.01	126.06 ± 18.25	128.04 ± 16.87	0.183	0.650	0.067
Diastolic BP (mm Hg)	77.22 ± 8.28	82.35 ± 10.38	78.18 ± 11.31	79.24 ± 10.12	0.060	0.681	0.488
Resting HR (bpm)	60.16 ± 10.25	62.23 ± 8.97	60.59 ± 10.41	61.33 ± 11.41	0.865	0.394	0.058
FMD (%)	8.17 ± 6.73	6.98 ± 4.97	8.55 ± 7.79	9.46 ± 4.69	0.226	0.883	0.322
Left IMT (mm)	0.713 ± 0.16	0.669 ± 0.158	0.717 ± 0.16	0.677 ± 0.218	0.371	0.288	0.089
Right IMT (mm)	0.654 ± 0.15	0.659 ± 0.171	0.686 ± 0.16	0.666 ± 0.202	0.532	0.594	0.495

Values are mean ± SD

Blood Biomarkers

There were no statistically significant differences in any of the measured blood biomarkers between UC and PATHway at baseline. The results of the MANOVA RM analysis with BMI as a covariate are summarized in table 5.7. With the exception of LDL-C and plasma insulin, there were no statistically significant main effects for group, time or group by time interactions among any of the other measured blood biomarkers. There was a significant time main effect ($p=0.047$) for plasma insulin and significant group by time interaction effect for LDL-C.

Table 5.7: Baseline to 6-month follow up for blood biomarkers in UC and PATHway

	UC		PATHway		Group	Time	Interaction
	Baseline	**6 Months**	**Baseline**	**6 month**			
Plasma glucose (mg·dL^{-1})	103.2 ± 31.97	108.10 ± 38.14	102.57 ± 23.14	101.63 ± 16.71	0.166	0.551	0.871
Plasma insulin (pmol·dL^{-1})	56.61 ± 30.47	80.66 ± 100.14	56.91 ± 29.92	69.52 ± 54.39	0.499	0.047	0.393
HbA1c (mg·dL^{-1})	41.15 ± 8.72	43.31 ± 10.67	39.27 ± 5.45	38.81 ± 5.76	0.660	0.093	0.069
Total cholesterol (mg·dL^{-1})	140.43 ± 38.29	150.74 ± 45.33	146.69 ± 38.74	141.04 ± 36.29	0.658	0.117	0.076
HDL – cholesterol (mg·dL^{-1})	50.71 ± 16.53	54.03 ± 20.39	50.35 ± 13.98	49.98 ± 12.41	0.617	0.230	0.292
LDL – cholesterol (mg·dL^{-1})	70.18± 30.67	80.26 ± 34.87	74.42 ± 31.35	70.60 ± 26.60	0.877	0.347	0.026
Triglycerides (mg·dL^{-1})	95.65 ± 51.25	102.51 ± 45.25	108.81 ± 61.43	108.30 ± 58.91	0.753	0.505	0.487

Values are mean ± SD

Absolute Changes

Statistically significant absolute changes from baseline to 6-month follow up are summarized in table 5.8. There was a statistically significant difference between UC and PATHway in waist circumference (p= 0.010), DBP (p=0.003) and LDL-cholesterol (p=0.040). Waist circumference increased in UC and decreased in PATHway.

Table 5.8: Absolute change from baseline to 6 month follow up

	Condition		
	UC	**PATHway**	**p value**
Waist circumference (cm)	0.58 ± 5.53	-2.29 ± 5.16	0.010
DBP (mmHg)	6.04 ± 9.24	0.830 ± 7.29	0.003
LDL – cholesterol ($mg \cdot dL^{-1}$)	10.03 ± 26.35	-1.09 ± 22.13	0.040

Values are mean ± SD

CHAPTER VI

DISCUSSION

CR services are an integral component in the continuum of care for patients with CVD with evidence that they reduce hospital readmissions, secondary events and mortality (5). However, despite the demonstrated benefits of CR, utilization and completion rates of traditional CBCR remains sub-optimal due to both patient and system barriers (3). The use of HBCR alone or in combination with CBCR represents a possible alternative that may improve the delivery of CR to eligible patients (28).

PATHway was a technology-based platform that combined online, and home-based interactive programs to deliver all core components of CR. Medical supervision along with ECG telemetry has contributed to the very low event rate in CBCR (3, 30). However, there is currently very little information regarding the clinical safety of HBCR, particularly in higher-risk patients with multiple comorbidities. As a proof of concept, PATHway recruited patients who had completed a phase III hospital-based CBCR program and who would have been transitioning to lifelong disease management.

Complex behavior change interventions involve a coordinated set of activities designed to change specified behavior patterns. Social Cognitive Theory (SCT) provided a theoretical framework to understand the complexities of the PATHway intervention (146). SCT focuses on individual self-efficacy working in conjunction with knowledge, goals, outcome expectations, perceived environmental

impediments and facilitators in the establishment of behavior, which in this case is engagement in CR.

PATHway Usage

Usage of PATHway peaked during the first month and gradually declined over the next 5 months. There was a 69% decrease in the combined number of AL and EC sessions between the first and sixth month of the program. The AL option was the most popular among participants. The ratio of AL to EC was constant at approximately 2.5:1 during the first 4 months of PATHway and, decreased to approximately 1.9:1 during the final 2 months. The number of AL sessions undertaken was 124%, 101% and 92% of the prescribed number of sessions per week (n=3) during the first, second and third month of PATHway, respectively. The levels decreased to 58% and 35% during month 5 and 6, respectively. In contrast, usage of the EC component of PATHway peaked at 50% during the first month and decreased to only 18% of the number of recommended sessions during the final month.

Reid et al., (2012) reported an adherence rate of 61% among CAD patients who participated in a 20-week HBCR program facilitated by online tutorials (15). In a systematic review and meta-analysis of telehealth based CR, a higher attendance (>66%) was reported among participants undertaking telehealth HBCR program compared to CBCR (17).

There was large interindividual variability in the total number of EC and AL sessions undertaken by the participants during the 6-month PATHway program (Figure 6.1). Only 4 participants completed the minimum recommended number of EC sessions compared to 19 who completed the minimum recommended number of AL sessions. Surprisingly, six participants failed to undertake a single EC session and nine did not undertake any AL sessions during the entire 6-month intervention. Furthermore, 16 participants undertook ≤ 10 EC sessions whereas eight participants undertook ≤ 10 AL sessions.

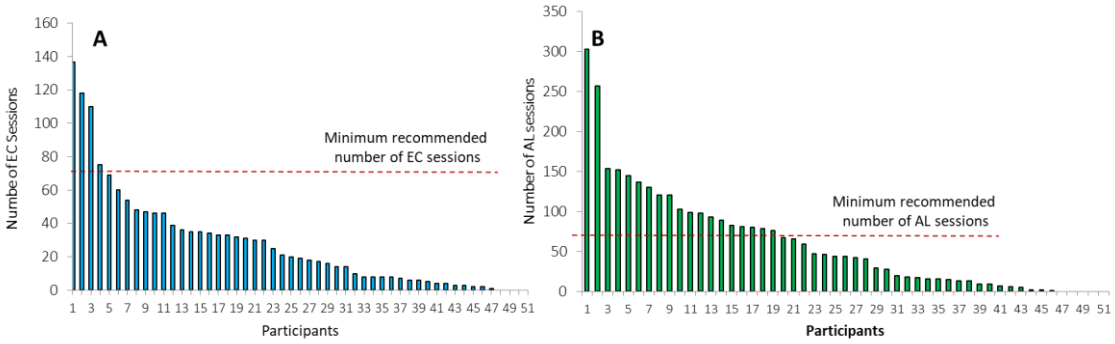


Figure 6.1: Total number of (A) EC and (B) AL sessions undertaken by each participant during the 6-month PATHway program

There was a steady decline in participant engagement with both the EC and AL components of PATHway (Figure 6.2 and Figure 6.3). After peaking during the first month of PATHway, only 20 (39%) and 17 (32%) of participants engaged with the EC and AL component during the final month.

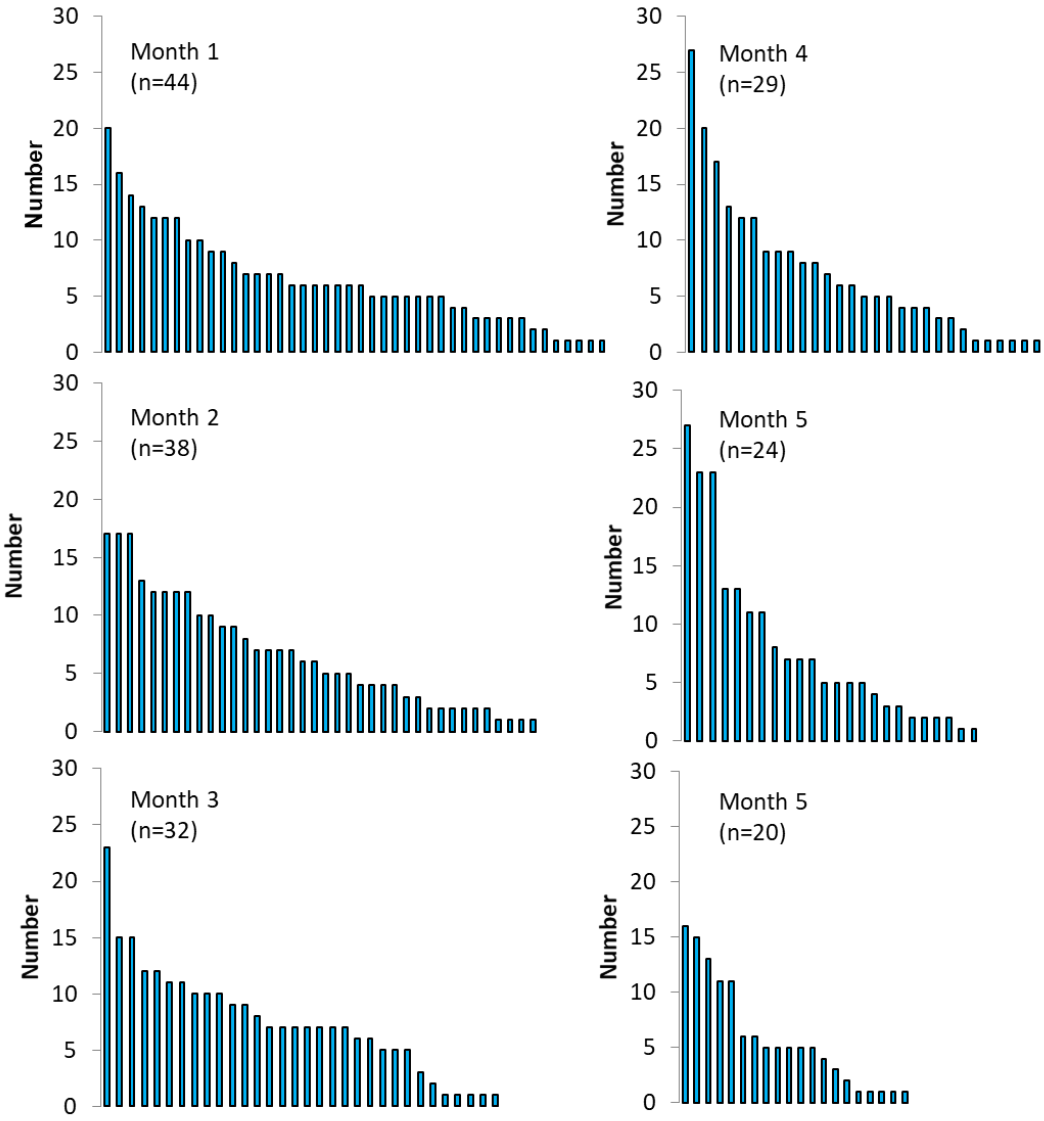


Figure 6.2: The number of EC sessions performed by participants who engaged with the EC component of PATHway

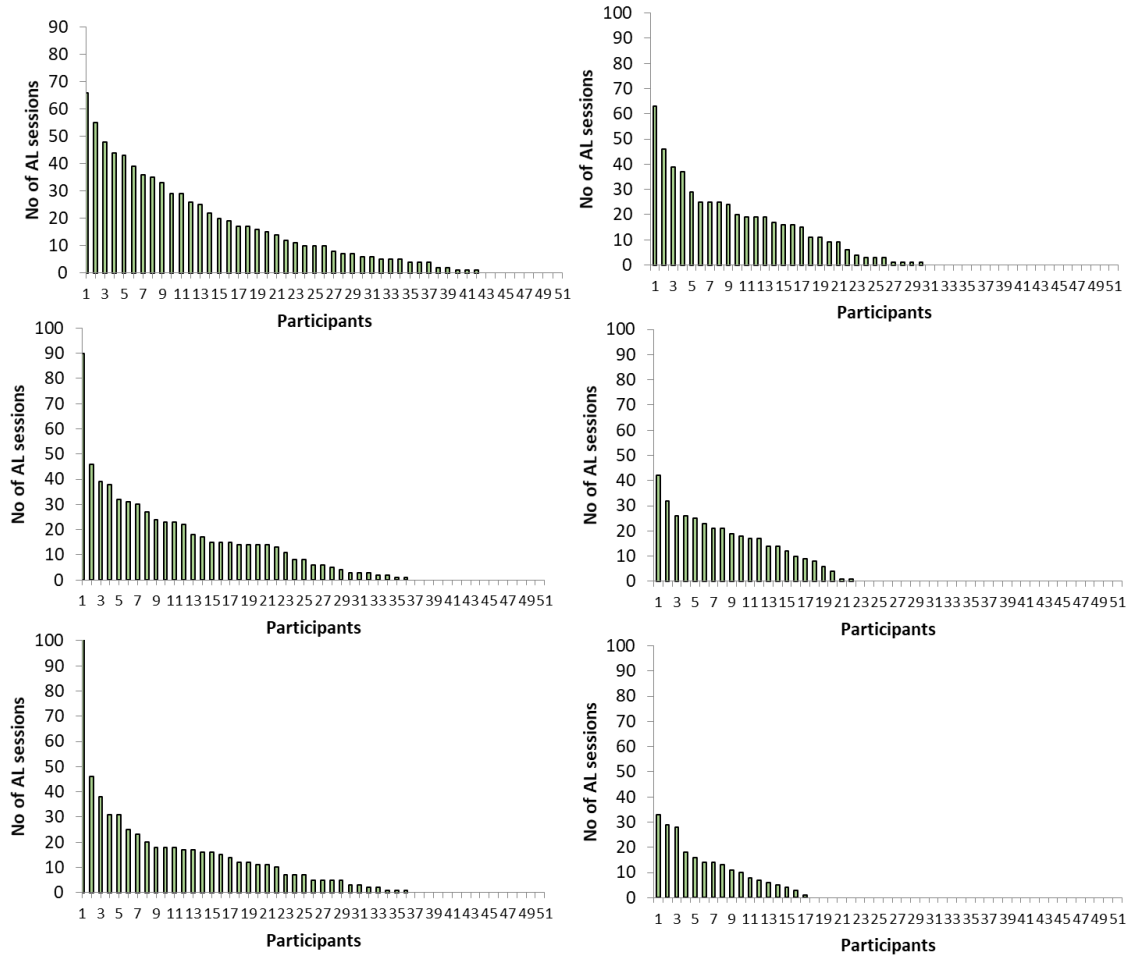


Figure 6.3: The number of AL sessions performed by each participant during each month of the PATHway program

In contrast, a pilot web-based CR program in the UK reported an adherence rate of 78% at 6-month follow up (147). Jurkiewicz et al., (2011) examined adherence rates to a hybrid CR program in stroke patients. Participants initially attended hospital based CR once a week for 6 months after which the number of session was reduced to one per month for two months. In addition, they were encouraged to complete four additional aerobic training sessions and one to two resistance-training sessions per week. Adherence rates were compared between participants currently attending the program and those who had graduated from the program for a mean of 28 weeks. Adherence to both aerobic and resistance sessions

was 100% for current participants and 76% and 55% for aerobic and resistance sessions, respectively for participants who had completed the program (148). Similar to PATHway, Krishnamurthi et al., (2019) reported an adherence rate of 48% among participants in a 3-month, HBCR program (149). A recent meta-analysis of interventions to promote patient utilization of CR found that unsupervised settings were more effective in increasing adherence (150).

A noticeable feature of PATHway is the fact that participants, who engaged with the program, completed a greater number of AL than EC sessions. According to the American College of Sports Medicine, the most effective exercise prescription for an individual is one that is most helpful in achieving behavioral change (132). The PATHway exercise prescription was based primarily on evidence of what is safe, maintains or improves physical fitness and reduces the risk for CVD. When prescribing exercise, there is however, a need to balance physiological effectiveness with enjoyment and pleasure in order to insure that adherence is sufficient to maintain or positively affect desired biological changes.

The EC component of PATHway involved participants undertaking a bout of exercise within a prescribed intensity range based on objectively measured thresholds. The average HR per EC session was 121.5 beats·min^{-1} and corresponded to 74% HRR. Although the HR was within the recommended prescribed range of 40% - 80% HRR, it is possible that some participants may have perceived this intensity as unpleasant or uncomfortable and may have negatively affected their decision to use the EC component of PATHway.

Individuals are more likely to make behavioral choices that increase their pleasure and conversely tend to avoid choices that consistently decrease their pleasure. RPE is a measure of the subjective perception of intensity of effort, strain, discomfort and/or fatigue experienced during physical exercise (151). During the EC sessions, participants selected a mean RPE of 5 on a 10-category scale. This numerical value is associated with the verbal descriptor 'hard'. It is unlikely that participating in an activity perceived as hard will positively impact affective responses.

Although the average HR was lower during AL than EC sessions, it was still within the prescribed range for EC, albeit at the lower end (52%). AL involved autonomously performed physical activity that may have been experienced as pleasant due to the greater sense of perceived autonomy in determining the mode, duration, frequency and intensity of PA. Allowing individuals to use effort perception to self-regulate exercise intensity may also improve affective and perceptual responses, increase enjoyment, and encourage the development of intrinsic motivation, a central element in promoting adherence to exercise. According to the hedonic theory of motivation, people are likely to repeat an activity if they derive pleasure, sense of energy, or enjoyment from their participation in the activity (152). In contrast, if people derive displeasure, sense of exhaustion, pain, or discomfort from their physical activity, the chances of them repeating the activity are likely decreased. A study involving adult women found that 86% used effort perception exclusively to determine exercise intensity during aerobic exercise (153).

This is perhaps not surprising considering that exertional feedback is commonly used to regulate the pace of many daily activities, and is often done without conscious awareness.

When allowed to self-regulate exercise intensity, individuals will normally adjust their effort to maximize affect. This is important considering that a positive affective response may lead to greater enjoyment of the exercise session, promote positive memory from that activity and consequently, contribute to increased motivation for future physical activity behaviors. In contrast, activities that are perceived to be difficult are more likely to lead to withdrawal from the activity. An ideal strategy would be to maximize the positive affective response while minimizing perceived exertion in order to enhance adherence to physical activity programs.

A number of technical issues that occurred during the intervention may also have contributed to the low number of EC sessions performed by the majority of participants. Some participants experienced minor technological issues during the first few weeks of PATHway. The majority of these issues were resolved in a timely manner. A major technological issue occurred a couple of months into the intervention when the majority of patients were using the system. The problem required a software update that took some time to resolve. Minor issues continued to arise until a major upgrade of the system was performed towards the end of the trial. Technical issues have been reported as the major reason for drop off in use of activity tracking devices (154).

Cardiorespiratory Fitness

Cardiorespiratory fitness is a strong predictor of cardiovascular and all-cause mortality (155). Some studies have found that low levels of CRF may be a stronger predictor of adverse CVD outcomes than traditional risk factors (156, 157). The baseline functional capacity of the PATHway participants prior to commencing the 6-month phase IV HBCR program was approximately 7.0 METs. Based on a meta-analysis on 33 studies involving 103,000 patients, individuals with a CRF < 7.9 METs had a substantially higher risk for cardiovascular and all-cause mortality compared to those with CRF levels ≥ 7.9 METs (33). Among patients referred to CBCR Vanhees et al., (1994) found that the highest cardiovascular and all-cause mortality occurred among patients with a mean functional capacity ≤ 4.4 METs. In contrast, no deaths occurred among patients with an average functional capacity ≥ 9.2 METs (41). Martin et al., (2013) classified 4282 men and 1359 women with CHD as low, moderate, or high fit based on a MET value of <5, 5-8, and >8, respectively (43).

CRF levels did not improve in response to the PATHway intervention. This may be due in part to the fact that the participants completed a hospital-based phase III CR program prior to commencing PATHway. Since no baseline measurements were taken, it was not possible to evaluate the changes in CRF in response to participating in the hospital-based phase III CR. It is well established that low fit individuals experience large improvement in CRF in response to exercise training. Based on a meta-analysis involving 31 studies, Sandercook et al., (2013) found an average improvement of 1.5 METs in response to participation in CBCR

(46). Increases in MET functional capacity tend to be greater in patients with the lowest baseline CRF. Martin *et al.*, (2013) found 1.41 METs (39%), 1.01 METs (15%), and 0.80 MET (8.6%) increase in CRF in the low, moderate, and high fit patients, respectively (43). Based on the available evidence, it is likely that the CRF levels of the PATHway participants improved significantly in response to the hospital-based phase III CR.

A number of studies have examined the effect of a hybrid phase III CR program on CRF in cardiac patients (16, 18, 158). These programs involved a combined centre and home based CR program within a relatively short period after the index event. Participation in a hybrid phase III involving a hospital-based CBCR with telemonitoring resulted in 3.0 $mL \cdot kg^{-1} \cdot min^{-1}$ increase in $\dot{V}O_2$ max (Frederix *et al.*, 2015). Participants in REMOTE-CR, a 12 week hybrid telerehabilitation platform obtained a 1.7 $mL \cdot kg^{-1} \cdot min^{-1}$ improvement in $\dot{V}O_2$ max (16). In contrast, CRF did not change following participation in the 24 week HEART intervention study, a phase III hybrid HBCR program where patients received a package of automated text messages via their phone in an aim to increase PA (18).

The UC group in the present study maintained their baseline CRF at the 6-month follow up. In a study involving high fit, moderately fit, and low fit patients, the improvements in CRF following completion of a 12 week exercise based CR program were maintained in all groups at 1 year follow-up and remained highest in low fit patients (159). It is possible that the lifestyle changes and behavioral management techniques learned during participation in the comprehensive hospital-

based phase III CR program were sufficient to maintain the minimum volume of PA required to maintain CRF levels.

There was a large interindividual variability among the PATHway cohort in terms of improvement in CRF (Figure 6.4). Based on absolute improvement in $\dot{V}O_2$ peak, De Schutter et al., (2018) stratified patients as non-responders (≤ 0.0 $mL \cdot kg^{-1} \cdot min^{-1}$ improvement), low-responders (≤ 2.5 $mL \cdot kg^{-1} \cdot min^{-1}$ improvement) and high responders (≥ 2.5 $mL \cdot kg^{-1} \cdot min^{-1} \cdot min^{-1}$ improvement) after 36 CR sessions (48). Using the same stratification system, almost half (47%) of the participants were classified as non-responders and an equal proportion were classified as low-responders (27%) and high responders (27%) (Figure 6.4). When the data for the low-responders and high responders were combined, the mean increase in $\dot{V}O_2$ max was 2.93 $mL \cdot kg^{-1} \cdot min^{-1}$ (0.84 MET). Martin et al., (2013) found that for each MET increase in functional capacity following participation in CBCR, there was a 13% reduction in mortality, with low fit patients having the greatest reduction per MET increase (30%) (43). Additionally, a number of studies have reported a reduction in risk for cardiovascular and all-cause mortality ranging from 8 to 20% in response to a one MET increase in functional capacity.

Large interindividual variability in response to exercise training has been reported in the HERITAGE study, a 20 week aerobic training program in healthy adults over the age of 18 years (160). The proportion of non-responders in the present study is much higher than the 10% reported in an analysis of six exercise training studies involving healthy individuals (161). The high proportion of non-

responders in the present study is probably due to a number of factors including poor uptake and adherence of the PATHway technology and genetic polymorphisms (160–162). A separate statistical analysis involving the combined low-and high responders found no significant effect of changes in fitness between baseline and 6-months on cardiovascular risk factors or vascular structure and function.

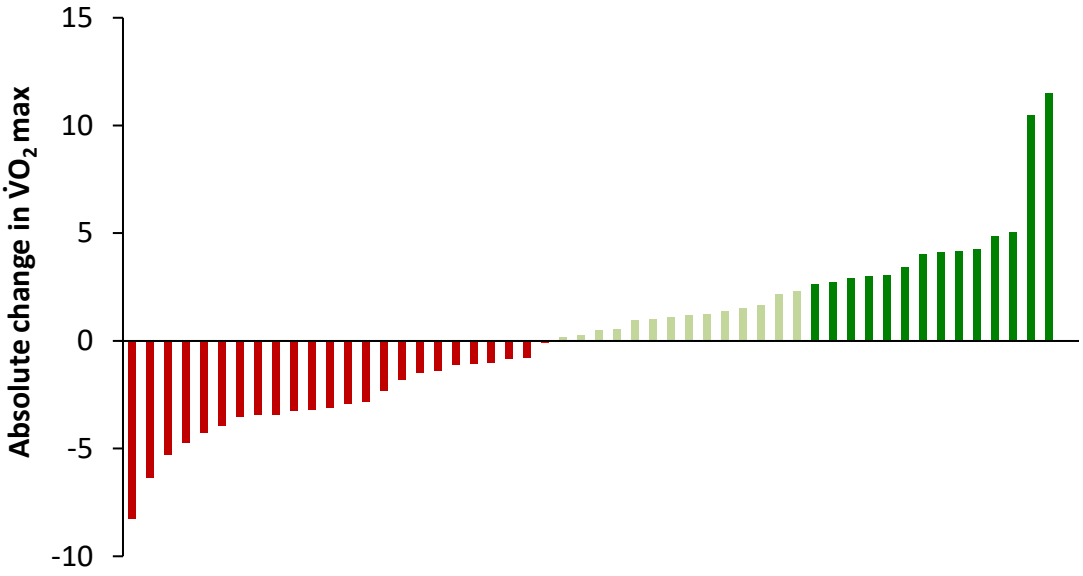


Figure 6.4: Inter-individual variability in changes in $\dot{V}O_2$ max

Vascular Function

Vascular function as measured by FMD did not change in either PATHway or UC at 6-months. In men with CAD, improvements in vascular function have been found to occur following moderate intensity exercise training (163). Shear stress and enhanced bioavailability of NO have been identified as important contributors to exercise mediated improvements in endothelial vasomotor function. The fact that baseline FMD measurements were taken immediately following the completion of a

phase III hospital-based CR program, increases the likelihood that endothelial dysfunction, if present, was significantly reversed prior to the beginning of PATHway.

In addition to changes in established modifiable CVD risk factors such as BP, lipids, diabetes, and body weight, regular exercise can improve cardiovascular health through non-traditional mechanisms including direct cardiac and vascular remodeling (164, 165). In a recent study Howden et al., (2018) found that 2 years of exercise training increased resting left ventricular end-diastolic volume and decreased cardiac stiffness in previously sedentary healthy middle-aged adults (166). Yoshikawa et al., (2013) used intravascular ultrasound imaging and optical coherence tomography to assess the impact of CRF on the characteristics of coronary atherosclerotic plaque. Among 88 patients undergoing elective PCI, there was a positive associated between CRF and a low percentage of lipid volume, high percentage of fibrous volume and greater fibrous cap thickness (167). Exercise training is also associated with formation of coronary collateral blood vessels that increases myocardial perfusion, particularly during bouts of ischemia. Regular exercise also improves baroreflex sensitivity and helps to normalize autonomic nervous system dysfunction (164).

In addition to cardiac hypertrophy, exercise training results in an increase in myosin heavy chain protein content and mitochondrial density, enlargement of the surface density of the SR per unit of myofibrils and a pronounced hyperplasia of the Golgi apparatus (53). Exercise training alter Ca^{2+} cycling by increasing the expression of SERCA2 and NCX pumps, PLB phosphorylation at both Ser-16 and Thr-17, RyR2

protein content and gene expression. Exercise training also modulates cardiac remodeling following MI by positively altering the extracellular matrix (ECM) (53).

Risk factors

There was no significant difference in body weight between PATHway and UC at baseline or at 6-months. Although not significant, body weight continued to increase in UC during the 6-months and decreased in PATHway. It is possible that significant group differences in body weight may have emerged if the study had duration had been longer. Varnfield et al., (2014) and Maddison et al., (2019) also found no significant difference in weight or BMI following participation in a home-based intervention (16, 125).

Risk stratification procedures, coronary reperfusion and revascularization, and newer pharmacotherapies have greatly improved the prognosis of patients referred to cardiac rehabilitation. Since the majority (92%) of PATHway participants reporting the use of statin therapy it was no surprise that baseline lipid levels were within normal (168). Contrary to the hypothesis of no changes in circulating lipid levels following participation in the PATHway, there was a significant increase in HDL-C in UC and no change in PATHway. However, circulating HDL-C levels remained with the desirable range in both PATHway and UC. Similarly, there was no change in BP levels among participants in PATHway. This may be explained by the fact that the majority of participants were medicated for BP and, BP levels were within the desired range.

There was no change in strength measures in participants following participation in PATHway. With the majority of participants partaking in the AL sessions compared to EC sessions it is not surprising that strength did not improve. Studies have shown improvements in strength following aerobic based exercise training but larger effects on muscle strength from programs, unlike PATHway, that specifically target strength using resistance exercises (169).

Future Recommendations

The use of technology enabled HBCR has the potential to be an attractive alternative to traditional hospital-based CR. However, concerns regarding safety should be addressed before HBCR can be fully integrated into the model of care for patients with established CVD. In the present study, safety was not a major concern as the PATHway participants were recruited immediately following completion of a supervised hospital based CR program.

During the early years of CR, concerns about the safety of unsupervised exercise led to the development of structured, medically-supervised CR programs. There was a consensus that exercise sessions should be supervised with ambulatory ECG monitoring to detect, document and characterize abnormal cardiac activity and/or abnormalities associated with the occurrence of myocardial ischemia in order to prevent cardiovascular-related complications. Additionally, ambulatory ECG monitoring is now also used to assess prognosis in specific clinical contexts, evaluate patient response to initiation, revision, or discontinuation of arrhythmic drug

therapy, monitor compliance with the exercise prescription, especially with respect to heart rate and increase patient self-confidence for independent activity. However, continuous ECG monitoring associated with the hospital based phase III CR often results in participants developing a dependency on ambulatory ECG monitoring and being overly concerned for their safety.

Various recommendations exist regarding the number of ECG-monitored sessions that are necessary and reasonable in a CR program. However, there is very little evidence for recommendations to be based for ambulatory ECG monitoring during traditional hospital-based phase III CR, and to date, no randomized controlled trials (RCTs) have specifically evaluated this issue. All previous studies are observational and a number predate the current medical management that has significantly improved the prognosis of patients referred to CR. Furthermore, the fact that the number of events in CR is very small makes it almost impossible to predict cardiac events based on ambulatory ECG monitoring. Although studies have proved the efficacy of a phase III HBCR programs, in Ireland, the culture in CR still involves participants exercising under continuous supervision including ECG monitoring by trained medical staff.

Serious adverse events are rare in hospital-based CR programs. Studies evaluating the safety of hospital-based CR that included low and high risk patients reported 1 event per 50,000 patient hours (170). The appropriate use of established screening mechanisms and monitoring procedures could be used to identify low to moderate risk patients who could safely undertake HBCR (53).

In Ireland, participants attend hospital based CR with no cost and, if HBCR were to be adopted as an alternative mode of delivery for CR a significant cost would be incurred for the hardware and software infrastructure. Until there is sufficient clinical evidence regarding the efficacy of technology-enabled HBCR, it is unlikely that the HSE will support technology-based platforms.

There was a significant decrease in adherence levels to PATHway during the 6-month intervention indicating that HBCR was not successful in addressing the adherence issue related to hospital-based CR. Allowing participants to freely choose to participate in a HBCR rather than random assignment, could potentially improve long-term adherence.

A further challenge with HBCR is the absence of face-to-face communication for education and counseling that is a critical part of a hospital-based CR program. Patients with access to face-to-face counseling sessions are more likely to maintain the improvements from CR at 6 months than those who receive telephone based help (171). A potential solution for this issue is a hybrid approach including both center-based education and counseling sessions and home-based exercise component or the availability of a health coach for participants to meet with during a home-based program.

Technologies are continually being developed and optimized to be more facile, robust, inexpensive and user friendly. The nature of research leaves it difficult to assess the efficacy of any particular piece of technology and subsequently roll it

out for use before the newer model has been developed. Perhaps, rather than testing individual components one at a time, technologies that support theory-based training for specific goals could be combined in interchangeable ways as a rehabilitation format (28). Technologies are tools to be exploited and need to be used as a means of delivering a behavioral intervention rather than being the intervention.

Limitations

Physical activity was measured in the present study. However, considering the population cohort in the study, it was concluded that the PA levels were greatly overestimated and a decision was made not to include the data. PA was measured using a wrist worn accelerometer (Actigraph GT3X). More accurate PA results are obtained when the device is worn on the hip compared to the wrist, which may be due to the lack of validated accelerometry algorithms for wrist-worn devices (172).

This was a pilot study with a convenience sample of 120 participants and was not statistically powered to detect significant changes in outcome variables. The follow-up period of six months may have been too short to assess lifelong behavioural changes. Despite extensive pilot testing of the PATHway platform during development, technical errors occurred throughout the trial that may have negatively impacted on usage. Technology, particularly systems that incorporate multiple components, hosted at different sites with use of the internet for communication should be more rigorously stress-tested prior to implementation in a

large scale clinical trial. Since participant medications were not recorded at follow-up testing, it was not possible to determine if dosage was reduced as a result of participating in PATHway.

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Appendices

Appendix A

Ollscoil Chathair Bhaile Átha Cliath
Dublin City University

DCU

Prof Niall Moyna
School of Health and Human Performance

30th May 2016

REC Reference: **DCUREC/2016/077**

Proposal Title: **Validity and reliability Microsoft Band 2 wrist watch to measure heart rate in healthy men and women**

Applicant(s): **Prof Niall Moyna, Dr Noel McCaffrey & Ms Clare McDermott**

Dear Niall,

Further to expedited review, the DCU Research Ethics Committee approves this research proposal.

Materials used to recruit participants should note that ethical approval for this project has been obtained from the Dublin City University Research Ethics Committee.

Should substantial modifications to the research protocol be required at a later stage, a further amendment submission should be made to the REC.

Yours sincerely,

Dónal O'Mathúna

Dr Dónal O'Mathúna
Chairperson
DCU Research Ethics Committee

DCU
Research & Innovation

Taighde & Nuálaíocht Tacaíocht
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Appendix B

Dublin City University
RESEARCH ETHICS COMMITTEE

APPLICATION FOR APPROVAL OF A PROJECT INVOLVING **HUMAN PARTICIPANTS**

Application No. *(office use only)* DCUREC/2016/____

Please read the following information carefully before completing your application. Failure to adhere to these guidelines will make your submission ineligible for review.

- **Applications must be e-mailed to the DCU Research Ethics Committee at rec@dcu.ie** –no hardcopy required**.**
- **Student applicants must cc their supervisor on that e-mail** – this applies to all masters and postgraduate students. **The form should be checked, approved and signed by the supervisor in advance of submission to REC.**
- **The application should consist of one electronic file only,** with an electronic signature from the PI. The completed application must incorporate all supplementary documentation, especially that being given to the proposed participants. It must be proofread and spellchecked before submission to the REC**.**
- **All sections of the application form must be answered as instructed and within the word limits given.**

Applications which do not adhere to all of these requirements will not be accepted for review and will be returned directly to the applicant.

Applications must be completed on the form; answers in the form of attachments will not be accepted, except where indicated. No hardcopy applications will be accepted. **Research must not commence until written approval has been received from the Research Ethics Committee.**

Note: If your research requires approval from the Biosafety Committee (BSC), or review by the School of Nursing and Human Sciences Ethics Advisory Committee (SNHSEAC), this must be in place prior to REC submission. Please attach the responses from these committees to this submission as directed below.

PROJECT TITLE	Validity and reliability Microsoft Band 2 wrist watch to measure heart rate **in healthy men and women**
PRINCIPAL INVESTIGATOR(S) .	Prof. Niall Moyna
START AND END DATE	April 2016 – December 2016
LEVEL OF RISK *Please indicate whether this project requires (a) expedited* ***or*** *(b) full committee review. Justification for your choice is required under section 3.1*	Expedited

Please confirm that all supplementary information is included in your application (in electronic copy). If questionnaire or interview questions are submitted in draft form, please indicate this by putting (draft) after YES. A copy of the final documentation must be submitted for final approval when available.

	My application has been collated as one electronic file which includes the following documentation:	INCLUDED (mark as YES)	NOT APPLICABLE (mark as N/A)
	Bibliography	**Yes**	
	Recruitment advertisement		N/A
	Plain language statement/Information Statement	Yes	
	Informed Consent form	Yes	
	Evidence of external approvals related to the research		N/A
	Questionnaire/Survey		N/A
	Interview/Focus Group Questions		N/A
	Debriefing material		N/A
	Other (e.g. BSC approval, SNHSEAC review letter)		

Please note:

1. Any amendments to the original approved proposal must receive prior REC approval.
2. As a condition of approval investigators are required to document and report immediately to the Secretary of the Research Ethics Committee any adverse events, any issues which might negatively impact on the conduct of the research and/or any complaint from a participant relating to their participation in the study

1. ADMINISTRATIVE DETAILS

PROJECT TYPE: (mark Y to as many as apply)	Research Project	Y	Funded Consultancy	
			Clinical Trial (No intervention)	No
	Student Research Project (please indicate level, e.g. PhD/MSc Research/MSc Taught)	Y	Other - Please Describe:	…
	PhD	Y		
	MSc Research	…		
	MSc Taught	…		

1.1 INVESTIGATOR CONTACT DETAILS

PRINCIPAL INVESTIGATOR(S):

NAME	*SCHOOL/UNIT*	*EMAIL*
Niall Moyna	Health and Human Performance	niall.moyna@dcu.ie
Noel McCaffrey	Health and Human performance	Noel.mccaffrey@dcu.ie

OTHER INVESTIGATORS:

NAME	*SCHOOL/UNIT*	*EMAIL*
Clare McDermott	Health and Human performance	clare.mcdermott26@mail.dcu.ie

1.2 WILL THE RESEARCH BE UNDERTAKEN ON-SITE AT DUBLIN CITY UNIVERSITY?

YES or NO
Yes

1.3 IS THIS PROTOCOL BEING SUBMITTED TO ANOTHER ETHICS COMMITTEE, OR HAS IT BEEN PREVIOUSLY SUBMITTED TO AN ETHICS COMMITTEE?

YES or NO
No

NA

DECLARATION BY PRINCIPAL INVESTIGATOR(S)

The information contained herein is, to the best of my knowledge and belief, accurate. I have read the University's current research ethics guidelines, and accept responsibility for the conduct of the procedures set out in the attached application in accordance with the form guidelines, the REC guidelines (https://www4.dcu.ie/researchsupport/research_ethics/guidelines.shtml), *the University's policy on Conflict of Interest, Code of Good Research Practice and any other condition laid down by the Dublin City University Research Ethics Committee. I have attempted to identify all risks related to the research that may arise in conducting this research and acknowledge my obligations and the rights of the participants.*

If there exists any affiliation or financial interest for researcher(s) in this research or its outcomes or any other circumstances which might represent a perceived, potential or actual conflict of interest this should be declared in accordance with Dublin City University policy on Conflicts of Interest.

I and my co-investigators or supporting staff have the appropriate qualifications, experience and facilities to conduct the research set out in the attached application and to deal with any emergencies and contingencies related to the research that may arise.

Electronic Signature(s):

Principal investigator(s): 

Print Name(s) here: **Niall Moyna**

Date: **April 2016**

2. PROJECT OUTLINE

2.1 LAY DESCRIPTION

The purpose of this project is to assess the validity and reliability of the Microsoft Band 2 wrist watch for measuring heart rate at rest and during exercise. Twenty healthy men and twenty healthy women between the age of 18 and 30 years will be recruited and will visit the Human Performance Laboratory in DCU on two occasions separated by a minimum of 7 days. During each visit they will wear a Microsoft Band 2 wrist watch and a special Holter monitor to measure heart rate at rest and during treadmill exercise. The readings from the Holter will be used as an accurate indication of heart rate (gold standard) and will be compared to the heart rate recorded on the Microsoft Band 2 wrist watch.

2.2 AIMS OF AND JUSTIFICATION FOR THE RESEARCH

The Microsoft Band 2 wrist watch has been developed to allow individuals unobtrusively measure ambulatory heart rate. To date no studies have assessed the validity and reliability of the Microsoft Band 2 wrist watch for measuring heart rate. The aim of the study is to assess the validity and reliability of the Microsoft Band 2 to monitor HR at rest and during exercise.

2.3 DESCRIBE THE METHODOLOGY BEING USED TO ACHIEVE YOUR STATED AIMS

Healthy men and women will visit the Clinical Exercise Physiology Laboratory in DCU on two occasions, separated by at least 7 days. They will fast for 4 h and refrain from strenuous physical activity for 24 h prior to each visit. During each visit they will wear a Microsoft band 2 wrist watch, and a Holter monitor (figure 1A). The study protocol is outlined in figure 1B. Heart rate will be measured during 3 min of supine rest. Participants will then walk for 3 min at 6 km/h followed by running for 3 min at 8, 9 and 10 km/h. Following the 3 min run at 10 km/h the participants will stand on the treadmill for 3 min to measure heart rate recovery and this will be proceeded by a final 3 min run at 12 km/h and a 3 min recovery period in a sitting position.

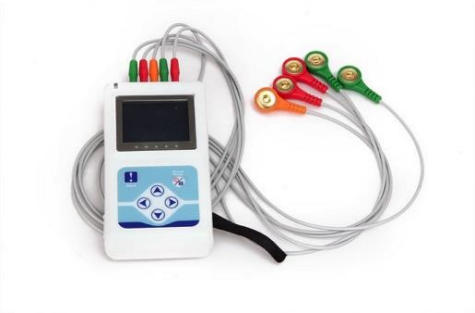


Figure 1A – Holter monitor

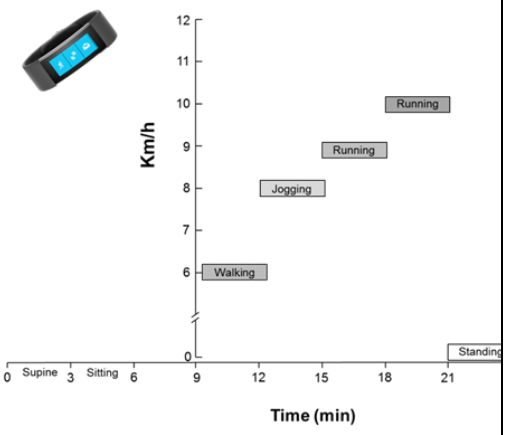


Figure 1B – Exercise protocol

2.4 PARTICIPANT PROFILE

A convenience sample of 20 healthy men and 20 healthy women between the age of 18 and 30 years will be recruited.

2.4(a) PARTICIPANT VULNERABILITY

NA

2.4(b) CHILD PARTICIPANTS

Please indicate your compliance with the following guidelines:	YES or NO
Have you made contact with the DCU Child Protection Officer?	**No**
Informed consent is being obtained from the parents/guardians of children under 18	**No**
Informed assent must also be obtained from the children themselves	**No**
The effect of the research on the child must be monitored to ensure that they feel comfortable with continuing with the research	**No**
In addition to the child one other person should be present during the research. There may be rare occasions when a confidential interview or a one-to-one meeting is necessary and in such circumstances, the interview should be conducted in a room with an open door or visual access	**No**

2.5 EXPLAIN HOW PARTICIPANTS ARE TO BE RECRUITED

An email will be circulated to students and staff at DCU requesting volunteers to participate in the study. Following an expression of interest, potential participants will be provided with a plain language statement, detailing the nature, benefits, risks and discomforts of the study. Informed consent will be explained and individuals who wish to participate in the study will have to provide written informed consent.

2.6 PLEASE EXPLAIN WHEN, HOW, WHERE, AND TO WHOM RESULTS WILL BE DISSEMINATED, INCLUDING WHETHER PARTICIPANTS WILL BE PROVIDED WITH ANY INFORMATION AS TO THE FINDINGS OR OUTCOMES OF THE PROJECT*?*

The results will form the basis for a graduate thesis and will be presented at scientific meetings and published in scientific journals. The identity of individual participants will not be divulged and data will only be presented as part of a group.

2.7 ARE OTHER APPROVALS REQUIRED TO GAIN ACCESS TO ANOTHER LOCATION, ORGANISATION ETC.?

YES or NO
NO

NA

2.8 HAS A SIMILAR PROPOSAL BEEN PREVIOUSLY APPROVED BY THE DCU REC?

YES or NO
NO

NA

3. RISK AND RISK MANAGEMENT

3.1 JUSTIFICATION OF STATED LEVEL OF RISK TO RESEARCH PARTICIPANTS

Submaximal treadmill exercise testing is low risk in healthy men and women between the age of 18 and 30.

3.2 DOES THE RESEARCH INVOLVE:

	YES or NO
• use of a questionnaire? (attach copy)?	No
• interviews (attach interview questions)?	No
• observation of participants without their knowledge?	No
• participant observation (provide details in section 2)?	No
• audio- or video-taping interviewees or events?	No
• access to personal and/or confidential data (including student, patient or client data) without the participant's specific consent?	No
• administration of any stimuli, tasks, investigations or procedures which may be experienced by participants as physically or mentally painful, stressful or unpleasant during or after the research process?	Yes
• performance of any acts which might diminish the self-esteem of participants or cause them to experience embarrassment, regret or depression?	No
• investigation of participants involved in illegal activities?	No
• procedures that involve deception of participants?	No
• administration of any substance or agent?	No
• use of non-treatment of placebo control conditions?	No
• collection of body tissues or fluid samples?	No
• collection and/or testing of DNA samples?	No
• participation in a clinical trial?	No
• administration of ionising radiation to participants?	No

3.3 POTENTIAL RISKS TO PARTICIPANTS AND RISK MANAGEMENT PROCEDURES

Exercise testing carries with it a very small risk of abnormal heart rhythms, heart attack, or death in less than one in 30,000 patients. Submaximal treadmill exercise testing is low risk in healthy men and women between the age of 18 and 30.

3.4 ARE THERE LIKELY TO BE ANY BENEFITS (DIRECT OR INDIRECT) TO PARTICIPANTS FROM THIS RESEARCH?

YES or NO
NO

3.5 ARE THERE ANY SPECIFIC RISKS TO RESEARCHERS?

YES or NO
NO

NA

3.6 DEALING WITH ADVERSE/UNEXPECTED OUTCOMES

The School of Health and Human Performance has a Health and Safety statement that includes an emergency plan for adverse events. The laboratory is equipped with an emergency crash cart and defibrillator. In the event of a minor adverse outcome, the research team will notify the study physician who will determine the appropriate action. In the event of a major adverse outcome, such as cardiac arrest during the exercise test, an ambulance will be called and the participant will immediately be sent to Beaumont Hospital. If any event occurs in DCU the

appropriate health and safety forms, incident reporting, will be completed and the Research Ethics Committee will be informed.

3.7 HOW WILL THE CONDUCT OF THE PROJECT BE MONITORED?

The research team will have weekly meetings to update all aspects of the study. The School of Health and Human Performance has a detailed list of Standard Operating Procedures for each of the protocols in this study. All researchers will be familiar with the procedures and the Safety Statement before beginning data collection.

3.8 SUPPORT FOR PARTICIPANTS

It is not anticipated that there will be the need for additional support for participants involved in this research project.

3.9 DO YOU PROPOSE TO OFFER PAYMENTS OR INCENTIVES TO PARTICIPANTS?

YES or NO
No

NA

3.10 DO ANY OF THE RESEARCHERS ON THIS PROJECT HAVE A PERSONAL, PHILOSOPHICAL, FINANCIAL OR COMMERCIAL INTEREST IN ITS OUTCOME THAT MIGHT INFLUENCE THE INTEGRITY OF THE RESEARCH, OR BIAS THE CONDUCT OR REPORTING OF THE RESEARCH, OR UNDULY DELAY OR OTHERWISE AFFECT THEIR PUBLICATION?

YES or NO
No

NA

4. INVESTIGATORS' QUALIFICATIONS, EXPERIENCE AND SKILLS *(Approx. **200 words**)*

Niall Moyna (PI) is a professor in clinical exercise physiology and has extensive experience assessing fitness and physiological responses to exercise in healthy individuals and men and women with CVD

Dr. Noel McCaffrey is a physician with extensive experience in exercise related research.

Clare McDermott completed the BSc Physical Education and Biology at Dublin City University (1.1 honors degree). Clare is familiar with all the procedures that will be employed in the study.

5. CONFIDENTIALITY/ANONYMITY

5.1 WILL THE IDENTITY OF THE PARTICIPANTS BE PROTECTED?

YES or NO
YES

NA

IF YOU ANSWERED YES TO 5.1, PLEASE ANSWER THE FOLLOWING QUESTIONS:

5.2 HOW WILL THE ANONYMITY OF THE PARTICIPANTS BE RESPECTED?

Participant confidentiality is an important issue during data collection. Participant's identity and other personal information will not be revealed, published or used in other studies. Participants will be assigned an ID number under which all personal information will be stored in a secure locked cabinet in the Vascular Health Research Unit in the School of Health and Human Performance in DCU and saved in a password- protected computer in DCU.

5.3 LEGAL LIMITATIONS TO DATA CONFIDENTIALITY

Information is included in the plain language statement and the informed contest form.

6 DATA/SAMPLE STORAGE, SECURITY AND DISPOSAL

6.1 HOW AND WHERE WILL THE DATA/SAMPLES BE STORED?

All electronic data will be stored on encrypted computers in DCU. Data recorded on paper will be catalogued and stored in a secure filing cabinet in the School of Health and Human Performance, DCU. Prof Moyna will be responsible for the security of the filing cabinet.
Data will only have the participant ID and relevant clinical or physiological information required to interpret the results. The password to access the encrypted data will not accompany the data or be delivered through the same medium.

6.2 WHO WILL HAVE ACCESS TO DATA/SAMPLES?

Only the named researchers will have accessed to the information collected during this project.

6.3 IF DATA/SAMPLES ARE TO BE DISPOSED OF, PLEASE EXPLAIN HOW, WHEN AND BY WHOM THIS WILL BE DONE?

Data will be kept for a **maximum** of 5 years following from the date of the publication of the research. The principal investigator will shred the data after 5 years. The principal investigator will be responsible for disposal of the data

7. FUNDING

7.1 HOW IS THIS WORK BEING FUNDED?

This project has received funding from the European Union's Horizon2020 research and innovation programme.

7.2 PROJECT GRANT NUMBER *(If relevant and/or known – otherwise mark as N/A)*

643491

7.3 DOES THE PROJECT REQUIRE APPROVAL BEFORE CONSIDERATION FOR FUNDING BY A GRANTING BODY?

YES or NO
No

7.4 HOW WILL PARTICIPANTS BE INFORMED OF THE SOURCE OF THE FUNDING?

Details of funding will be included in the Plain Language Statement.

7.5 DO THE FUNDERS OF THIS PROJECT HAVE A PERSONAL, FINANCIAL OR COMMERCIAL INTEREST IN ITS OUTCOME THAT MIGHT COMPROMISE THE INDEPENDENCE AND INTEGRITY OF THE RESEARCH, OR BIAS THE CONDUCT OR REPORTING OF THE RESEARCH, OR UNDULY DELAY OR OTHERWISE AFFECT THEIR PUBLICATION?

YES or NO
No

NA

8. PLAIN LANGUAGE STATEMENT *(Include in this document. Approx. 400 words)*

PLEASE CONFIRM WHETHER THE FOLLOWING ISSUES HAVE BEEN ADDRESSED IN YOUR PLAIN LANGUAGE STATEMENT/ INFORMATION SHEET FOR PARTICIPANTS:

	YES or NO
Introductory Statement (PI and researcher names, school, title of the research)	**Yes**
What is this research about?	**Yes**
Why is this research being conducted?	**Yes**

What will happen if the person decides to participate in the research study?	**Yes**
How will their privacy be protected?	**Yes**
How will the data be used and subsequently disposed of?	**Yes**
What are the legal limitations to data confidentiality?	**Yes**
What are the benefits of taking part in the research study (if any)?	**Yes**
What are the risks of taking part in the research study?	**Yes**
Confirmation that participants can change their mind at any stage and withdraw from the study	**Yes**
How will participants find out what happens with the project?	**Yes**
Contact details for further information (including REC contact details)	**Yes**

DUBLIN CITY UNIVERSITY

Plain Language Statement

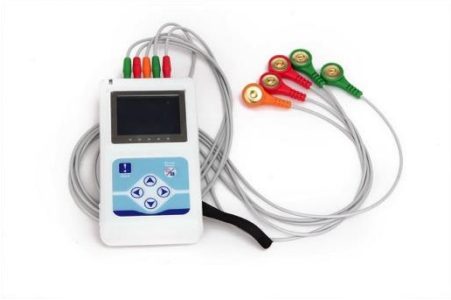
Project Title: Validity and reliability Microsoft Band 2 wrist watch to measure heart rate **in** healthy men and women

Principal investigator Professor Niall M. Moyna
Centre for Preventive Medicine
School of Health and Human Performance
Tel: 01-7008802; Fax 01-7008888

Email: niall.moyna@dcu.ie

II. Details of what involvement in the Research Study will require

Participation in this study will require that you to attend the Human Performance Laboratory in DCU on two separate occasions. The two visits will be separated by a minimum of 7 days. During each visit you will run on treadmill for 3 min at each of 5 different speeds. The speeds will be 6 km/h, 8 km/h, 9 km/h, 10 km/h and 12 km/h. You will wear a special wrist watch and a Holter monitor to measure your heart rate. Each v e hour ir



III. Potential risks to participants from involvement in the Research Study (if greater than that encountered in everyday life)

Exercise carries with it a very small risk of abnormal heart rhythms, heart attack, or death in less than one in 30,000 patients.

IV. Benefits (direct or indirect) to participants from involvement in the Research Study

There will be direct or indirect benefit to you from your participation in the study.

V. Advice as to arrangements to be made to protect confidentiality of data,

including that confidentiality of information provided is subject to legal limitations

Dublin City University will protect your confidentiality with regard to your part in this study. Your information will be assigned a unique code, which will protect your identity. All information will be stored securely and saved in a password-protected file in a computer at DCU. Hardcopy files will be stored in a secure, locked filing cabinet in DCU. Your identity or personal information will not be revealed or published. The study findings may be presented at scientific meetings and published in a scientific journal but your identity will not be divulged and only presented as part of a group. Confidentiality of information provided can only be protected within the limitations of the law. It is possible for data to be subject to subpoena, freedom of information claim or mandated reporting by some professions.

VI. Advice as to whether or not data is to be destroyed after a minimum period

The original documentation will be stored for a maximum of 5 years. Thereafter the documentation will be shredded.

VII. Statement that involvement in the Research Study is voluntary

Involvement in this study is completely voluntary. You may withdraw from the Research Study at any point. There will be no penalty for withdrawing before all stages of the Research Study have been completed.

If participants have concerns about this study and wish to contact an independent person, please contact: The Secretary, Dublin City University Research Ethics Committee, c/o Office of the Vice-President for Research, Dublin City University, Dublin 9. Tel 01-7008000, email rec@dcu.ie

9. INFORMED CONSENT FORM

DUBLIN CITY UNIVERSITY
Informed Consent Form

I. **Research Study Title:** Validity and reliability Microsoft Band 2 wrist watch to measure heart rate in healthy men and women

Principle Investigator: Prof. Niall Moyna, School of Health and Human Performance
Contact details: 01 7008802, niall.moyna@dcu.ie
Other investigators: Dr. Noel McCaffrey, Ms. Clare McDermott

II. Clarification of the purpose of the research

The aim of the study is to assess how accurate and reliable the Microsoft Band 2 write watch is at measuring heart rate at rest and during exercise.

III. Confirmation of particular requirements as highlighted in the Plain Language Statement

Participant – please complete the following (Circle Yes or No for each question)

I have read the Plain Language Statement (or had it read to me)
Yes/No
I understand the information provided
Yes/No
I have had an opportunity to ask questions and discuss this study
Yes/No
I have received satisfactory answers to all my questions
Yes/No
I am aware that my interview will be audiotaped
Yes/No

IV. Confirmation that involvement in the Research Study is voluntary

I may withdraw from the Research Study at any point.

V. Advice as to arrangements to be made to protect confidentiality of data, including that confidentiality of information provided is subject to legal limitations

Your personal information will not be revealed, published or used in further studies. You will be assigned an ID number under which all personal information will be stored in a secure locked cabinet and saved in a password protected file in a computer at DCU. The named investigators will have access to the data. Data will be shredded after 5 years by Prof. Moyna.

Confidentiality is insured, but you must be aware that confidentiality of information provided can only be protected within the limitations of the law. It is possible for data to be subject to subpoena, freedom of information claim or mandated reporting by some professions.

VI. Any other relevant information

If you are in a dependent relationship with any of the researchers, your involvement/non-involvement in the project will not affect your ongoing assessment/grades/management

VII. Signature:

I have read and understood the information in this form. My questions and concerns have been answered by the researchers, and I have a copy of this consent form. Therefore, I consent to take part in this research project

Participants Signature: _____

Name in Block Capitals: _____

Witness: _____

Date: _____

Appendix 1:

Recruitment email

Dear Staff and Students:

We are currently looking for healthy 18-30 year old men and women to take part in a study to assess the accuracy and reliablility of the Microsoft Band 2 wrist-watch for measuring heart rate at rest and during exercise. If you agree to take part in this study you will visit the Clinical Exercise Physiology Laboratory in DCU on two occasions, separated by at least 7 days. You will be asked to fast for 4 h and refrain from strenuous physical activity for a 24 h prior to each visit. During each visit you will wear a Microsoft band 2 wrist-watch, and a Holter monitor. Each visit will be approximately one hour in duration.

If you would like to take part in the study contact Clare McDermott at 017008470 or email clare.mcdermott26@mail.dcu.ie

Kindest Regards,

Niall M. Moyna, PhD., FACSM

Appendix C

Ollscoil Chathair Bhaile Átha Cliath
Dublin City University

DCU

Prof Niall Moyna
School of Health and Human Performance

7th July 2016

REC Reference: **DCUREC/2016/123**

Proposal Title: **PATHway (Physical Activity Towards Health): Human intervention study design**

Applicant(s): **Dr Catherine Woods, Prof Niall Moyna, Dr Kieran Moran, Dr Noel McCaffrey, Dr Deirdre Walsh, Clare McDermott, Ivan Casserly, Anne Gallagher, Brendan McAdam, Helen Newton**

Dear Niall,

Further to ethical review, the DCU Research Ethics Committee approves this research proposal. Copies of approvals from organisations participating in the research should be forwarded when available.

Materials used to recruit participants should note that ethical approval for this project has been obtained from the Dublin City University Research Ethics Committee.

Should substantial modifications to the research protocol be required at a later stage, a further amendment submission should be made to the REC.

Yours sincerely,

Dónal O'Mathúna

Dr Dónal O'Mathúna
Chairperson
DCU Research Ethics Committee

DCU
Research & Innovation

Taighde & Nuálaíocht Tacaíocht
Ollscoil Chathair Bhaile Átha Cliath,
Baile Átha Cliath, Éire

Research & Innovation Support
Dublin City University,
Dublin 9, Ireland

T +353 1 700 8000
F +353 1 700 8002
E research@dcu.ie
www.dcu.ie

Appendix D

Dublin City University
RESEARCH ETHICS COMMITTEE

APPLICATION FOR APPROVAL OF A PROJECT INVOLVING **HUMAN PARTICIPANTS**

Application No. *(office use only)* DCUREC/2016/**123**

Please read the following information carefully before completing your application. Failure to adhere to these guidelines will make your submission ineligible for review.

- **Applications must be e-mailed to the DCU Research Ethics Committee at rec@dcu.ie** –no hardcopy required**.**
- **Student applicants must cc their supervisor on that e-mail** – this applies to all masters and postgraduate students. **The form should be checked, approved and signed by the supervisor in advance of submission to REC.**
- **The application should consist of one electronic file only,** with an electronic signature from the PI. The completed application must incorporate all supplementary documentation, especially that being given to the proposed participants. It must be proofread and spellchecked before submission to the REC**.**
- **All sections of the application form must be answered as instructed and within the word limits given.**

Applications which do not adhere to all of these requirements will not be accepted for review and will be returned directly to the applicant.

Applications must be completed on the form; answers in the form of attachments will not be accepted, except where indicated. No hardcopy applications will be accepted. **Research must not commence until written approval has been received from the Research Ethics Committee.**

Note: If your research requires approval from the Biosafety Committee (BSC), or review by the School of Nursing and Human Sciences Ethics Advisory Committee (SNHSEAC), this must be in place prior to REC submission. Please attach the responses from these committees to this submission as directed below.

PROJECT TITLE	PATHway (Physical Activity Towards Health): Human intervention study design
PRINCIPAL INVESTIGATOR(S) *The named Principal Investigator is the person with primary responsibility for the research project. In the case of Taught Masters projects the supervisor is the Principal Investigator.*	Dr. Catherine Woods
START AND END DATE	January 2017
LEVEL OF RISK *Please indicate whether this project requires (a) expedited **or** (b) full committee review. Justification for your choice is required under section*	Low level of risk

3.1	

Please confirm that <u>all</u> supplementary information is included in your application (in electronic copy). If questionnaire or interview questions are submitted in draft form, please indicate this by putting (draft) after YES. A copy of the final documentation must be submitted for final approval when available.

	My application has been collated as one electronic file which includes the following documentation:	**INCLUDED (mark as YES)**	**NOT APPLICABLE (mark as N/A)**
	Bibliography	**yes**	
	Recruitment advertisement		n/a
	Plain language statement/Information Statement	**yes**	
	Informed Consent form	**yes**	
	Evidence of external approvals related to the research		n/a
	Questionnaire/Survey	**yes**	
	Interview/Focus Group Questions		**n/a**
	Debriefing material		**n/a**
	Other (e.g. BSC approval, SNHSEAC review letter)		n/a

Please note:

3. Any amendments to the original approved proposal must receive prior REC approval.
4. As a condition of approval investigators are required to document and report immediately to the Secretary of the Research Ethics Committee any adverse events, any issues which might negatively impact on the conduct of the research and/or any complaint from a participant relating to their participation in the study

1. ADMINISTRATIVE DETAILS

PROJECT TYPE: (mark Y to as many as apply)	Research Project	Y	Funded Consultancy	…
			Clinical Trial	Y
	Student Research Project (please indicate level, e.g. PhD/MSc Research/MSc Taught)	…	Other - Please Describe:	…
	PhD	…		
	MSc Research	…		
	MSc Taught	…		

1.1 INVESTIGATOR CONTACT DETAILS

PRINCIPAL INVESTIGATOR(S): *Doctoral researchers and Research Masters or their supervisors may be listed as Principal Investigators, depending on the conventions of the discipline and on the individual case. It should be made clear, in subsequent sections of this application, who is carrying out the research procedures.*

NAME	*SCHOOL/UNIT*	*EMAIL*
Dr. Catherine Woods	SHHP	Catherine.woods@dcu.ie

OTHER INVESTIGATORS: *(including Taught Masters students)*

NAME	*SCHOOL/UNIT*	*EMAIL*
Prof. Niall Moyna	SHHP	niall.moyna@dcu.ie
Dr. Noel McCaffrey	SHHP	Noel.mccaffrey@dcu.ie
Dr. Deirdre Walsh	SHHP/ Insight Centre for Data analytics	Deirdre.walsh@dcu.ie
Ms. Clare McDermott	SHHP	clare.mcdermott26@mail.dcu.ie
Mr. Ivan Casserly	Mater Hospital	stentman@gmail.com
Ms. Anne Gallagher	Mater Hospital	agallagher@mater.ie
Mr. Brendan McAdam	Beaumont Hospital	brendanmcadam@beaumont.ie
Ms. Helen Newton	Beaumont Hospital	cardiacrehab@beaumont.ie

1.2 WILL THE RESEARCH BE UNDERTAKEN ON-SITE AT DUBLIN CITY UNIVERSITY?

YES or NO
Yes

(If NO, state details of the off-campus location – provide details of the approval to gain access to that location in section 2.7.)

1.3 IS THIS PROTOCOL BEING SUBMITTED TO ANOTHER ETHICS COMMITTEE, OR HAS IT BEEN PREVIOUSLY SUBMITTED TO AN ETHICS COMMITTEE?

YES or NO
Yes

(If YES, please provide details and attach copies of approval(s) received etc.)

Applied to Beaumont Hospital REC and Mater Hospital REC (pending REC review)

DECLARATION BY PRINCIPAL INVESTIGATOR(S)

The information contained herein is, to the best of my knowledge and belief, accurate. I have read the University's current research ethics guidelines, and accept responsibility for the conduct of the procedures set out in the attached application in accordance with the form guidelines, the REC guidelines (https://www4.dcu.ie/researchsupport/research_ethics/guidelines.shtml), *the University's policy on Conflict of Interest, Code of Good Research Practice and any other condition laid down by the Dublin City University Research Ethics Committee. I have attempted to identify all risks related to the research that may arise in conducting this research and acknowledge my obligations and the rights of the participants.*

If there exists any affiliation or financial interest for researcher(s) in this research or its outcomes or any other circumstances which might represent a perceived, potential or actual conflict of interest this should be declared in accordance with Dublin City University policy on Conflicts of Interest.

I and my co-investigators or supporting staff have the appropriate qualifications, experience and facilities to conduct the research set out in the attached application and to deal with any emergencies and contingencies related to the research that may arise.

Electronic Signature(s):

Principal investigator(s): _____

Print Name(s) here:
Catherine Woods

Date: __10th of June____

2. PROJECT OUTLINE

2.1 LAY DESCRIPTION *(Approx. 300 words)*

Please outline, in terms that any non-expert would understand, what your research project is about, including what participants will be required to do. Please explain any technical terms or discipline-specific phrases.

Cardiovascular disease (CVD) is the leading cause of premature death and disability in Europe, costing the EU economy almost EUR 196 billion a year. While effective cardiac rehabilitation (CR) improves mortality and morbidity rates, uptake of community-based CR, which represents the long-term rehabilitation phase (III), is very low (approximately 11%). Numbers are further diminished by low adherence rates. Key reasons for this include lack of programmes, travel time and scheduling issues. PATHway will provide individualised rehabilitation programs that use regular, socially inclusive exercise sessions as the basis upon which to provide a personalized, comprehensive lifestyle intervention program (managing exercise/physical activity (PA), smoking, diet, stress management, alcohol use etc.) to enable patients to both better understand and deal with their own condition and to lead a healthier lifestyle in general. This will be made possible by the provision of an internet- enabled, sensor-based home exercise platform that allows remote participation in CR exercise programs at any time, either by one-self or by a small number of patients, from the comfort of their own living room.
The goal of this trial is to assess the acceptability, short-term effectiveness on lifestyle and health related physical fitness and cost-effectiveness of the PATHway intervention in patients with CVD in a single blind multicentre pilot randomised controlled trial (RCT).

2.2 AIMS OF AND JUSTIFICATION FOR THE RESEARCH *(Approx. 400 words)*

State the aims and significance of the project. Where relevant, state the specific hypothesis to be tested. Please provide a brief description of background research, a justification as to why this research project should proceed in that context and an explanation of any expected benefits to the community. NB – all references cited should be listed in an attached bibliography.

The primary hypothesis is that PATHway (as received by participants in the 'intervention group') compared tousual care (as received by the control group) will result at six months in an increased uptake of physical activity defined as a total weekly volume of active (activities requiring an energy expenditure above 3 metabolic units) energy expenditure (EE in kcal).

2.3 DESCRIBE THE METHODOLOGY BEING USED TO ACHIEVE YOUR STATED AIMS

Provide an outline of the proposed method and state who is doing which task – include details of data collection techniques, the tasks participants will be asked to do, the estimated time commitment involved, and how data will be analysed. If the project includes any procedure which is beyond already established and accepted techniques please include a description of it. There should be enough detail provided to facilitate ethical review, but applicants are encouraged to keep it as succinct as possible.

Outcome measures will be assessed by researchers blinded to the group allocation. All assessments will be performed at baseline (t1) which coincides with the completion of the outpatient CR program, at 3 months (t2) and 6 months (t3) of follow-up unless otherwise specified *Figure 1. Table 1* gives a tabulated summary of the study schedule. A detailed description of the standard operation procedures (SOP) and case report form (CRF) for the primary outcome and each of the

secondary outcomes can be found in appendix 1.

	Allocation T0	Baseline T1	3 month FU T2	6
Enrolment				
Eligibility screen	X			
Informed consent	X			
Intervention				
PATHway intervention		◆———		
Usual care (control) intervention		◆———		
Assessments				
Physical activity (Motion Sensor)		X	X	
Demographic characteristics	X	X		
Health related physical fitness tests				
CPET		X	X	
Muscle strength and flexibility		X	X	
Quality of the vascular system		X	X	
Blood sampling		X		
Body composition		X	X	
Health related QoL & psychosocial wellbeing by means of questionnaires		X		
- *PHQ-9 / WEMWBS*		X	X	
- *EQ-5D-5L questionnaire*		X	X	
- *SF-12 questionnaire*		X	X	
- *Exercise self-efficacy scale*		X	X	
- *Medication Adherence*		X	X	
- *Exercise Barriers*		X	X	

2.4 PARTICIPANT PROFILE

Provide the number, age range and source of participants. Please provide a justification of your proposed sample size. Please provide a justification for selecting a specific gender, age, or any other group if this is done in your project.

The primary outcome of this study, *total volume of weekly active energy expenditure* (> 3 METs), will be objectively measured by means of the SenseWear mini Armband (BodyMedia, Inc., Pittsburgh, PA, USA). Patients will be asked to wear the device for 24h a day except during water-based activities, for seven consecutive days. Measurements will be performed starting the last week of the ambulatory CR program (= baseline T1), the last week of the 3 month follow-up period (= t2) and last week of the 6 month follow-up period (Appendix 1: SOP1; CRF1). Physical activity measurement by means of the SenseWear device ends on the day of the laboratory assessments (see 3.9.2). The SenseWear is a multisensor body monitor, worn over the triceps muscle of the right arm. It enables continuous collection of various physiological and movement parameters through multiple sensors, including a three-axis accelerometer and sensors measuring heat flux, galvanic skin response, skin temperature and near body ambient temperature. Data from these sensors are combined with gender, age, body weight and height to generate data on energy expenditure, physical activity intensity and sedentary time using algorithms developed by the manufacturer (SenseWear Professional software, version 8.0).
Data on health related outcomes will be assessed during one single visit performed in the morning between 9-12 AM in the following order:

- *Quality of the arterial system* will be assessed by means of endothelial function measures of the brachial artery using the flow mediated dilation method. The arteriography will be used to measures vascular stiffness. Blood pressure (BP) will be measured at rest (office BP) and by means of a 24h ambulatory BP monitor. (Appendix 4: SOP 2; CRF 2)
- *Blood sampling* for cardiovascular risk biomarkers (glucose, insulin, total cholesterol and HLD and LDL cholesterol) (Appendix 4: SOP3; CRF 3))
- *Body composition* (weight, height, circumferences, % body fat) (Appendix 4: SOP4; CRF 4)
- *Functional flexibility* will be assessed by means of the sit and rise test (Appendix 4: SOP5; CRF5)
- *Muscle strength testing* involving maximal isometric handgrip strength and isometric and isokinetic quadriceps strength and endurance (Appendix 4: SOP5; CRF5)
- *Exercise capacity* (maximal graded cardiopulmonary exercise test on cycle) (Appendix 4: SOP6; CRF 6)

Patients will be asked to come in fasted state. After the measurements of vascular health, anthropometrics and the blood sampling have been performed they will be given the time to consume a light breakfast. During this time, they will be asked to fill in the questionnaires (see 3.9.3) which will be administered as an online survey. Following this, measurements on flexibility, strength and exercise capacity will be performed. All measurements will be performed by the same blinded researcher at each participating site.
Patients will be asked to fill in a booklet of questionnaires which will be administered as an online survey a portable PC (see **Table 2** and Appendix 3)

Questionnaire	Questionnaire
- SF-12	Ware J, Jr, Kosinski M, Keller SD.: A 12-Item Health Survey: construction of scales and preli of reliability and validity. Med Care 34: 220–233,
- Physical Health Questionnaire (PHQ-9)	Razykov, I., Ziegelstein, R., Whooley, M., & (2012). The PHQ-9 versus the PHQ-8 - Is item assessing suicide risk in coronary artery disea Data from the Heart and Soul Study. Psychosomatic Research, 73, 163–168.
- Perceived Stress Scale	Cohen, S., Kamark, T., Mermelstein, R. (198 measure of perceived stress. Journal of Health Behaviour, 24, 4: 385-396.
- ENRICHD	Vaglio J., Conard M., Poston W.S., O'Keefe J., H House J. and Spertus J.A. (2004) Testing the per the ENRICHD Social Support Instrument in card Health and Quality of Life Outcomes 2: 24. Social support inventory is a 7-item instrumen social support for patients recovering from infarction. This instrument is evaluating support in the areas
- WEMWBS	Tennant R, Hiller L, Fishwick R, Platts S, Joseph S, Parkinson J, Secker J, Stewart-Brown S. The War Edinburgh Mental Well-being Scale (WEMWBS): development and UK validation. Health Qual Life 2007 Nov 27;5:63.
- ESES	Shields CA, Brawley LR. (2006). Preferring pr impact on self-efficacy for exercise. J Heal 11(6):904-14. Shields (2009). The Exercise Self-Efficacy S assesses an individual's beliefs in their ability exercising on a three time per week basis a intensities for 40+ minutes per session in the fut
- Exercise barriers (assessment)	McAuley, E. (1992). The role of efficacy cogni prediction of exercise behavior in adults. *Journal of Behavioral Medicine*, 15(1), 65

The health economic evaluation will evaluate the health outcome and resource use consequences of the Pathway intervention. The analysis will be conducted from a

societal perspective to include resource costs falling on the health service and on the individual, together with potential productivity benefits associated with return to work where applicable. Health outcomes will be estimated in terms of Quality Adjusted Life Years in order to estimate a cost per quality adjusted life years gained associated with the intervention that can be compared to other potential uses of scarce societal resources. To achieve this objective information form the short-term clinical trial will need to be extrapolated in order to estimate final health outcomes over participating patients remaining lifetimes. As part of the clinical trial, the economic analysis will measure the costs of the intervention programmes, the health service costs, the costs falling on the participants and the productivity effects in terms of subjects' employment. In addition, a measure of health related quality of life will be used. In the lifetime analysis a model will be developed that links changes in exercise capacity and cardiovascular risk profiles to recurrent cardiovascular events and CVD mortality in order to estimate the cost-per-quality adjusted life year associated with the PATHway programme. Patient's use of health care resources not captured elsewhere in the clinical trial will be obtained by the researcher consulting the patient medical records and retrieving information up to 12 months prior to the cardiac event. During follow-up, health care resource use will be gathered concerning the health care costs of the patient at each follow-up visit for the three months preceding the visit. Information (appendix 4, CRF 7) on patients own resource use and health related quality of life will be obtained by a researcher by means of an interviewer-administered questionnaire during the follow-up visit as shown in Error! Reference source not found..

Direct health care costs	
Concomitant medications Visits to health care professionals Hospital Outpatient visits Hospital Accident and ER visits Hospital Admissions (daycase or overnight)	Patient Resource Use Questionnaire
Direct costs to the patient/carer	
Fees/subscriptions Travel costs Other (clothing, equipment etc) Over-the-counter medication	Patient Resource Use Questionnaire
Productivity costs to patient/carer	
Time spent on exercise/counselling/therapies Time away from employment/main activity	Patient Resource Use Questionnaire
Quality of Life	
Quality of life	EQ-5D-5L questionnaire

2.4(a) PARTICIPANT VULNERABILITY

Are some or all of participants vulnerable in any way? (e.g by virtue of the group they belong to, people who have undergone traumatic or adverse emotional events, people with diminished cognitive ability, power relations between researchers and participants etc.)? If they are, state what this vulnerability (or vulnerabilities) is and justify why this research is being done with such participants.

Participants will have established stable cardiovascular disease. The investigators are trained and experienced in working with individuals with chronic conditions in a safe and professional manner.

2.4(b) CHILD PARTICIPANTS

If your participants include children, please confirm that you are in compliance with the following research specific guidelines as detailed in the DCU Child Protection framework. Further information on the framework is available online at http://www.dcu.ie/equality/crc.shtml

Please indicate your compliance with the following guidelines:	**YES or NO**
Have you made contact with the DCU Child Protection Officer?	**NO**
Informed consent is being obtained from the parents/guardians of children under 18	**NO**
Informed assent must also be obtained from the children themselves	**NO**
The effect of the research on the child must be monitored to ensure that they feel comfortable with continuing with the research	**NO**
In addition to the child one other person should be present during the research. There may be rare occasions when a confidential interview or a one-to-one meeting is necessary and in such circumstances, the interview should be conducted in a room with an open door or visual access	**NO**

2.5 EXPLAIN HOW PARTICIPANTS ARE TO BE RECRUITED

Please provide specific details as to how you will be recruiting participants. How will people be informed that you are doing this research? How will they be approached and asked if they are willing to participate? If you are mailing or phoning people, please explain how you have obtained their names and contact details. If a recruitment advertisement is to be used, please ensure you attach a copy to this application.

The study population will involve 120 patients diagnosed with CVD. Men and women between the ages of 40-80 years with documented CVD, who enrolled for the first time in an outpatient CR program in the University Hospital Leuven (Belgium), Beaumont Hospital (Ireland) or Mater Hospital (Ireland) will be recruited during a one-year period starting in January 2017. Patients entering the CR program will be assessed for eligibility by the local hospital cardiac nurse (Ireland) or physiotherapist (Belgium).
All identified eligible patients will be contacted by a member of the research team of each participating site (DCU for Ireland, KU Leuven for Belgium) and basic socio-demographic data will be collected. The case report form (CRF) to be filled in for each identified eligible patient can be found in appendix 1 (CRF - eligibility). At this point in time, a local investigator of the research team will give a full oral explanation of the design and purpose of the study, responsibilities of the participants, reasonable foreseeable inconveniences, confidentiality of the information collected and contact details to patients interested in participating. Agreeing patients will be asked to sign the informed consent form (Appendix 2-3).

2.6 PLEASE EXPLAIN WHEN, HOW, WHERE, AND TO WHOM RESULTS WILL BE DISSEMINATED, INCLUDING WHETHER PARTICIPANTS WILL BE PROVIDED WITH ANY INFORMATION AS TO THE FINDINGS OR OUTCOMES OF THE PROJECT*?*

Results will be disseminated via peer-reviewed scientific journals and presentations at local, national and international congresses and events. A final report will be submitted to the European Commissionwhich will be made publicly available on the PATHway website: (http://www.pathway2health.eu/).

Participants will be provided with a report of their individual test results and the results of the overall study.

2.7 ARE OTHER APPROVALS REQUIRED TO GAIN ACCESS TO ANOTHER LOCATION, ORGANISATION ETC.?

YES or NO
Yes

(If YES, please specify from whom and attach a copy of the approval documentation. If this is not yet available, please explain when this will be obtained.)

We are currently waiting ethical review for all partners and sites (i.e., Mater, Beaumont and KUL).

2.8 HAS A SIMILAR PROPOSAL BEEN PREVIOUSLY APPROVED BY THE DCU REC?

YES or NO
Not to my knowledge

(If YES, please state both the REC Application Number and Project Title)

3. RISK AND RISK MANAGEMENT

3.1 JUSTIFICATION OF STATED LEVEL OF RISK TO RESEARCH PARTICIPANTS

You must provide a justification for the stated level of risk, as indicated on the cover page of your application. Note that the level of risk may be influenced by the vulnerability of the research group, the methods employed and the nature of the research itself. For further information on risk levels, please refer to the Types of Submission information on the website: https://www4.dcu.ie/researchsupport/research_ethics/guidelines/types.shtml

A full committee review is indicated for this study. The study involves exercise in participants with established cardiovascular disease, including maximal exercise tests.

3.2 DOES THE RESEARCH INVOLVE:

	YES or NO
• use of a questionnaire? (attach copy)?	Yes
• interviews (attach interview questions)?	No
• observation of participants without their knowledge?	No
• participant observation (provide details in section 2)?	No
• audio- or video-taping interviewees or events?	
• access to personal and/or confidential data (including student, patient or client data) without the participant's specific consent?	No
• administration of any stimuli, tasks, investigations or procedures which may be experienced by participants as physically or mentally painful, stressful or unpleasant during or after the research process?	No
• performance of any acts which might diminish the self-esteem of participants or cause them to experience embarrassment, regret or depression?	No
• investigation of participants involved in illegal activities?	No
• procedures that involve deception of participants?	No
• administration of any substance or agent?	Yes
• use of non-treatment of placebo control conditions?	No
• collection of body tissues or fluid samples?	Yes
• collection and/or testing of DNA samples?	No
• participation in a clinical trial?	Yes
• administration of ionising radiation to participants?	

3.3 POTENTIAL RISKS TO PARTICIPANTS AND RISK MANAGEMENT PROCEDURES

Identify, as far as possible, all potential risks to participants (physical, psychological, social, legal, economic, etc.), associated with the proposed research. Please explain what risk management procedures will be put in place to minimise these risks.

Exercise carries with it a very small risk of abnormal heart rhythms, heart attack, or death in less than one in 30,000 patients. In this participant cohort of participants with established chronic illness the risk is higher. In cardiac rehabilitation programmes the occurrence of major cardiovascular events ranges from 1/50,000 to 1/120,000 patient- hours of exercise, with only 2 fatalities reported per 1.5 million patient-hours of exercise. The School of Health and Human Performance has the facilities and personnel to deal with any emergencies that arise and an emergency plan is in place. Dr. McCaffrey will provide medical supervision onsite during testing. An emergency room and automated external defibrillator (AED) are available onsite. The research team are appropriately qualified and experienced in working with clinical populations in a safe and professional manner.

3.4 ARE THERE LIKELY TO BE ANY BENEFITS (DIRECT OR INDIRECT) TO PARTICIPANTS FROM THIS RESEARCH?

YES or NO
Yes

(If YES, provide details.)

Participants will be provided with a copy of their results, summarising information such as blood pressure, body composition, arterial function, strength and fitness levels.

3.5 ARE THERE ANY SPECIFIC RISKS TO RESEARCHERS?

Examples include use of dangerous materials, asking certain types of questions, research being undertaken in certain locations, researchers working alone in isolated areas, etc.

YES or NO
Yes

(If YES, please describe and explain what risk management procedures will be put in place to minimise these risks.)

Risk is associated with working with blood and handling needles. The research team has been immunized for hepatitis B. Standard operating procedures for the handling of biological products exist within the School of Health and Human Performance.

3.6 DEALING WITH ADVERSE/UNEXPECTED OUTCOMES

Please describe what measures/protocols you have put in place in the event that there are any unexpected outcomes or adverse effects to participants arising from involvement in the project.

The School of Health and Human Performance has established an emergency protocol for adverse events. In the unlikely event of a major adverse outcome, an ambulance will be called and the participant will be sent immediately to Beaumont Hospital. Any minor adverse outcomes will be dealt with by the study physician who will then refer the participant, if required, to the VHI- swift care clinic in Swords for further attention.

3.7 HOW WILL THE CONDUCT OF THE PROJECT BE MONITORED?

Please explain how the principal investigator will monitor the conduct of the project (especially where several people are involved in recruiting or interviewing, administering procedures, etc.) to ensure that it conforms with the procedures set out

in this application. In the case of student projects please give details of how the supervisor(s) will monitor the conduct of the project.

The research team will have meetings on a weekly basis to update on all aspects of the study. All researchers involved in the study will be familiar with testing procedures and the safety statement prior to commencing data collection. A number of practice sessions will be undertaken by all the research team to ensure proficiency and reliability in performing the data collection procedures.

3.8 SUPPORT FOR PARTICIPANTS

Depending on risks to participants you may need to consider having additional support for participants during/after the study. Consider whether your project would require additional support, e.g., external counselling available to participants. Please advise what support will be available.

Participants will be provided with a phone number for the research team should any concerns arise due to direct participation in the study. Participants will be encouraged to speak directly to their GP should they be concerned about their physical well-being. It is not envisaged that external supports will be needed due to participation in this study.

3.9 DO YOU PROPOSE TO OFFER PAYMENTS OR INCENTIVES TO PARTICIPANTS?

YES or NO
Yes

(If YES, please provide further details.)

All taxis and parking will be paid for all participants should they require transport to DCU for the testing.

3.10 DO ANY OF THE RESEARCHERS ON THIS PROJECT HAVE A PERSONAL, PHILOSOPHICAL, FINANCIAL OR COMMERCIAL INTEREST IN ITS OUTCOME THAT MIGHT INFLUENCE THE INTEGRITY OF THE RESEARCH, OR BIAS THE CONDUCT OR REPORTING OF THE RESEARCH, OR UNDULY DELAY OR OTHERWISE AFFECT THEIR PUBLICATION?

YES or NO
No

(If YES, please specify how this conflict of interest will be addressed.)

4. INVESTIGATORS' QUALIFICATIONS, EXPERIENCE AND SKILLS *(Approx. **200 words**)*

List the academic qualifications and outline the experience and skills relevant to this project that the PI, other researchers and any supporting staff have in carrying out the research and in dealing with any emergencies, unexpected outcomes, or contingencies that may arise.

Dr. Catherine Woods:
Dr. Woods is a senior lecturer in physical activity psychology and public health in DCU's School of Health and Human Performance. Catherine joined the School in 2000, was Head of the School from 2008-2012 and was instrumental in the development of its sport science and health and its physical education B.Sc. programmes. In DCU, Catherine is Chair of the B.Sc. in Physical Education with Biology/Maths, and leads a research cluster on Childhood and Physical Activity. She is one of the founding Directors of DCU's MedEx programme and currently sits on its steering committee.

In Ireland, Catherine is part of SAGO, a Special Action Group on Obesity who advise the Minister of Health on the prevention and management of obesity in Ireland. She is also an advisor to *Healthy Ireland* (HI), Ireland's new health and wellbeing framework, and is currently assisting HI to write a National Physical Activity Plan; and has previously advised the Department of Education on the assessment of the National Physical Education curricula at both junior and senior cycle.

On a European level, Catherine is an active member of the WHO network on Health Enhancing Physical Activity, where she is Chair of the working group on children and young people. Catherine undertook the role of temporary advisor to the WHO, regional office for Europe, at their technical consultation meeting on the European Physical Activity for Health Strategy (EPAS), Zurich, January 2015. This was attended by forty-eight out of the fifty-three Member States. In December 2013, she was invited to attend a WHO Europe Region Expert Group meeting on physical activity promotion in health care settings, where along with Dr. Noel McCaffrey she presented on the MedEx model (see below). Catherine is also part of the DEDIPAC consortium (Determinants of Diet and Physical Activity), a knowledge hub set up to integrate and develop infrastructure for research on the determinants of diet and physical activity across Europe. She was on the Management Committee of a successful COST Action entitled *Cyberparks*, which aims to examine how technology can help to get people outdoors, and actively engaging with public spaces in order to improve health; she is currently an active member in this Action.

Catherine currently has two post-doctoral research fellows, one in MedEx and one in PATHway (Horizon 2020), she is supervising three postgraduate research students; has published numerous book chapters, peer-reviewed journal articles and has presented her work at national and international conferences.

Current research priorities include:

1. Design, evaluation and implementation of evidence-based interventions – particularly using mHealth - to promote physical activity and healthy lifestyles in clinical (MedEx participants) and community (schools) settings.
2. Social ecological approach to understanding walkability in the Greater Dublin Area.
3. Determinants of physical activity and sedentary behaviour in children.
4. Physical activity policy evaluation and development.

Prof. Niall Moyna:
Niall is a Professor and Head of the School of Health and Human Performance and a member of the Centre for Preventive Medicine in DCU. He received his masters degree from Purdue University, Indiana, USA and Ph.D. from the University of Pittsburgh, Pennsylvania, USA. He completed a three-year National Institute of Health Post Doctoral Research Fellowship in immunology at the University of Pittsburgh Medical Center. He was Director of the Clinical Exercise Research Laboratory in the Division of Cardiology at the University of

Pittsburgh Medical Centre and later moved to Connecticut to take a position as a Senior Research Scientist in Nuclear and Preventive Cardiology at Hartford Hospital. He has published over 150 research papers in international peer reviewed journals and presented his work at international conferences. Niall is a Fellow of the American College of Sports Medicine. Prof. Moyna's vast experience in the areas of clinical physiology and cardiovascular disease are integral for the PATHway trial.

Dr. Deirdre Walsh: Dr. Deirdre Walsh is health psychologist with expertise in the areas of health behaviour change and psycho-oncology. Dr. Walsh completed an MSc in Applied Positive Psychology in the University of East London and a PhD in Psychology and Health at NUIG. The focus of her research to date has been examining how a health-related trauma may lead to adoption of healthier lifestyle behaviours as well as a greater appreciation and awareness of health. Dr. Walsh has received training in health behaviour change theory. This is an important aspect in relation to this study as the rationale and design will be based on health behaviour change theory. Dr. Walsh has expertise in qualitative research and quantitative research including Interpretative phenomenological analysis and thematic analysis, as well as mixed methods research including factor analysis and structural equation modelling and will be in a position to provide guidance on study design and analysis. Dr. Walsh is also a member of the MedEx research cluster and is familiar with recruitment among this population, including potential barriers and ethical considerations that need to be addressed and can assist in planning achievable targets and timelines.

Dr. Noel McCaffrey:
Dr. McCaffrey graduated from UCD (Medical School) 1983. Studied Sports Medicine in London 1986-88. Worked in UCD Medical School 1990-1996 developing and directing MSc (Sports and Exercise Medicine) Program. In DCU since 2000 working in School of Health and Human Performance (primarily in the BSc(ATT) Program area and also in DCU Sport (special populations exercise programs). Outside DCU acting as director of Exwell Medical, Sports Medicine Consultant in Cappagh National Orthopaedic Hospital.

Ms.Clare McDermott:
Ms. Clare McDermott has a BSc. in Physical Education and Biology and is currently undertaking a Phd. In Clinical Exercise Physiology in DCU. This involves assessing the changes of physical outcomes in individuals with cardiovascular disease following participation in a home-based cardiac rehabilitation programme. Current work includes the validation of various wrist worn devices, performing the clinical assessment on participants in TV3 documentary 'Doctor's in the House' and RTE's 'Operation Transformation', continuously testing and analysing fitness and welfare of Elite Athletes and performing Venepuncture, blood analysis and planning the development of MedEX (medical supervised exercise programme in DCU Sport).

Mr. Ivan Casserly:
See CV in appendices

Ms. Anne Gallagher:
See CV in appendices

Ms. Helen Newton:
See CV in appendices

Prof. McAdam:
See CV in appendices

5. CONFIDENTIALITY/ANONYMITY

5.1 WILL THE IDENTITY OF THE PARTICIPANTS BE PROTECTED?

YES or

NO
Yes

(If NO, please explain why.)

IF YOU ANSWERED YES TO 5.1, PLEASE ANSWER THE FOLLOWING QUESTIONS:

5.2 HOW WILL THE ANONYMITY OF THE PARTICIPANTS BE RESPECTED?

Please bear in mind that where the sample size is very small, it may be impossible to guarantee anonymity/confidentiality of participant identity. Participants involved in such projects need to be advised of this limitation in the Plain Language Statement/Information Sheet.

Each randomized person, after providing consent, will be assigned a **personal identification code (PIC).** This unique identification number will be used on all case report forms and in all electronic databases.
The PIC will be a 7-digit code using the following information:

- Control (C) or experimental (E) arm: e.g., experimental: **E**
- Sequential number enrolled: e.g., 90th participant: **090**
- Initial of first name: e.g., Niall: **N**
- Two digits to reflect the year of birth: e.g. 1955 would be: 55

In this example the 7-digit PIC would be**: e.g., E090N55**
Test data will be collected at three time points: at completion of the outpatient CR program (T1= baseline), at three months of follow up (T2=follow-up three) and at 6 months of follow-up (T3=follow up 6 months).

5.3 LEGAL LIMITATIONS TO DATA CONFIDENTIALITY

Participants need to be made aware that confidentiality of information provided cannot always be guaranteed by researchers and can only be protected within the limitations of the law - i.e., it is possible for data to be subject to subpoena, freedom of information claim or mandated reporting by some professions. This information should be included in your Plain Language Statement and Informed Consent Form. Depending on the research proposal and academic discipline, you may need to state additional specific limitations.

State how and where participants will be informed of these limitations, or give a justification if this will not be done.

Within the plain language statement, participants will be informed that confidentiality of information provided can only be protected within the limitations of the law and that it is possible for data to be subject to subpoena, freedom of information claim or mandated reporting by some professions.

6 DATA/SAMPLE STORAGE, SECURITY AND DISPOSAL

For the purpose of this section, "Data" includes that in a raw or processed state (e.g. interview audiotape, transcript or analysis). "Samples" include body fluids or tissue samples.

6.1 HOW AND WHERE WILL THE DATA/SAMPLES BE STORED?

Note that the REC recommends that all data be stored on campus – please justify any off-site storage.

At the time of the measurement, data will be recorded in hardcopy and afterwards will be entered electronically in 'open clinica', an open source clinical trial software for electronic data capture and data management, at each participating site where the data is collected. The database will be hosted and secured Hardcopies will be stored in a secured filing cabinet at the participating site (DCU or KU Leuven). The data entry screens in Open Clinica will resemble the hard copy case report forms. Checks will be automatically applied when entering the data in the database based on preset ranges. Missing data will also be automatically detected and data query reports will be sent to the data manager. The type of activity that an individual user may undertake is regulated by the privileges associated with his/her user identification code and passwords. After submission of the data, researchers responsible at the participating sites cannot make any changes. Appropriate changes can only be made by the data manager.

6.2 WHO WILL HAVE ACCESS TO DATA/SAMPLES?

If people other than the main researchers have access, please name who they are and explain for what purpose.

Clinical researchers, setting up the PATHway system in the Clinical environment have access to their own patients, only. On the other hand researchers of the PATHway system (DSS) have access to all data from all patients, however the data presented to the researchers will be filtered and patient identifiable data will be (pseudo-)anonymized.

The Health Data Management System (HDMS) used by clinical researchers is called the c-HDMS. From a logical perspective the c-HDMS is in the Clinical environment. The HDMS that DSS-researchers will use is called the r-HDMS and is in the Research environment

6.3 IF DATA/SAMPLES ARE TO BE DISPOSED OF, PLEASE EXPLAIN HOW, WHEN AND BY WHOM THIS WILL BE DONE?

Note that simply deleting files is not sufficiently secure. The additional steps to be taken to maintain data security should be given. If data/samples are NOT being disposed of, please justify this decision.

The data will be stored in a secure locked cabinet in the Vascular Health Research Unit in the School of Health and Human Performance in DCU and saved in a password- protected in a computer in DCU. Data will be kept for a **maximum** of 5 years following from the date of the publication of the research. The principal investigator will be responsible for the security of the data. Only the other investigators listed on this ethics application form will have access to the data. The data will be shredded by the principal investigator after 5 years.

7. FUNDING

7.1 HOW IS THIS WORK BEING FUNDED?

This project has received funding from the European Union's Horizon2020 research and innovation programme.

7.2 PROJECT GRANT NUMBER *(If relevant and/or known – otherwise mark as N/A)*

643491

7.3 DOES THE PROJECT REQUIRE APPROVAL BEFORE CONSIDERATION FOR FUNDING BY A GRANTING BODY?

YES or NO
No

7.6 HOW WILL PARTICIPANTS BE INFORMED OF THE SOURCE OF THE FUNDING?

Details of funding will be included in the Plain Language Statement.

7.7 DO THE FUNDERS OF THIS PROJECT HAVE A PERSONAL, FINANCIAL OR COMMERCIAL INTEREST IN ITS OUTCOME THAT MIGHT COMPROMISE THE INDEPENDENCE AND INTEGRITY OF THE RESEARCH, OR BIAS THE CONDUCT OR REPORTING OF THE RESEARCH, OR UNDULY DELAY OR OTHERWISE AFFECT THEIR PUBLICATION?

YES or NO
No

8. PLAIN LANGUAGE STATEMENT *(Include in this document. Approx. 400 words)*

A Plain Language Statement (PLS) should be used in all cases. This is written information in plain language that you will be providing to participants, outlining the nature of their involvement in the project and inviting their participation. The PLS should specifically describe what will be expected of participants, the risks and inconveniences for them, and other information relevant to their involvement. Please note that the language used must reflect the participant age group and corresponding comprehension level – if your participants have different comprehension levels (e.g. both adults and children) then separate forms should be prepared for each group. The PLS can be embedded in an email to which an online survey is attached, or handed/sent to individuals in advance of their consent being sought. See link to sample templates on the website:
http://www4.dcu.ie/research/research_ethics/rec_forms.shtml

PLEASE CONFIRM WHETHER THE FOLLOWING ISSUES HAVE BEEN ADDRESSED IN YOUR PLAIN LANGUAGE STATEMENT/ INFORMATION SHEET FOR PARTICIPANTS:

	YES or NO
Introductory Statement (PI and researcher names, school, title of the research)	**yes**
What is this research about?	**Yes**

Why is this research being conducted?	**Yes**
What will happen if the person decides to participate in the research study?	**Yes**
How will their privacy be protected?	**Yes**
How will the data be used and subsequently disposed of?	**Yes**
What are the legal limitations to data confidentiality?	**Yes**
What are the benefits of taking part in the research study (if any)?	**Yes**
What are the risks of taking part in the research study?	**Yes**
Confirmation that participants can change their mind at any stage and withdraw from the study	**Yes**
How will participants find out what happens with the project?	**Yes**
Contact details for further information (including REC contact details)	**Yes**

If any of these issues are marked NO, please justify their exclusion:

Plain Language Statement

Project Title: PATHway (Physical Activity Towards Health): Pilot Randomised Controlled Trial
Principal Investigator: Dr. Catherine Woods, School of Health and Human Performance,
Other Investigators: Dr. Deirdre Walsh, School of Health and Human Performance, Prof. Niall Moyna, School of Health and Human Performance, Ms. Clare McDermott, School of Health and Human Performance, Anne Gallagher, Cardiac Rehabilitation Coordinator, Mater Hospital, Dr.Ivan Casserly, Consultant Cardiologist, Mater Hospital, Helen Newton, Cardiac Rehabilitation Co-ordinator, Beaumont Hospital. Dr. Brendan McAdam, Consultant Cardiologist, Beaumont Hospital.

II. Details of what involvement in the Research Study will require

Involvement in this study will require you to take part in a 6-month technology-enabled remote randomised control trial. As part of this trial, you will be randomly assigned into groups that will either i) receive 'usual care' or ii) take part in an intervention that will receive the PATHway system which will allow you to engage with a tailored exercise and health behaviour change programme. All participants will be asked to make a visit to the Vascular research unit in DCU. A pre-paid taxi service will be provided for all participants and a research team member will meet all participants at the taxi drop-off point to escort everyone to the Vascular research unit for physiological tests and questionnaires at baseline, 3months and finally at 6months regardless of group. During the visit to DCU, i) a blood sample will

be drawn, ii) your height, weight, waist and hip circumference, and the amount of muscle and fat will be measured, iii) a picture will be taken of a blood vessel in your neck, iv) the health of a blood vessel in the arm will be assessed, v) your blood Pressure will be measured, vi) you will undergo a fitness level on a treadmill vii) your muscle strength and endurance will be measured and viii) you will complete questionnaires. You will be asked to fast for from 10pm the night before the visit to the VRU and will not be allowed to exercise for at least 24 hours before the visit to DCU.

- Two tablespoons of blood will be taken to measure a variety of biomarkers in the blood that are used to predict the risk of CVD. A bioelectrical impedance scale will be used to measure amount of muscle and fat. Your waist and hip circumference will be measured with a measuring tape. The blood samples, body fat and waist and hip measurements will be taken in a private room. A female researcher will measure height and weight and take the skinfold measurements in female participants.
- A special machine called an ultrasound will take a picture of a blood vessel in your neck. (figure A). The health of a blood vessel in your arm will be also measured using the ultrasound machine and involves two steps. The first step will involve blocking the blood flow to your lower arm for 5 minutes by inflating a blood pressure cuff, and then taking a picture when the blood pressure cuff in released. The second step involves spraying a medicine called glyceryl trinitrate under your tongue in order to widen the artery and then taking a picture 3 minutes later (figure B).

Figure A

Figure B

- Your fitness will be assessed by having running on a treadmill while wearing a special headgear that is attached to a mouthpiece and connected to and ECG machine which looks at the activity of your heart.
- Your strength will be measured using three different ways. You will complete a hand grip test, a sit to stand test where you will sit and rise from a chair in a given time frame and finally using an isokinetic machine which will require you to sit in a chair while your leg is strapped in and you will push against a fixed force.

III. Potential risks from involvement in the Research Study

- You may experience some muscle soreness in his/her legs or nausea following exercise.
- Exercise carries with it a very small risk of abnormal heart rhythms, heart attack, or death in less than one in 30,000 patients. . In patients with established chronic illness the risk is higher. In cardiac rehabilitation programs the occurrence of major cardiovascular events ranges from 1/50,000 to 1/120,000 patient- hours of

exercise, with only 2 fatalities reported per 1.5 million patient-hours of exercise. The School of health and Human performance in DCU have the facilities and personnel to deal with any emergencies that arise and an emergency plan is in place. A GP will provide medical supervision on site during testing. An emergency room and automated external defibrillator (AED) are available onsite. The research team are appropriately qualified and experienced in working with clinical populations in a safe and professional manner.

- Drawing blood may cause a slight pain where the needle is inserted and can leave a bruise. A person trained to take blood will be used to decrease these risks. The amount of blood drawn is not harmful.
- Stopping the flow of blood for a period of 5 minutes may induce slight discomfort in your arm which will go away when the blood pressure cuff is deflated.
- Gyceryl trinitrate, is a type of medicine called a nitrate that works by being converted in the body to a chemical called nitric oxide. This chemical (nitric oxide) is also made naturally by the body and has the effect of making the veins and arteries relax and widen (dilate). This makes it easier for the heart to pump blood around the body. There is a very small chance that you may get a headache that may last 5-10 minutes after glyceryl trinitrate is sprayed under your tongue.

IV. Benefits from involvement in the Research Study

You will receive a report summarizing the results of the tests undertaken during the study. No other benefits have been promised.

V. Arrangements to protect confidentiality of data

Your identity and other personal information will not be revealed, published or used in further studies. You will be assigned an ID number under which all personal information will be stored and saved in a password protected file in a computer at DCU. The person is charge of the study and the other researchers listed on this ethics application will have access to the data. You need to be aware that confidentiality of information provided can only be protected within the limitations of the law. It is possible for data to be subject to subpoena, freedom of information claim or mandated reporting by some professions.

VI. Advice as to whether or not data is to be destroyed after a minimum period

The original documentation will be stored for a maximum of 5 years. Thereafter the documentation will be shredded.

VII. Involvement in the Research Study is voluntary

Involvement in this study is completely voluntary. You may withdraw from the Research Study at any point. There will be no penalty for withdrawing before all stages of the Research Study have been completed.

If participants have concerns about this study and wish to contact an independent person, please contact: The Secretary, Dublin City University Research Ethics Committee, c/o Office of the Vice-President for Research, Dublin City University, Dublin 9. Tel 01-7008000

9. INFORMED CONSENT FORM *(Include in this document. Approx. 300 words)*

In most cases where interviews or focus groups are taking place, an Informed Consent Form is required. This is an important document requiring participants to indicate their consent to participate in the study, and give their signature. If your participants are minors (under 18), it is best practice to provide them with an assent form, while their parents/guardians will be given the Informed Consent Form. In cases where an anonymous questionnaire is being used, it is enough to include a tick box in the questionnaire (underneath the information section for participant), where participants can indicate their consent.
See link to sample templates on the website: http://www4.dcu.ie/research/research_ethics/rec_forms.shtml

NB – IF AN INFORMED CONSENT FORM IS NOT BEING USED, THE REASON FOR THIS MUST BE JUSTIFIED HERE

n/a

Patient Informed Consent

DUBLIN CITY UNIVERSITY
PATHway (Physical Activity Towards Health): Pilot Randomised Controlled Trial

Principal Investigator: Dr. Catherine Woods, School of Health and Human Performance,

Other Investigators: Dr. Deirdre Walsh, School of Health and Human Performance, Prof. Niall Moyna, School of Health and Human Performance, Ms. Clare McDermott, School of Health and Human Performance, Anne Gallagher, Cardiac Rehabilitation Coordinator, Mater Hospital, Dr.Ivan Casserly, Consultant Cardiologist, Mater Hospital, Helen Newton, Cardiac Rehabilitation Co-ordinator, Beaumont Hospital. Dr. Brendan McAdam, Consultant Cardiologist, Beaumont Hospital.
The purpose of this study is to assess the acceptability, short-term effectiveness on lifestyle and health related physical fitness and cost-effectiveness of the PATHway intervention in patients with cardio-vascular disease.

Involvement in this study will require you to take part in a 6-month technology-enabled remote randomised control trial. As part of this trial, you will be randomly assigned into groups that will either i) receive 'usual care' or ii) take part in an intervention that will receive the PATHway system which will allow you to engage with a tailored exercise and health behaviour change programme. All participants will be asked to complete physiological tests and questionnaires at baseline, 3months and finally at 6months regardless of group.

Participant – please complete the following (Circle Yes or No for each question)

I have read the Patient information sheet (or had it read to me)
Yes/No
I understand the information provided
Yes/No
I have had an opportunity to ask questions and discuss this study

Yes/No
I have received satisfactory answers to all my questions
Yes/No

If at any point during your participation in the study you feel as if you wish to withdraw this is not a problem. You are under no obligation to stay involved if you do not wish too. However, you will be asked to arrange a convenient time to have the PATHway equipment collected/returned to the research team.

Please make sure to contact the investigators if you are unable or unwilling to continue in the project so as we can address any issues within the project.

Dublin City University will protect all the information about you, and your part in this study. All your personal data will be anonymised and assigned a unique code which all will protect your identity. All your information will be stored securely and saved in accordance with EU law and best conduct guidelines. Your identity or personal information will not be revealed or published.

The study findings may be presented at scientific meetings and published in a scientific journal but your identity will not be divulged and only presented as part of a group. Please be aware that the confidentiality of information provided can only be protected within the limitations of the law.

If you have questions about the research project, please feel free to call Dr. Deirdre Walsh at 01-7007653.

I have read and understood the information in this form.

My questions and concerns have been answered by the researchers, and I have a copy of this consent form.

Therefore, I consent to take part in this research project:

Participants Signature:_____

Name in Block Capitals:_____

Date:_____

Appendix E

Dublin City University
RESEARCH ETHICS COMMITTEE

AMENDMENT / EXTENSION REQUEST FORM

If you wish to make an amendment or request an extension for an approved study you will need to complete this form and submit with a covering email to REC@dcu.ie. Please note that student applicants must cc their supervisor on this email communication.

If your study involves animal subjects, any amendment or extension to the study must be pre-approved by the Bio-Resource Advisory Group - BRAG@dcu.ie . Please forward this form to BRAG in the first instance.

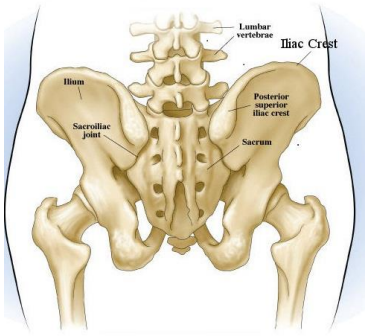
REC REFERENCE NUMBER:	DCUREC/2016/123
PROJECT TITLE:	PATHway (Physical Activity Towards Health): Human intervention study design
PRINCIPAL INVESTIGATOR ON ORIGINAL REC APPLICATION:	Prof. Niall Moyna
APPLICANT NAME (if different from original PI):	Dr. Deirdre Walsh
Supervisor Details *(if applicable):*	n/a
SCHOOL/UNIT:	School of Health and Human Performance
APPLICANT EMAIL:	Deirdre.walsh@dcu.ie
Do you wish to amend your approved study? **If so, please provide details of the proposed amendments and a justification for why this is requested.** (Amended participant documentation, if required, should accompany this form for review)	The research team would like to also name Ms. Anne Gallagher [listed investigator] in the task of providing medical supervision onsite during testing at times when Dr.McCaffrey is unavailable. An emergency room and automated external defibrillator (AED) are available onsite. Ms. Gallagher is the cardiac rehabilitation coordinator in the Mater Hospital and supervises exercise stress tests in her daily role. She is trained and certified to fulfil this role in a safe and appropriate manner.
Do you wish to extend the approval for your study? **If so, please provide details of how long you require and the justification for the extra time**	n/a
Any other Comments:	n/a

Signature of Applicant: **Date:** 30-06-17	
Signature of Principal Investigator *(if Applicant is not the P.I.):* **Date:** 30-06-17	

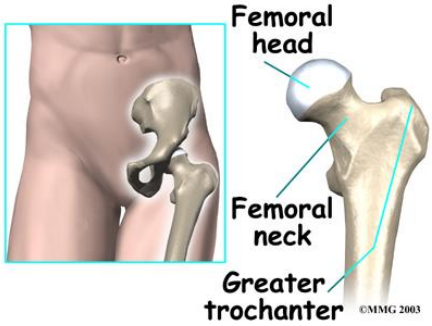
Measurement will be performed

- Baseline - 3 months - 6 months

- The participant is asked to remove all loose clothing and footwear
- **First**, the participants height is measured
- **Second**, the participants weight is measured using a scale
- **Third,** fat mass and fat % is measured using BEI
- **Fourth**, waist and hip circumference are measured using a measuring tape. Waist circumference is measured right above the crista iliaca level. Hip circumference is measured at the level of the trochanter major of the femur. Both measurements are repeated twice, alternating between waist and hip. If the difference between the 2 measurements is more than 1 cm, a third measurement is performed.



Crista iliaca



Greater Trochanter

Materials

Secca scales and stadiometer

Bioelectrical impedance scales

Measuring tape

Baseline ❑ **3 Months ❑** **6 Months ❑**

PIC Number	DOB:	DCU
Patient Initials:	Test Date:	Experimental visit:

Height: cm BMI: kg/m²	Weight: Kg	Fat Mass 1: Kg %	Fat Mass 2: Kg %
Not Measured:			
• Participant unable to stand up unassisted • Refusal	☐ Participant unable to stand up unassisted ☐ Participant to heavy for scale ☐ Refusal	• Device error • Refusal	• Device error • Refusal

	Waist circumference	**Hip circumference**
ATTENTION	Order: waist 1 → hip 1 → waist 2 → hip 2 → (if needed: 3rd)	
Trial 1	cm	cm
Trial 2	cm	cm
Difference	cm	cm
	Difference > 1 cm? • No • Yes = 3rd measurement	Difference > 1 cm? • No • Yes = 3rd measurement
Trial 3	cm	cm
Remarks:	• Waist circumference measured at belly button; couldn't find bones • Measured over clothing • Measured while seated	☐ Waist circumference measured at belly button; couldn't find bones ☐ Measured over clothing ☐ Measured while seated

Not measured:	• Refusal	□ Participant can't stand □ Refusal

Measurement will be performed

- Baseline - 3 months - 6 months

CPET:

- Connect 12-lead ECG and BP device
- Measure baseline HR and BP in sitting position on the bike
- Connect gas analyser and select test protocol for VO_2 peak
- Allow patient to sit on the bicycle for a 1min resting to acclimatize
- Measure VE, VO_2, VCO_2 while sitting
- Optimal test duration 8 – 12 minutes
- Choose individualized protocol 10 + 10W/min, 20W + 20W/min, 50 + 25W/min depending on fitness level of participant. (Incremental protocol/ workload increases every minute – same protocol at Baseline, 3 months and 6 months)
- Terminate the test when participant reaches volitional exhaustion:
  Aim to
  1. Surpass the respiratory compensation point (RCP = rise of $EQCO_2$)
  2. Achieve at RQ > 1.05
  3. RPE > 18 on the Borg scale (6-20)
- Criteria to stop the test:
  Muscle fatigue
  Shortness of breath
  Combination of both muscle fatigue and shortness of breath
  Psychological
  Symptoms
  Test stopped by supervisor
- Complete CRF data collection sheet. Calculate 20 sec average will be and record the highest value for VE, VO_2, VCO_2 and RQ
- HR, RPE, Watt and BP will be recorded during the last 10 sec of each stage during the test
  HR max = highest heart rate attained during the CPET
  VO_2 max = highest value during a period of minimum 20 seconds
- Recovery: Participant will cycle for 5 min at 25W and approx. 60 rpm, blood pressure and ECG will be recorded during the five minute cool – down period

* Modified from the report of the Working Group on Cardiac Rehabilitation & Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology. *European Heart Journal 2001; 22: 37-45* ***and*** Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section

of the European Association of Cardiovascular Prevention and Rehabilitation. Mezzani A et al *Eur J Cardiovasc Prev Rehabil* 2009

Baseline ❑ **3 Months ❑** **6 Months ❑**

PIC Number ☐☐☐☐☐☐☐	DOB: ☐☐☐☐☐	DCU
Patient Initials: ☐☐	Test Date: ☐☐☐☐☐	Experimental visit: ☐☐☐☐

Protocol: _____ DPB @ 80W: _____ SBP @ 80 W _____

Stage	Time	Workload (Watts)	HR	RPE	BP
Comments:					

Signed: _____

Baseline ❑ **3 Months ❑** **6 Months ❑**

PIC Number	DOB:	
Patient Initials:	Test Date:	Experimental visit:

Paramater	**Units**
Rest HR (on bike)	Bpm
Rest BP (on bike)	mmHg
Peak VO_2	Ml/min
Peak CO_2	Ml/min
Peak VE	L/min
Peak HR	Bpm
Peak Load	W
Peak BP	mmHg
Peak RER	
HRR min 1 (relative rest)	Bpm
HRR min 2 (relative rest)	Bpm
HRR min 3 (relative rest)	Bpm
Total test duration	Seconds
% predicted VO2 (Wasserman)	%
%VO_2peak at VAT	%
Absolute VO2 at VAT	Ml/min
Workload at VAT	W

Heart rate at VAT	Bpm
%VO_2peak at RCP	%
BORG	
Test stopped by (patient, test leader)	
Reason for termination	- Muscle fatigue - Shortness of breath - Muscle fatigue + shortness of breath - Unable to maintain a cadence of approx. 60 rpm - Physiological deterioration (ECG, Wasserman curves)
Symptoms/signs patient reports	

Measurement will be performed at

- Baseline - 3 months - 6 months

- Have you fasted overnight: Yes/No
- Have you refrained from the following for at least 6 h:
  - Nicotine Yes/No
  - Alcohol Yes/No
  - Caffeine Yes/No
  - Excessive exercise for 24 h Yes/No
- Measurements should be performed at the **same time of day within each individual**
- Room **temperature** maintained between **21 and 23° Celsius**
- **Lights** in the rooms are **dimmed – no noise**
- **Explain test procedures**. Stress, participant **is not allowed to fall asleep.**

- Measure the circumference at the middle of the left upper arm and the distance from the jugular bone to the symphysis pubis, record on CRF 3

Materials
Automatic blood pressure device
Sphygmomanometer
Stethoscope
Ultrasound
Ultrasound gel
GTN

Blood Pressure

- The patient is positioned in a sitting position in a comfortable chair.
- The blood pressure device is attached on the left upper arm.
- After a 15 min sitting rest period, 3 measurements are performed with 1 min interval between measurements.
- Write down SBP, DBP and HR on CRF 3

Coratid Intima thickness

Equipment settings

- Position the screen so the patient cannot see the screen (avoids biofeedback)
- Rest subject supine

The same blinded investigator performs all the measurements

- Measure Carotid artery on left and right side
- Record reading for near and far wall of each artery

Flow Mediated Dilation of the brachial artery

Equipment settings

- Position the participant so they cannot see the screen (avoids biofeedback)
- Participant rests in a supine position for 10 min
- Apply blood pressure cuff to the right mid-arm

The same blinded investigator performs all the measurements according to the protocol of Corretti

- Place a blood pressure cuff distal to the elbow (forearm)
- Measure baseline internal diameter of the brachial artery in supine position after 10 minutes of supine rest
- Inflate to 200 mmHg or 50 mmHg above the peak systolic pressure for 5 min
- Deflate cuff
- Measure post-occlusion diameters over the following 150 seconds
- Store video data on the PC for later off-line analysis.
- Express flow-mediated dilation as percentage dilation from baseline diameter to maximal post-occlusion value

Baseline ❑ **3 Months ❑** **6 Months ❑**

PIC Number ☐☐☐☐☐☐☐	DOB: ☐☐☐☐	DCU
Patient Initials: ☐☐	Test Date: ☐☐☐☐	Experimental visit: ☐

OFFICE BLOOD PRESSURE AND HEART RATE		
Trial 1	BP: _____ mmHg	HR: _____ BPM
Trial 2	BP: _____ mmHg	HR: _____ BPM
Trial 3	BP: _____ mmHg	HR: _____ BPM

CIMT MEASURMENTS:

Right IMT		Labelled as:
Left IMT		Labelled as:

FMD:		
Timing Protocol:		
FMD:		
Labelled as:		
Issues:		

Vasodilation:		
Timing Protocol:		
Vasodilation:		
Labelled as:		
Issues:		

Measurement will be performed

- Baseline - 3 months - 6 months

Sit and stand test

- The participant is seated in the middle of the chair with arms crossed and held against their chest.
- Following a demonstration, the participant is asked to rise to a complete stand and return back to the initial seated position as many times as possible within 30 sec
- Allow the participant a practice attempt to ensure the are completing the exercise correctly
- Advise the participant you are going to start recording after ‘go’ and count down from 3
- Record the number of complete stands the participant completes in 30 sec

Maximal Isometric handgrip force

- The participant is seated with his upper arms next to his body and a 90° angle in the elbow joint. The elbow and forearm are supported.
- The participant takes the hand dynamometer in their dominant hand and it is adjusted to size.
- The participant performs a maximal handgrip test.
- Each side is tested 3 x alternating left and right arm
- Between each measurement – 30 second rest is provided
- Maximal encouragement is given by the blinded assessor

Biodex quadriceps force and endurance

- The participant sits on the Biodex machine (Biodex medical systems, NY, USA) and is strapped in correctly
- The chair adjusted to the following position: the knee gap of the patient is in contact with the rounding of the chair, the knee joint is at the height of the hinge of the Biodex machine
- The first protocol consists of 3 isometric leg extensions of 6 seconds with 1 minute rest in between
- The last isometric leg extension is also followed by 1 minute rest
- The second protocol consists of 2x25 isokinetic leg extension/flexion movements with 2 between.

Baseline ❑ **3 Months ❑** **6 Months ❑**

PIC Number	DOB:	
Patient Initials:	Test Date:	Experimental visit:

	Trial 1	**Trial 2**	**Best score**
No. of complete stands in 30 sec			

Maximal Isometric Hand Grip	
Dominant Side	Non Dominant side
Trial 1: NKg	Trial 1: NKg
Trial 2: Nkg	Trial 2: NKg
Trial 3: Nkg	Trial 3: NKg

Quadricep Strength and Endurance	
Isometric Attempt	Quadricep endurance
Trial 1:	Trial 1:

☐ N	☐ Nm
Trial 2: ☐ N	Trial 2: ☐ Nm
Trial 3: ☐ N	

Biodex Measurements			
Arm	Chair Distance to Arm	Chair Backrest	Chair Height

Appendix G

Eligibility

Site: Mater ☐ ☐ **Beaumont**

To be filled out by the local cardiac nurse (Ireland) or physiotherapist (Belgium) for all CVD patients aged 40-80 years, enrolled in phase II CR for the first time. **(0 = no; 1 = yes)**

Initials (N_S)	DOB (DD/MM/YYYY)	Gender
		M ☐ F ☐

CR pathology (tick all that apply):

Coronary Bypass Graft	
PCI	
AMI	

Valve Disease	
ICD	
Other (specify)	

Inclusion Criteria:	Yes	No
Age 40 - 80		
Medically stable		
Theraputically stable		
Internet access at home		
Enrolled in phase II CR for the 1st time		

Exclusion Criteria:	Yes	No
Significant ilness druing the last 6 weeks		
Known severe ventricular arrhythmia with functional or prognotic signifigance		
Significant myocardial ischemia, hemodynamic deterioration or exercise-induced arrhythmia at baseline testing		
Cardiac disease that limits exercise tolerance (valve disease with significant hemodynamic conseqiences, hypertrophic cardiomyopathyetc.)		
Co-morbidity that may significantly influence one-year prognosis		
Acute or chronic inflammatory diseases or malignancy, the use of anti-inflammatory drugs or immune suppression		
Functional or mental disability that may limit exercise		
GRF < 25ml/min/1.73m^2		
Hemoglobin < 10 g/dlL		

Severe chronic obstructive pulmonary disease (FEV1 < 50%)		
Participation in another clinical trial		

Agreement to participate	Yes	No
Participant eligible for randomisation		
Participant confirms participation		
Signed informed consent		

Appendix H

Author	n	Mean age (yr)	Duration	Home based technique/ Technology used	Mode	Outcome measures	Results
Arthur HM, Smith KM, Kodis J, McKelvie R (2002)	242	Hosp: 62.5 Home:64.2	6 months	Telephone calls weekly	Home based (6.5 per week avg 42.7 min) V Hospital Based	VO_2max SF-36 Social support	VO_2max Hosp: ↑ 36.2% Home: ↑ 30.6% Physical Composite score sig increased in both groups but more in Home group Home group greater social support
Gordon NF, English CD, Contractor AS, Salmon RD, Leighton RF, Franklin BA, Haskell WL (2002)	155	Hosp: 60 Home: 61 Comm: 60	3 months	2 physician visits Nurse telephone call every 2 weeks Individualized exercise program updated over each call	Hospital based CR v Home based V Community based	Anthropometrics BP VO_2max	Decrease in weight greatest in community then home then hosp BP Decreased in all groups VO_2max (ml/kg/min) Hosp ↑ 1.6 Home ↑ 0.9 Comm ↑ 1.6
Zutz A, Ignaszewski A, Bates J, Lear S (2007)	15	Home based: 58 Control: 59	3 months	Home based (laptop, heart rate monitor and BP monitor) One-to-one chat sessions with nurse and dietician	Home based v control	Anthropometrics Bloods VO_2max QA (PA, self efficacy)	VO_2 Home ↑ 1.5 MET Usual care ↑ 0.7 MET PA (Kcal/week) Home ↑ 5036

				Education sessions on ppt weekly			Usual care ↑ 778 BMI – no change
Salvetti XM, Filho JAF, Servantes DM, de Paolo AAV (2008)	39	Home: 53 Control: 54	3 months	2 gym classes followed by individualized program with illustrations of warm up and cool down and QA about presence of symptoms Frequency of ex to be completed Two telephone calls/week	Home based v control	VO_2max QOL	VO_2max Home: ↑ 2.9 ml/kg/min Control: Decrease 0/6 ml/kg/min QOL improved
Guiraud T, Granger R, Gremeaux V, Bousquet M, Richard L, Soukarie L, Babin T, Labrubee M, Sanguignol F, Bosquet L, Golay A, Pathak A (2012)	29	Mean age 57.4	8 weeks	Wore an accelerometer for 8 weeks and received a Phone call every 15 days giving feedback on PA guidelines and goals Control wore accelerometer on week 8	Home based v control	PA (accelerometer)	Sig diff in MIPA at 8th week Control 45.7 min/week Intervention 137.2
Reid RD, Morrin LI, Beaton LJ, Papadakis S, Kocourek J, McDonnell L, Slovinec D'Angelo	223	Mean age 56.4	12 months	5 online tutorials ober 20 weeks – each tutorial prescribed a new PA plan Emails with motivational feedback	Cardiofit V Usual care	PA (pedometer and self report)	Steps at 6 months UC = 6168 CF = 7079 12 month

ME, Tulloch H, Suskin N, Unsworth K, Blanchard C, Pipe AL (2012)				and access to exercise specialist via email			UC = 6750 CF 7392 MIPA 6 months UC = 163.4 CF = 201.0 12 month UC = 169/6 CF = 201.4
Lee YH, Hur SH, Sohn J, Lee HM, Park NH, Cho YK, Park HS, Yoon HJ, Kim H, Nam CW, Kim YN, Kim KB (2013)	60	Home: 54 UC: 57	3 months	1 phone call per week Exercise program to be completed 4-5 times weekly with walking and flexibility exercises Wireless HR monitor worn (ECG)	Home based v Usual care	VO_2max	Home base ↑ 2.47 UC ↑ 1.43
Kraal JJ, Peek N, Van den Akker-Van Marle ME, Kemps HMC (2014)	50	Home 60.6 Centre 56.1	3 month	At least 2 sessions per week 45-60 min at 70-85% of max HR Home based group had 3 supervised sessions to learn how to use wearable's and upload data to app – patient physical therapist and exercise specialist could view this data Feedback was provided	Home based v centre based	VO_2max	Home ↑ 10% 22.8 – 26.0 Centre ↑ 14% 23.7 – 26.1

				once a week via phone call on frequency, duration and intensity of exercise			
Varnfield M, Karunanithi M, Lee CK, Honeyman E, Arnold D, Ding H, Smith C, Walters DL (2014)	120	Centre = 55.7 Home = 55.5	6 month	1 hour technology training Smart phone – activity monitor, health diary BP monitor and weighing scales Text messages for motivation and education 2/4 per day Relaxation Audio	Smart phone based home based v centre based	6 MWT	Centre= BL 537 – 6W 584 Home BL 510 – 6W 570 No further change from 6 week to 6 month
Maddison R, Pfaeffli L, Whittaker R, Stewart R, Kerr A, Jiang Y, Kira G, Leung W, Dalleck L, Carter K, Rawstorn J (2015)	171	Home = 61.4 Control 59.0	24 weeks	Exercise prescription Participants received 3-5 text messages per week Were encouraged to log on to the website once per week to view videos	Home based Intervention v control	VO_2max Self reported PA	
Frederix I, Van Driessche N, Hansen D, Berger J, Bonne K, Alders T, Dendale P (2015)	80	Control:63 Home: 58	18 weeks	Motion sensor which was uploaded weekly Feedback provided by email and SMS designed to increase steps by 10% per week	Home based telemonitoring v control	VO_2max	Control 22 -23 ml/min/kg ↑1 Intervention 24 – 28 ml/min/kg ↑ 4